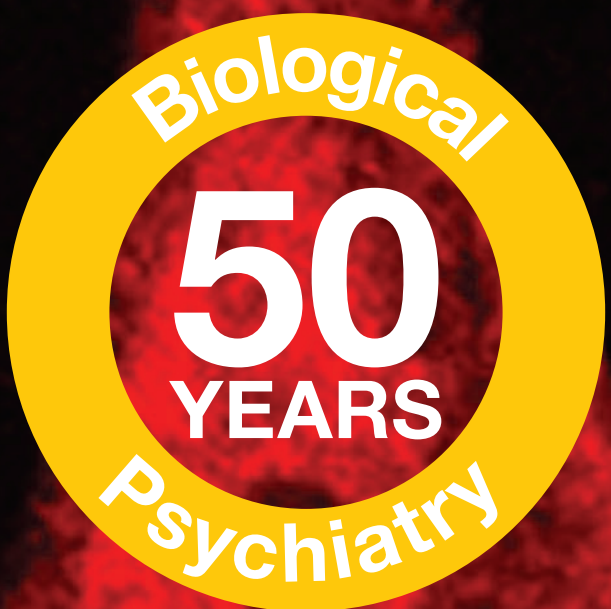
Supplement to:

Biological Psychiatry

Volume 85, Number 10S
May 15, 2019

Supplement: 74th Annual Scientific Convention and Meeting



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Official Journal of the Society of Biological Psychiatry

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Published since 1969

Aims and Scope

Biological Psychiatry is an official journal of the Society of Biological Psychiatry, whose purpose is to promote excellence in research investigating the nature, causes, mechanisms, and treatments of disorders of thought, emotion, and behavior. In accord with this mission, this peer-reviewed, rapid-publication, international journal publishes both basic and clinical contributions from all disciplines and research areas relevant to the pathophysiology and treatment of major psychiatric disorders.

Biological Psychiatry publishes novel results of original research that represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also published.

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Biological Psychiatry *is cited in Beck Medical Information, Biological Abstracts, CABS/Current Awareness in Biological Sciences, Chemical Abstracts, Current Contents, Excerpta Medica, Index Medicus, Inpharma, LMS Alerts Online (DataStar), Mental Health Abstracts, Psychological Abstracts, Reactions, Referativnyi Zhurnal, Reference Update, Science Citation Index, and Selected List of Tables of Contents of Psychiatric Periodicals.*

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

Volume 85, Number 10S, May 15, 2019

74TH ANNUAL SCIENTIFIC CONVENTION AND MEETING

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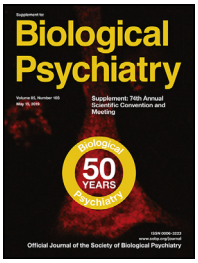

In honor of the *Journal's* 50th anniversary year, the cover of this annual supplement pays homage to one of our all-time favorite covers. It features the pyramidal neuron that was originally highlighted on the cover of issue 60/8, which was the first of our redesigned covers originally unveiled in 2006.

From Maldonado-Avilés JG, Wu Q, Sampson AR, Lewis DA (2006): Somal size of immunolabeled pyramidal cells in the prefrontal cortex of subjects with schizophrenia. Biol Psychiatry 60:226–234.

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

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QUESTIONS? CONTACT US

Biological Psychiatry is the official journal of the Society of Biological Psychiatry. The *Journal* rapidly publishes reports of novel results on a broad range of topics related to the pathophysiology and treatment of major neuropsychiatric disorders. Both basic and clinical neuroscience contributions are encouraged, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches.

Except where explicitly stated otherwise, *Biological Psychiatry* conforms to the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE) (see Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (December 2017): Available from http://www.ICMJE.org).

All new manuscripts must be submitted through the journal website: https://www.editorialmanager.com/bps. All correspondence should be directed to the Editorial Office at Biol.Psych@sobp.org.

ARTICLE TYPES

Archival Reports

Archival Reports are original research papers reporting novel results on a broad range of topics related to the pathophysiology and treatment of major neuropsychiatric disorders. Clear explication of methods and results is critical to facilitate review of papers and replicability of findings.

Word Limit: 4000 words in main body of text*
Abstract: 250 word limit; Structure as follows: Background, Methods, Results, Conclusions
Main Text: Structure as follows: Introduction, Methods and Materials, Results, Discussion
Tables/Figures: No limit, as needed
References: No limit, as needed
Supplement: Allowed, unlimited length

Priority Communications

These are Archival Reports that clearly document novel experimental findings of unusual and timely significance. These papers should represent a conceptual advance in the field and are not intended for publication of preliminary results. They are expected to be acceptable for publication in essentially the form submitted. Papers that require substantial revisions or do not fit the criteria will be considered as Archival Reports. See Archival Reports for structure, word length, and other requirements.

Reviews

Reviews are concise and focus on current aspects of interest and research. Reviews should be novel and have sufficient supporting literature, which should be integrated into a mechanistic model when applicable. Reviews should generally not focus solely on the authors' own work. Note that meta-analyses report original data and thus are not considered review papers; meta-analyses should be submitted as Archival Reports. Unsolicited reviews may be submitted directly. Invited reviews must first complete a pre-submission evaluation and consultation process with the Reviews Editor. The Editorial Office will provide specific details and the proposal form to all invited authors when warranted.

Word Limit: 4000 words in main body of text*
Abstract: 250 word limit; unstructured
Main Text: Structure with headings as needed
Tables/Figures: Allowed to summarize or illustrate important points
References: 150 maximum
Supplement: Allowed, unlimited length

Techniques and Methods
These articles feature new, improved, or noteworthy comments about techniques or methods relevant to basic or clinical research in, or treatment of, psychiatric disorders.

Word Limit: 3000 words in main body of text*
Abstract: 150 word limit; unstructured
Main Text: Structure as follows: Introduction, Methods and Materials, Results, Discussion
Tables/Figures: Maximum of two
References: No limit, as needed
Supplement: Allowed, unlimited length

Correspondence
These letters to the editor are directly related to methods, procedures or interpretation of data presented in work recently published in our journal and uses new analysis of data presented, the support of previously published work, and/or scientific points to be addressed based on methodological issues. They may also present a case report that clearly and unambiguously illustrates important new principles that have not yet been demonstrated in clinical trials. When warranted, a reply from author(s) of the original work is solicited; in such cases, the editor does not issue a final decision until both articles are submitted and the pair is then published together. Correspondence is published online only as e-content.

Word Limit: 1000 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured
Tables/Figures: Not encouraged, but 1-2 allowed if needed to illustrate important points
References: No limit, as needed
Supplement: Not permitted

Commentaries and Editorials
These articles address points directly related to articles in the concurrent issue, and/or focus on topics of current research and interest. These are generally invited, but interested contributors may contact the Editor.

Word Limit: 1500 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured, headings are not permitted
Tables/Figures: A single summarizing figure or table is encouraged
References: 10 maximum
Supplement: Not permitted

Early Career Investigator Commentaries
These articles provide publishing opportunities to early career investigators (ECI), as part of a joint project between the *Journal* and the Education Committee of the Society of Biological Psychiatry. These are invited articles for which an ECI serves as the sole and corresponding author. Each ECI shall be 1) a current member of the Society of Biological Psychiatry, 2) no more than 10 years out from terminal degree, and 3) not hold an academic faculty rank higher than Assistant Professor. A senior investigator mentors each ECI, acts as the content reviewer, and is recognized in the Acknowledgments section. ECI commentaries are published online only as e-content.

Word Limit: 1500 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured, headings are not permitted
Tables/Figures: A single summarizing figure or table is encouraged
References: 10 maximum
Supplement: Not permitted

Clinical Commentaries
These invited-only commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). Unlike regular commentaries, these articles have a specific clinical focus and are intended for a clinical audience, including medical students, residents, and clinicians. Clinical commentaries are published online only as e-content.

Word Limit: 1500 words in main body of text*
Abstract: Not permitted
Main Text: Unstructured
Tables/Figures: A single summarizing figure or table is encouraged
References: 10 maximum
Supplement: Not permitted

*Word limits include main text of the article only, e.g., for Archival Reports, the word count includes the Introduction, Methods and Materials, Results, and Discussion sections. When calculating word counts, exclude abstract, references, table/figure legends, acknowledgments, and disclosures.

PREPARATION & FORMATTING REQUIREMENTS

The basic elements of all submissions are as follows:

- Cover letter
- Manuscript
  - Title page
  - Abstract
  - Main text of article
  - Acknowledgments
  - Disclosures
  - References
  - Legends for tables and figures
- Tables
- Figures
- Supplemental Information

Further details on each element are provided below, followed by guidance on style.

Cover Letter
Cover letters are optional for all submissions. A cover letter must be uploaded as a separate file, as it is not made available to peer reviewers.

Manuscript
Manuscripts should contain the following sections: title page, abstract, main article text, acknowledgments, disclosures, references, footnotes, and table/figure legends. The manuscript may also include tables, in text format, at the end of the file. Begin all sections on separate pages. The manuscript file should be supplied in Word, not in PDF.

Title Page
The title page should be the first page of the manuscript file and should include the following elements:

- Full article title, 200 characters or less; acronyms/abbreviations are prohibited
- Full names of all authors, in order, and their affiliations
- Corresponding author's complete mailing address, phone, and email
- Short/running title, 55 characters or less (including spaces); standard acronyms are permitted
- Six keywords
- Number of words in the abstract
- Number of words in the main text
- Number of figures, tables, and supplemental information, each listed separately; if zero, state zero

Abstract
Abstracts should be structured or unstructured according to the article type and should not exceed the word limits as detailed above. Structured abstracts should have the following sections: Background, Methods, Results, Conclusions. The Methods section should explicitly state the sample size and sex/species of subjects, when applicable. For those manuscripts that require clinical trials registration (see Clinical Trials Registration section, below), the registry name, URL, and registration number should be included at the end of the abstract. References are not permitted in abstracts. Avoid the use of abbreviations/acronyms that are not used at least three times.

Main Text
The text of papers should be double-spaced and structured according to the article type. It should not exceed the word limits as detailed above. Articles reporting original research (Archival Reports, Priority Communications, Techniques and Methods) should be structured with the following headings: Introduction, Methods and Materials, Results, Discussion. The introduction should provide a brief background and state the objectives/hypotheses of the current work; it should not include the findings/results of the study. The Methods and Materials section should include sufficient detail to allow other investigators to replicate the work. It is not appropriate to move the entire text of the methods to the supplement to adhere to the *Journal's* word count limits. Manufacturer name and location should be included at first mention, where applicable. Authors may reference other publications for methods that have previously been published in full detail elsewhere. Relevant ethics statements must be included; see Ethical Considerations section, below. The Results section should clearly present the experimental findings and test statistics in a logical order. The Discussion section should describe the results, interpret them in the context of prior literature, and discuss the implications and significance of the finding(s). Limitations of the current work should also be discussed.

Acknowledgments
This section should include detailed information regarding all sources of funding, including grant and other material or financial support. Specify granting agency, grant number, and recipient for each funding source. The role of study sponsor(s), if any, should be stated. Identify any data that was published previously, in abstract/poster form or on a preprint server. This section may also be used to acknowledge non-author contributors/collaborators and individuals who provided personal and technical assistance. If a consortium/group is listed as an author, then the individual members must be named here. Authors should secure written permission from all individuals named in this section.

GUIDE FOR AUTHORS

Disclosures

This section must include the required financial disclosures and conflict of interest statements for each author. Even if every author has nothing to disclose, this must be explicitly stated. See section on Disclosure, below.

References

References should be numbered and listed by their order of appearance in the text. Refer to references in the text with the appropriate number in parentheses. References in tables and figures should also be numbered. List all authors; if there are more than seven authors, list the first six then *et al.* Periodical abbreviations should follow those used by Index Medicus. It is not appropriate to reference papers that have not yet been published (i.e., are submitted or under review). The following are sample references for a published journal article (1), a book (2), and an edited book (3).

1. Krystal JH, Carter CS, Geschwind D, Manji HK, March JS, Nestler EJ, *et al.* (2008): It is time to take a stand for medical research and against terrorism targeting medical scientists. *Biol Psychiatry* 63: 725-727.
2. American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Publishing.
3. Martin JH (1985): Properties of cortical neurons, the EEG, and the mechanisms of epilepsy. In: Kandel ER, Schwartz JH, editors. *Principles of Neural Science, 2nd ed.* New York: Elsevier, pp 461-471.

The *Journal* also encourages the citation of underlying or relevant datasets in manuscripts by citing them in the text and including a data reference in the reference list. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so that it can be properly identified as a data reference. The [dataset] identifier does not appear in published articles.

Figure/Table Legends

Provide a brief title and legend for each figure and table. For multi-part figures, describe each panel. Avoid duplicating information in the figure/table legends that is already presented in the Methods and Materials or Results sections.

Tables

Tables should be cited in the text and numbered consecutively (i.e., 1, 2, 3) in the order of their mention. Each table should have a title, along with a brief description (legend). Do not duplicate information that is already presented in the text. Tables must be supplied in an editable format (Word or Excel). They may either be included at the end of the manuscript file, or uploaded individually, but not both. Table footnotes should use superscript lowercase letters, rather than symbols or bold/italic text. Colored text or shading is not permitted in tables.

Figures

Basic figure instructions are provided here. Further details regarding electronic artwork quality and preparation can be found at https://www.elsevier.com/authors/author-schemas/artwork-and-media-instructions.

Key Requirements for Figures

File Formats	› TIFF, EPS, or PDF are preferred; JPEG is acceptable
Resolution	› Halftone or combination art: 300-500 dpi › Line art: 1000 dpi or supply as vector image
Image Size	› Single column width: 90 mm (255 pt) › 1.5 column width: 140 mm (397 pt) › Double column (full page) width: 190 mm (539 pt) › Note: 72 points = 1 inch
Font	› 8-12 point (minimum size variability) › Standard typeface (e.g., Arial, Times New Roman) › Consistent throughout
Multi-Panel Figures	› Label each panel/part with a capital letter (A, B, C,…)
Figure Titles/Legends	› Include in manuscript file, not in figure files
File Naming	› Use the figure number (Fig1.tif, Fig2.pdf, etc.)
Upload	› Supply as individual files (a single file for each figure)

Figures should be cited in the text, numbered consecutively (i.e., 1, 2, 3) in the order of their mention, and have brief legends. Each figure should be consistent in color, size, and font, and be designed proportionally so that it can later be sized as needed without loss of legibility or quality. Letters and numbers, in particular, should not vary greatly in size. RGB color mode is preferred over CMYK. High quality versions of each figure should be uploaded individually (i.e., two figures should be uploaded separately as Figure 1 and Figure 2). To reduce TIFF file size, flatten layers and then save with LZW compression before uploading. A minimum resolution of 300 dpi is required. Note that the quality of a low-resolution figure cannot be improved by artificially increasing the resolution in graphics software; figures must be initially created with sufficient quality/resolution. Figure titles and legends should be included as editable text in the manuscript file and not in the figure files.

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Supplemental information, relevant to the work but not critical to support the findings, is strongly encouraged by the *Journal* and is made available via links in the online article but not published in print. All such material is peer-reviewed, but not typeset or proofed and so should be carefully prepared. Unlike other files, all supplemental information (including text, tables, and figures) should be uploaded in a single Word file whenever possible. Exceptions are large and/or lengthy tables, which may be submitted in Excel. Word documents will automatically be converted to PDF before being posted online.

Do not number sections of text; rather, use textual headings to clearly differentiate sections. Supplementary figures and tables should appear with their titles/legends, and be numbered consecutively (i.e., Figure S1, Figure S2, Table S1). References should be included as a separate list from those in the main manuscript; number beginning with (1) and include a reference list at the end of the supplemental document. The CONSORT diagram for randomized controlled trials, when applicable, will be published in the supplement.

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Multimedia content, in formats such as AVI or MPG, is encouraged and should be uploaded as an "e-component" in the drop-down menu at the upload screen.

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The *Journal* also encourages enrichment of online articles via support of 3D neuroimaging data visualizations. Authors may provide 3D neuroimaging data in either single (.nii) or dual (.hdr and .img) NIfTI file formats. Recommended size of a single uncompressed dataset is $\leq$100 MB. Multiple datasets can be submitted. Each dataset should be zipped and uploaded separately as "3D neuroimaging data" in the drop-down menu at the upload screen. Please provide a short informative description for each dataset by filling in the 'Description' field when uploading a dataset. If an article is accepted, the uploaded datasets will be available for download from the online article on ScienceDirect. For more information, see: https://www.elsevier.com/authors/author-resources/data-visualization.

Style

Basic style points are as follows:

Layout	› Double-space all text › Number each page › Line numbering is not necessary
Spelling	› Use American, as opposed to British, spellings
Language	› English
Font	› Any standard typeface is acceptable (e.g., Arial, Times New Roman) › Be consistent throughout (use the same typeface and size)
Acronyms/ Abbreviations	› Define at first use in the abstract › Define again at first use in the text and also in each legend › Avoid unnecessary/uncommon abbreviations
Nomenclature	› See below

Our readership is diverse, and authors should consider that many readers are in specialty areas other than their own. It is important, therefore, to avoid jargon. Manuscripts with the broadest appeal are focused and clearly written. In highly specialized areas, the introduction should be a concise primer.

We encourage authors whose first language is not English to ask a native English speaker to review their manuscript or to use a professional language editing service prior to submission. Accepted manuscripts are copyedited to conform to the *AMA Manual of Style*.

Psychopharmacology Nomenclature

Biological Psychiatry supports the Neuroscience-based Nomenclature (NbN) project (http://nbnomenclature.org/), which aims to promote the use of mechanism-based nomenclature that is pharmacologically-driven, rather than indication-based. The NbN system characterizes medications based on their pharmacological

domain and mode(s) of action. Authors should use NbN's glossary or official apps in order to translate between the old and new nomenclature.

Gene/Protein Nomenclature

Gene symbols should be italicized and differentiate by species. Human symbols should be all uppercase (*DISC1*), whereas symbols for rodents and other species should be lowercase using only an initial capital (*Disc1*). Protein products, regardless of species, are not italicized and use all uppercase letters (DISC1).

Authors should use approved nomenclature for gene symbols by consulting the appropriate public databases for correct gene names and symbols. Approved human gene symbols are available from HUGO Gene Nomenclature Committee (HGNC) at http://www.genenames.org/. Approved mouse symbols are provided by The Jackson Laboratory at http://www.informatics.jax.org/marker/. Use symbols (e.g., *SLC6A4, DISC1*) as opposed to italicized full names, and avoid listing multiple names separated by a slash, such as *'Oct4/Pou5f1'*. Use one name throughout and include any alias(es) upon the first reference. Authors should submit proposed gene names that are not already approved to the appropriate nomenclature committees as soon as possible. It is the authors' responsibility to ensure these are deposited and approved before publication of an article.

SUBMISSION PROCESS

All manuscripts must be submitted in electronic form through the *Biological Psychiatry* online submission and review website (https://www.editorialmanager.com/bps). Submission is a representation that all authors have personally reviewed and given final approval of the version submitted, and neither the manuscript nor its data have been previously published (except in abstract or preprint form) or are currently under consideration for publication elsewhere.

The *Journal* has created checklists to assist authors in the efficient submission of both new and revised manuscripts. They are entirely optional and intended solely to help authors adhere to our submission guidelines and save time so that submissions do not need to be returned for correction. The checklists are available here: http://www.biologicalpsychiatryjournal.com/content/bps-submission-checklists.

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New Submission

When submitting a new manuscript, authors will be asked to provide the following: valid email addresses for all authors; the names, emails and affiliations of 6 individuals who would be appropriate to review the work; and all submission files. Further details are as follows.

New Submission Files

To ease the burden of the submission process, we permit authors to upload the entire submission (minus a cover letter) as a single file, with pages numbered, in Word or PDF. Tables and figures may either be placed within the body of the manuscript or presented separately at the end. Authors must ensure that all elements are clearly legible for editors and peer reviewers. Alternatively, authors may upload individual files (cover letter, manuscript, figures, etc.) separately. All files should be labeled with appropriate and descriptive names (e.g., SmithText.doc, Fig1.eps, Table1.doc). The system will build a single PDF of the submission from the uploaded files. Regardless of how files are uploaded at this stage, all essential components of a manuscript are still required. See Manuscript section, above.

Author Notifications

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Referee Suggestions

For all new submissions (except Commentaries and Correspondence), authors are required to provide the full names and contact information (affiliation and email) of 6 individuals who are especially qualified to referee the work and would not have a conflict of interest in reviewing the manuscript. Affiliations of the suggested referees should all be different, and none should share an affiliation with any of the authors. Editors are not appropriate to suggest as a reviewer. Authors are also permitted to identify reviewers who should be excluded from reviewing their work, but final peer reviewer selections remain at the editors' discretion.

Revised Submission

Except for the additional guidelines noted here, requirements for revised submissions are the same as for new submissions. When submitting a revised manuscript, authors are asked to provide a detailed response to reviewers, which must be uploaded as a unique Word or PDF file (separate from the cover letter). Authors may upload a 'tracked changes' version of their revision, but must always include a 'clean' non-marked version of the manuscript. If revisions are a condition of publication, only two revised versions of the paper will be considered. Unsolicited revisions are not allowed.

Revised Submission Files

All files (cover letter, response to reviewers, manuscript, figures, etc.) must be uploaded separately at revision, and should be labeled with appropriate and descriptive file names (e.g., SmithText.doc, Fig1.tif, Table1.doc). File format requirements are specified in the below table. The system will build a single PDF of the submission from the uploaded files. Authors should be careful to replace all files that have been updated since original submission and ensure all files are correctly labeled (particularly if figures and/or tables have been rearranged and subsequently renumbered). On the title page, update word, figure, and table counts as necessary.

File Type Requirements

Cover Letter	Word or PDF
Detailed Response to Reviewers	Word or PDF
Manuscript	Word
Tables	Word or Excel
Figures	TIFF, EPS, or PDF
Supplement	Word

Word Limits

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Updated 11/28/18

Welcome

We are delighted to welcome you to the Windy City for the 2019 Annual Meeting of the Society of Biological Psychiatry. This year's theme, **Innovations in Clinical Neuroscience: Tools, Techniques, and Transformative Frameworks**, illustrates the emerging consensus that catalytic change is nigh for psychiatry and related fields of work. The utilization of innovative and transformative frameworks emphasizes the new ways of thinking about, and understanding, psychiatric illnesses. There are also enhanced and emerging tools for measurement and intervention. The format additionally highlights how certain techniques and experimental designs can elucidate the biological pathways and markers of psychiatric illness processes. In addition, the program includes new developments in computational modeling, real-time measurements, and alternative interventions, showcasing all that is growing and building in SOBP over recent years. We are therefore very excited to highlight these developments at this year's meeting in the presentations, discussions, networking, and sidebars that are a hallmark of the SOBP conference format.

The number of presentations attest to the continued and growing strength of SOBP, with 12 plenary speakers, 60 symposia, and 6 oral sessions. This year, we bring into the spotlight emerging scientists with the Rising Star Showcase. In these new oral sessions, 12 mentees at a critical period of professional development present their work in a format that encourages feedback from mentors, editors, and grant reviewers. The standard and Late Breaking posters continue to provide a presentation format for scientists in different phases of their careers and for the SOBP membership to present their work, network, solicit feedback, and enhance the quality and purpose of their science. This year's meeting includes 661 posters and 275 Late Breaking posters. We would also highlight the special session on the role of basic animal research, and the parallel models that are used and still needed to marshal, expand, and transform basic neuroscience research to help patients and families who struggle with brain illnesses.

We would like to thank the Program Committee for their astute and timely feedback. In particular we would like to continue to encourage those who submitted symposia that did not receive priority scores high enough to warrant acceptance to please submit their work in future years. We were, unfortunately, unable to accept many high-quality submissions, as the format for the conference is very densely packed.

The 2019 SOBP meeting, as in years past, is a virtual roller coaster of high-quality presentations and discussions. It is tightly packed with opportunities to catch a bite to eat or a cup of coffee with your next collaborator, mentor, or colleague. We particularly like the format of the SOBP Annual Meeting and are grateful to continue this tradition. Enjoy the ride, which features striking new areas of science broadly spread throughout the 3-day meeting. We will learn more about discoveries in neuroscience, study follow-ups, and data reports, in addition to new knowledge regarding neural mechanisms underlying psychiatric disorders. Our attendees will be varied, from clinicians to full-time researchers and science and medical educators, and will include seasoned scientists and clinicians as well as graduate students, postdoctoral fellows, and junior clinicians training in the field. We particularly welcome first-time attendees. It may be overwhelming at first, but we guarantee that this will become one of your favorite meetings! The SOBP Annual Meeting is an exciting venue for industry, academia, and government scientists to have the opportunity to gather, bound by a common passion for understanding the brain and seeing new knowledge applied to mechanisms of psychiatric disorders and stimulating the development of new treatments.

In addition to the Program Committee, we would like to thank Council and the Parthenon Management Group staff, in particular Tori Swinehart and John White, who have made this an enjoyable and engaging year of planning and development.

In closing, we welcome you to the 2019 Annual Meeting of the Society of Biological Psychiatry to participate, network, learn, and share.

Mary L. Phillips
SOBP President

Scott A. Langenecker
SOBP Program Committee Chair

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Plenary and Symposium Abstracts

Thursday, May 16, 2019

PLENARY
Positive Emotion and Reward: Innovative Tools and Multimodal Methodology

7:45 a.m. - 11:30 a.m.
Chair: Scott Langenecker

1. Dissecting the Neural Circuits for Motivated Behavior

Garret Stuber

University of Washington

In order to survive and effectively navigate an ever-changing and unpredictable environment, organisms must readily adapt their behavior to seek out needed resources, while simultaneously avoiding life-threatening situations. These opposing processes are controlled by neural circuitry that is readily engaged by both environmental and physiological factors to promote behavioral output. The work of my lab studies the precise neural circuits that control both reward and aversive-related behavioral responses. By utilizing optogenetic and other circuit mapping tools, we aim to delineate the precise functional synaptic connections between molecularly distinct neuronal populations that are critical for the generation of these critical behavioral states. A holistic understanding of the interconnected neural circuit elements that mediate diverse motivational behaviors will likely provide important insight into a variety of complex neurological and neuropsychiatric illnesses such as addiction, anxiety, and depression.
Keywords: Reward Learning, Optogenetics, Neurocircuitry

2. Prefrontal Cortex and Striatum Hubs: Integrating Information From Reward, Cognitive, and Motor Control Regions

Suzanne Haber

University of Rochester

The cortico-cortical and cortico-basal ganglia networks are central to incentive-based learning and good decision making. There is growing consensus that obsessive-compulsive disorder, major depressive disorder, and addiction are manifestations of dysfunction of these networks. Behavioral responses to environmental cues depend not only on the ability to evaluate different aspects of reward, but also the ability to inhibit inappropriate choices. Integrating reward information with that involved in cognition and motor control is thus essential for developing motivational control and appropriately adaptive behaviors. Human imaging studies have characterized large scale distributed networks and the location of 'hubs'. Hubs are regions that have an unusually high connectivity to other brain areas and are central for integrating and distributing information across multiple regions. Characterizing hub locations that integrate information across reward and cognitive processes is the first step for probing these circuits in psychiatric disorders. This talk will combine the precision of anatomy in nonhuman primates (NHPs) with high resolution imaging in both NHPs and humans to localize and characterize key hub locations within the cortex and striatum. Using this cross-species, cross-modal approach, NHP anatomic tracing experiments, high resolution NHP diffusion MRI, and diffusion and functional MRI in humans, we identified hubs in the rostral anterior cingulate cortex and rostral striatum that receive a convergence of inputs from areas involved in reward processing (ventromedial prefrontal cortex, orbitofrontal cortex), cognitive processing (rostral cingulate cortex, dorso- and ventrolateral prefrontal cortex), and motor control areas (preSMA and premotor). These uniquely positioned hubs are likely to be important integrative stations, central for the development of adaptive behaviors and good decision-making.
Keywords: Decision-Making, Cognitive Control, Reward Processing, Striatum, Prefrontal Cortex

3. The Genomic Architecture of Individual Differences in Stress Susceptibility

Michael Meaney

McGill University

Stress is a well-established 'trigger' for multiple forms of chronic illness including mental disorders. Despite the compelling epidemiological evidence, most individuals exposed to chronic, severe stress during development or adulthood are largely unaffected with respect to serious health outcomes. These findings reflect the remarkable individual variation in susceptibility to stress. In the studies reported here we attempted to integrate this knowledge into an analysis of the genetic architecture of stress susceptibility in humans. We used a publicly-available, genome-wide association study of addictions that included measures of environmental adversities known to increase the risk for psychopathology. We identified individual single-nucleotide polymorphisms (SNPs) that distinguished adversity-exposed individuals with (susceptible) or without (resilient) substance abuse in a training data set. The resulting SNPs were to develop a genomic profile score for stress susceptibility (GPSsus) that was subsequently validated in a test dataset. The resulting GPSsus also predicted adversity-related mental disorders in multiple independent samples of individuals exposed to early life adversity. The GPSsus genes are highly enriched for SNP's associated with levels of DNA methylation, suggesting epigenetic mediation.

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Animal models identify transcriptional pathways and neural circuits associated with individual differences in susceptibility to adversity. We used one such model, chronic social defeat, and found a highly significant overlap between the genes that comprised our GPSsus and differentially expressed genes using RNAseq from the ventral hippocampus in resilient vs susceptible mice. Informatic analyses of both human and rodent data sets implicate both estrogen- and glucocorticoid-signalling pathways. Direct manipulation of ESR1 expression resulted in significant alterations in stress susceptibility in the murine chronic social defeat model. In sum, our findings reveal a distinct genetic architecture that underlies individual differences in susceptibility to adversity in humans. Functional genomic analysis implies a role for brain region-specific, steroid-sensitive transcriptional signalling in defining individual differences in susceptibility to stress.

Keywords: Stress, Differential Susceptibility, Functional Genomics, Translational Neuroscience, Epigenetics

4. Emotion-Related Impulsivity: Outcomes and Putative Mechanisms

Sheri Johnson

University of California Berkeley

Emotion-related impulsivity, or the tendency to become impulsive in response to positive and negative emotion states, is conceptually and empirically distinct from other forms of impulsivity. A large body of work now indicates that emotion-related impulsivity is more robustly related to psychopathology than other forms of impulsivity are. Cross-sectional and longitudinal work indicates this form of impulsivity is related to internalizing, externalizing, and psychotic disorders. Early findings indicate that emotion-related impulsivity is tied to neurocognitive deficits in response inhibition, particularly during states of high arousal. Implications for treatment development will be discussed.

Keywords: Impulsivity, Emotion, Response Inhibition, Psychopathology, Mood Disorders

SYMPOSIUM
Neuroimaging Markers of Risk, Resilience, and Clinical Outcome in Youth With and At-Risk for Bipolar Disorder

12:30 p.m. - 2:30 p.m.
Chair: Manpreet Singh

5. Emotion Network Predictors of Clinical Outcome in Youth at High Risk for Bipolar Disorder

Manpreet Singh[1], Akua Nimarko[2], Sara Momi Leslie[3], and Adina Fischer[1]

[1]Stanford University School of Medicine, [2]Stanford University, [3]UC Santa Barbara

Background: Youth at familial risk for bipolar disorder (BD) have aberrant emotion-relevant networks. However, function of these networks leading to resilience versus the emergence of BD and other mood disorders in these high-risk youth is poorly understood.

Methods: We examined fMRI data at rest and during implicit emotion processing in healthy offspring of parents with BD (BD-risk, n=31) and compared them to healthy MDD offspring (MDD-risk, n=44) and healthy controls (HCLs, n=28). Then, baseline neural activation and connectivity in response to happy and fearful faces were compared among 24 HCLs, 23 high-risk who developed psychopathology (CVT), and 27 high-risk who did not develop psychopathology (RES) at follow-up.

Results: During Rest: Limbic network connectivity was strongest in BD-risk; MDD-risk had greater salience and default mode network connectivity; HCLs showed strongest executive control network connectivity (ps$<$0.05).

During Implicit Emotion: With happy faces, MDD-risk and HCL youth had higher activation in bilateral putamen and hippocampi compared to BD-risk group whereas BD-risk youth had lower activation in the right inferior parietal lobe (IPL) and left medial prefrontal cortex compared to HCLs ($Z>2.3$ FDR-corrected $p<.05$). With fearful faces, BD-risk group had lower right IPL activation ($Z>2.3$, FDR-corrected $p<.05$).

Clinical Outcome: In RES youth, stronger IPL-left precuneus connectivity correlated with positive change in prosocial behaviors ($r(15)=.771$, $p=.001$). Improved global functioning was inversely associated with increased left caudate-left middle temporal gyrus connectivity ($r(20)=-.509$, $p=.016$).

Conclusions: Intrinsic limbic hyperconnectivity may be specific to BD-risk. IPL, caudate, and precuneus activation and connectivity during emotion processing may represent a resilience marker from symptom development.

Supported By: NIMH K23MH085919; Stanford Child Heath Research Institute

Keywords: Bipolar Disorder, At-Risk Youth, Functional Neuroimaging, Emotional Facial Processing, Intrinsic Connectivity Networks

6. Multimodal Neuroimaging and Neurocognitive Investigation of Bipolar Youth and Youth at Risk for Bipolar Disorder

Jair Soares[1]

[1]McGovern Medical School

Background: We have investigated fronto-limbic brain mechanisms in youth with bipolar disorder (BD), as well as the at-risk children of a BD parent.

Methods: A total of 145 subjects (66 males, 79 females) were studied in our most recent cohort, including 47 BD youth, 39 BD offspring and 59 healthy controls.

We investigated fronto-limbic brain (FLB) abnormalities with multimodal imaging (MRI, MRS, DTI, fMRI), alongside with neurocognitive testing. All participants performed the Affective Go/No-Go (AGN) and Rapid Visual Processing (RVP) tasks of the CANTAB.

Results: The available findings indicate FLB abnormalities in BD youth, and to a lesser extent, in the unaffected BD

offspring. FLB abnormalities seem to start early in illness course and may be proxy markers of vulnerability for BD. Youth with BD had pronounced FLB abnormalities (corrected $p<0.05$), including changes in brain connectivity (corrected $p<0.05$). Relative to HC, youth with BD responded faster to correct trials and committed an elevated number of commission errors across all affective conditions of the AGN task ($p<0.05$). Affected BD offspring performed the AGN task as accurately as HC but their response times to affective stimuli were shorter($p<0.05$).

Conclusions: FLB abnormalities are present in BD youth, as well as the high-risk BD offspring. Children with BD displayed inefficient processing of emotional information.

The possibility that these findings may constitute viable biomarkers of vulnerability for BD and inform future diagnosis and intervention trials may bring opportunities for early intervention and significantly transform the course of this illness with much improved outcomes.

Supported By: NIH grants MH68766, MH 085667, the John S. Dunn Foundation, and the Pat Rutherford Chair in Psychiatry (UT Health).

Keywords: Bipolar Disorder, Bipolar Offspring, Youth, Pediatric Bipolar Disorder, Multimodal Neuroimaging

7. Neural Predictors of a Mood Episode in Youth With a Familial Risk for Bipolar Disorder

Melissa DelBello[1], Wenjing Zhang[2], Su Lui[2], Max Tallman[3], Caleb Adler[3], Rodrigo Patino[3], and Stephen Strakowski[4]

[1]University of Cincinnati, [2]West China Hospital, Sichuan University, [3]University of Cincinnati College of Medicine, [4]Dell Medical School University of Texas Austin

Background: Recent findings suggest that youth with bipolar disorder exhibit structural and functional alteration in prefrontal brain regions. We investigated whether these abnormalities are present prior to illness onset in order to identify biomarkers that may serve as predictors of illness.

Methods: 120 youth with a bipolar parent were evaluated over time for the development of a mood episode. All participants underwent a proton magnetic resonance spectroscopy scan. Over the course of follow-up, 19 participants developing a mood episode (major depressive or manic episode). Nineteen age- and sex-matched youth who did not develop a mood episode during follow-up were used as a comparison group. LC modeling and supervised machine learning were used to evaluate which baseline metabolite levels in three regions of interest (ROIs): anterior cingulate gyrus (ACG) and left and right ventral lateral prefrontal cortices (VLPFC), contributed to differentiating at-risk youth who did vs. did not develop a mood episode.

Results: Among the three ROIs, baseline left VLPFC metabolites had the greatest contribution to the correct classification of developing a mood episode. The combination of choline (Cho), creatinine (Cr), and myo-inositol (mI) in left VLPFC achieved the highest sensitivity (84%, specificity=0.74, $p=0.001$), while the combination Cr and mI achieved the highest specificity (79% and sensitivity=0.79, $p=0.001$).

Conclusions: Our findings suggest that left VLPFC neurometabolites associated with membrane and energy metabolism predict the development of a mood episode in youth with a familial risk for bipolar disorder. Future studies examining left VLPFC neurochemicals as predictors of a mood episode are needed.

Supported By: NIMH

Keywords: Bipolar Disorder, MR Spectroscopy, Predictors

8. Neural Markers of Treatment Response of First-Episode Mania in Adolescents

Stephen Strakowski[1], David Fleck[2], Jeffrey Welge[2], Caleb Adler[2], and Melissa DelBello[2]

[1]Dell Medical School University of Texas Austin, [2]University of Cincinnati

Background: Bipolar I disorder is defined by the occurrence of mania, typically starts in adolescence and then progresses into a recurrent lifelong condition. If the early disease course progression could be prevented, long-term outcomes might improve. Identifying neural markers of treatment response at illness onset might guide treatment and clarify the evolving neurobiology of this condition.

Methods: From a previously published dataset, we completed a new analysis of a subset of 31 adolescents (ages 12-18 years) with bipolar I disorder at their first manic episode. Subjects were pseudorandomized to either lithium or quetiapine treatment for eight weeks. Subjects received fMRI scans at baseline, 1- and 8-weeks. Patients who achieved remission at week 8 (total YMRS<10; N=20) were compared to those who did not (N=11). We also studied 12 healthy subjects. Ventral prefrontal network Regions of Interest were reduced using factor analysis to 4 factors: prefrontal cortex, amygdala, subcortical, and anterior cingulate.

Results: Significant time-by- group effects were observed ($p<.05$ in all cases) for amygdala, prefrontal and subcortical factors. At baseline, patient subgroups exhibited greater activation than healthy subjects in these same factors ($p<.004$ to .06) but did not differ from each other. By week 8, these differences diminished, although different patterns of response were observed between the patient subgroups.

Conclusions: Integrating neuroimaging and treatment trials early in the course of bipolar I disorder may both clarify the underlying neurobiology of illness progression while identifying possible treatment response markers. Doing so may lead to strategies to prevent illness progression of bipolar disorder.

Supported By: NIMH CIDAR award P50 MH077138

Keywords: Bipolar Disorder-I, Brain Imaging, fMRI, Prediction of Treatment Outcome, Lithium, Quetiapine

SYMPOSIUM
Altered Task-Related Changes in Glutamate and its Association With Disrupted Excitatory and Inhibitory (E/I) Synaptic Drive in Psychiatric Disorders: Evidence From ^{1}H Functional MRS

12:30 p.m. - 2:30 p.m.
Chair: John Krystal
Co-Chair: Jeffrey Stanley

9. Excitatory and Inhibitory Synaptic Transmission and Cortical Circuits Function

Arianna Maffei[1]

[1]Stony Brook University

Background: The balance between excitatory and inhibitory synaptic transmission shapes cortical circuit excitability and neuronal responses to incoming stimuli. While transient alterations of this balance may occur during learning or during experience-dependent reorganization of neural circuits, long lasting disruption of the balance between excitation and inhibition, especially during postnatal development, may render networks unstable possibly leading to disease states.
Methods: Here we use patch clamp recordings in acute slices of rodent sensory cortex to determine how excitatory and inhibitory synaptic transmission are co-regulated during postnatal development. Sensory manipulations are used to assess the role of sensory experience on the establishment and modulation of the E/I balance.
Results: We show that both excitatory and inhibitory synaptic transmission undergo a tightly regulated process of postnatal maturation, although the time course for the maturation of inhibition is delayed compared to excitation. Brief manipulations of sensory drive (3 days) delay the maturation of both excitatory and inhibitory circuits without shifting the E/I balance. However, sensory manipulations with longer duration (7 days) showed a larger effect on inhibition and led to a shift in the E/I balance toward excitation.
Conclusions: Our results demonstrate that postnatal maturation and sensory experience contribute to shaping circuit excitability via coordinated regulation of excitatory and inhibitory synaptic transmission. These results highlight the importance of the mechanisms involved in coordinating the maturation of synaptic transmission and suggest that such co-regulatory pathway are candidate mechanisms for future studies regarding neurodevelopmental disorders.
Supported By: Whitehall Foundation, Swiss National Science Foundation, NIH R01- DC015234, NIH R01-DC013770
Keywords: Glutamatergic Neurons, GABAergic Interneurons, Cortical Excitability, Synaptic Plasticity

10. Acute Stress Suppresses Prefrontal Cortex Excitability and Potentiates Nicotine-Seeking Among Cigarette Smokers: Evidence of a Neurobiological Mechanism

Eric Woodcock[1], Mark Greenwald[2], Dalal Khatib[2], Vaibhav Diwadkar[2], and Jeffrey Stanley[2]

[1]Yale University School of Medicine, [2]Wayne State University School of Medicine

Background: Relapse rates among cigarette smokers remain unacceptably high. Patients often cite 'stress' as a precipitating factor. Indeed, experimental stress reliably potentiates drug-seeking in rodents: yet, neurobiological mechanisms remain poorly understood. Herein, we examined dorsolateral prefrontal cortex (dlPFC) excitability as a mechanism through which acute stress may potentiate nicotine-seeking.
Methods: Non-treatment-seeking cigarette smokers were screened for contraindications. Using a double-blind, randomized crossover design, participants (N=21) completed two oral-dosing sessions: yohimbine 54mg + hydrocortisone 10mg ('acute stress') and lactose ('placebo'). dlPFC excitability was measured via glutamate modulation using functional proton magnetic resonance spectroscopy (1H fMRS) during working memory performance (letter 2-back). Nicotine-seeking was measured using an 11-trial progressive ratio choice task: cigarette puff vs. money. Subjective and physiological effects were measured throughout.
Results: Relative to placebo, acute stress increased heart rate, blood pressure, and saliva cortisol levels (ps$<$.05); indicative of a physiological stress response. Relative to placebo, acute stress impaired dlPFC function (2-back response accuracy; p=.03), suppressed dlPFC excitability (glutamate modulation; p=.025), and increased nicotine-seeking/self-administration (p=.04), controlling for nicotine-dependence level. Finally, greater stress-potentiated nicotine-seeking behavior was correlated with more stress-suppressed dlPFC excitability (p=.036). Acute stress did not alter self-reported craving, withdrawal, or affect; nor were any subjective measures correlated with nicotine-seeking (ps$>$.10).
Conclusions: Our results suggest acute stress may potentiate nicotine-seeking/self-administration via suppressed dlPFC excitability. Suppressed dlPFC excitability/function may dis-inhibit nicotine-seeking via impaired 'top-down' executive control. Future research is needed to evaluate 'anti-stress' medications. Finally, this study highlights a novel experimental approach with widespread applicability for investigating acute stress effects among psychiatric disorders.
Supported By: F31 DA040369 (EAW); New Investigator Grant (Wayne State University; EAW); R01 DA015462 (MKG); Joe Young Sr./Helene Lycaki funds (State of Michigan); and Detroit Wayne Mental Health Authority (MKG)
Keywords: Stress, Nicotine Dependence, Glutamate, Dorsolateral Prefrontal Cortex, Executive Function

11. Detecting Age-Related Changes in Brain Chemistry Using Magnetic Resonance Spectroscopy

Craig Stark[1]

[1]University of California, Irvine

Background: Understanding neurocognitive aging will help us better characterize pathological and non-pathological changes in the brain throughout the lifespan and identify preclinical markers for cognitive decline. Human studies have often relied on the indirect and relative measures provided by BOLD fMRI,

but using magnetic resonance imaging spectroscopy (MRS), we can measure the metabolic signatures for excitatory and inhibitory activity (e.g. GABA, glutamate, choline, etc.), which provides a more direct mechanism for hippocampal dysfunction related to aging and dementia.
Methods: In a sample of 20 young and 21 older adults, we collected 3 separate MRS scans from the hippocampus (left and right) and the left prefrontal cortex. Participants also completed the Rey Auditory Verbal Learning Test (RAVLT) outside of the scanner.
Results: We found a positive relationship between hippocampal Glx (a composite score including glutamate and glutamine) and delayed word recall performance (left hippocampus: $r = 0.65$, $p < 0.01$; right hippocampus: $r = 0.42$, $p = 0.07$) (Nikolova et al., 2017). In contrast, we found no relationship Glx in the PFC with memory performance in the older adults and no relationship with any of the three regions and performance in young adults.
Conclusions: These data support the hypothesis that alterations in glutamate levels may influence age-related memory declines and set the stage for investigations of dementia-related dysfunction in the hippocampus. Alterations in concentrations of glutamate, have been reported in numerous neurological disorders, including Alzheimer's disease, making it an important target for investigations of age and dementia-related changes in the hippocampus.
Supported By: NIA R21 AG053040, NIH R21 AG054092
Keywords: Aging, MRS Imaging, Glutamate, GABA, MCI

12. ^{1}H fMRS Provides Direct Evidence for the Impaired Modulation of Hippocampal Glutamate During Memory Consolidation in Schizophrenia

Jeffrey Stanley[1], Patricia Thomas[1], Dalal Khatib[1], Asadur Chowdury[1], Usha Rajan[1], Luay Haddad[1], Alireza Amirsadri[1], and Vaibhav Diwadkar[1]

[1]Wayne State University School of Medicine

Background: Glutamate-related dysfunctional neuroplasticity is proposed as a critical mechanism mediating learning and memory deficits in schizophrenia (SZ), though direct neurochemical evidence has been lacking. Here we provide the first ever application of in vivo ^{1}H fMRS (to access functional neurochemistry) to demonstrate dysfunctional modulation of hippocampal glutamate in SZ patients during memory consolidation.
Methods: ^{1}H fMRS data from the right hippocampus (27s temporal resolution) was acquired on 18 SZ and 18 healthy (HC) adults matched for age and sex using an established memory consolidation task (Stanley et al., 2017). Glutamate modulation during task conditions (memory encoding, memory retrieval) was quantitated relative to a task-active, non-memory baseline (visual checkerboard). Rates of memory consolidation were modeled using the Gompertz function.
Results: Repeated measures confirmed significant increases in glutamate modulation during Encoding (HC: $p=0.0001$; SZ: $p<=0.0034$) and Retrieval (HC: $p=0.0009$; SZ: $p=0.035$). Notably, the degree of glutamate modulation during Encoding was significantly lower in SZ compared to HC ($p=0.039$). Behavioral analyses confirmed task-engagement in both groups, but SZ demonstrated poorer rates of memory consolidation (modeled using Gompertz functions; $p=0.0042$).
Conclusions: Evidence for dysfunctional neurochemistry in SZ was achieved without the confounding effects of hemodynamics (that limit fMRI inference) and provide relatively direct evidence for alterations in the functional role of glutamate in SZ. ^{1}H fMRS is emerging as a significant tool in unveiling brain function, and our data suggest its clinical relevance in revealing important aspects regarding the pathophysiology of SZ.
Supported By: NIMH R01 MH111177 (JAS and VAD); Lycaki-Young Funds from the State of Michigan
Keywords: Glutamate, Schizophrenia, Functional MRS, Learning and Memory, Hippocampus

SYMPOSIUM
Biological Mechanisms Underlying ADHD Comorbidities
12:30 p.m. - 2:30 p.m.
Chair: Andreas Reif

13. The Role of Common and Rare Variants in ADHD Risk and Genetic Overlap With Other Phenotypes

Ditte Demontis[1], Kyle F. Satterstrom[2], Jinjie Duan[1], Francesco Lescai[1], Søren Dinesen Østergaard[3], Klaus-Peter Lesch[4], Thomas Werge[5], Preben Mortensen[1], Simon Glerup[1], Barbara Franke[6], David M. Hougaard[7], Andreas Reif[8], Mark Daly[2], Benjamin Neale[9], and Anders Børglum[10], The iPSYCH-Broad ADHD Workgroup and the ADHD working group of the Psychiatric Genomics Consortium[1]

[1]Aarhus University, [2]Broad Institute, [3]Aarhus University Hospital, [4]University of Würzburg, [5]Mental Health Centre, Capital Region, [6]Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, [7]Statens Serum Institute, [8]University Hospital of Frankfurt, [9]Massachusetts General Hospital, [10]Aarhus University, Centre for Integrative Sequencing (iSEQ)

Background: Attention-deficit hyperactivity disorder (ADHD) is a highly heritable childhood behavioural disorder affecting 3-6% of children and 4% of adults. Here we will present results from our latest research elucidating the role of common and rare variants in ADHD.
Methods: We performed a GWAS meta-analysis including samples from the Danish iPSYCH initiative and 11 samples from the Psychiatric Genomics Consortium, in total 20,200 ADHD cases and 35,200 controls. Genetic correlations of ADHD with other phenotypes were evaluated using LDhub. Rare risk variants were identified based on exome-sequencing of a German/Dutch ADHD cohort (1,100 cases; 1,700 controls) and the Danish iPSYCH cohort (4,400 cases; 4,700 controls).
Results: The GWAS meta-analysis identified 12 genome-wide significant loci ($P < 5x10-8$), revealing important information on the underlying biology of ADHD. The genetic correlation (rg)

analyses revealed a strong negative genetic overlap with measures of cognition (e.g. years of schooling, rg= -0.54, P=1.44x10-80) and a strong positive genetic correlation with obesity related phenotypes (e.g. BMI rg=0.26, 1.68x10-15).

Analyses of the rare variants identified a significant increased burden in ADHD cases of ultra-rare deleterious variants in constrained genes highly expressed in the brain (P=5,67x10-7). Additionally, the distribution of genes hit by these variants were not distinguishable from what is found in autism spectrum disorder.

Conclusions: We have for the first time identified genome-wide significant risk loci for ADHD and have extensively characterized the polygenic architecture revealing important overlap with comorbid phenotypes. Additionally, our results demonstrate that ultra-rare deleterious risk variants play a role in ADHD risk.

Supported By: Lundbeck Foundation

Keywords: ADHD, Exome Sequencing, Genome-Wide Association Data, Genetic Correlation, Rare Variants

14. Conditional Knockout of Rbfox1, a Cross-Disorder Psychiatric Risk Gene, Causes an Autism-Like Phenotype in Mice

Andreas Reif[1], Florian Freudenberg[1], Esin Candemir[1], Noèlia Fernàndez-Castillo[2], Bru Cormand[2], Andreas Chiocchetti[3], David A. Slattery[1], and Aet O'Leary[1]

[1]University Hospital Frankfurt, [2]Universitat de Barcelona, [3]University of Frankfurt

Background: The splicing regulator Rbfox1 has been identified as a candidate for aggressive behaviors (Fernandez-Castillo, 2018). In parallel, it emerged as one of the most significant candidate gene in the latest mood spectrum and cross-disorder GWAS making it a candidate gene to be prioritized for functional studies.

Methods: We have generated neuron-specific Rbfox1 knockout mice. These were subjected to a battery of behavioral tests (Open Field, Social Interaction, Resident-Intruder, Light-Dark-Box, Marble Burying, PPI, Y-Maze, Fear Conditioning, etc. n>10 for each test). Gene expression was measured following acute and escalated aggression.

Results: Knockout mice showed a robust behavioral phenotype. They displayed by thigmotaxis in the Open Field with reduced center time and increased total distance traveled ($p<0.01$). Increased compulsivity was present in the Marble Burying test ($p<0.05$), and they spent more time in the dark zone of the LDB ($p<0.05$). Furthermore, knockouts were unable to acquire fear conditioning ($p<0.01$) and showed cognitive inflexibility in a reversal learning task. While aggression was absent, social interaction was greatly diminished ($p<0.01$ for head sniffs, anogenital sniffs, following, grooming). After acute and escalated aggression, Rbfox1 expression was significantly increased in the N. Accumbens and ACC of wildtypes.

Conclusions: The behavioral phenotype of neuron-specific Rbfox1 knockout mice is characterized by deficits in fear conditioning and social interaction, as well as thigmotaxis and behavioral rigidity. This can be conceptualized as an autism-related trait, which relevant as Rbfox1 regulates autism genes (Lee, 2016). Furthermore, Rbfox1 is upregulated in the reward circuitry after aggressive encounters, suggesting that its increase predisposes towards aggressive behavior.

Supported By: EU FP7 "Aggressotype" (grant no. 602805)

Keywords: Aggression, Autism, Animal Model

15. Predicting Comorbid Disorders in ADHD Using Machine Learning

Stephen Faraone[1], Yanli Zhang James[1], Qi Chen[2], and Henrik Larsson[2]

[1]SUNY Upstate Medical University, [2]Orebro University

Background: Substantial research shows that ADHD is frequently comorbid with other psychiatric disorders and with some medical outcomes such as obesity and asthma. We also know from genome-wide association studies that common genetic variants account for some of this comorbidity. Because ADHD is typically an early-onset disorder, ADHD youth are an ideal group for applying prediction models to predict comorbidity from clinical and biological data.

Methods: We will apply machine learning models to the prediction of comorbid disorders (substance abuse, depression, anxiety & obesity) in a sample of 34,009 ADHD patients from the Swedish medical registries. Predictors are social and environmental exposures (e.g., SES, pregnancy and delivery complications), the presence of other diagnoses and family history of diagnoses known to be comorbid with ADHD.

Results: Applying a random forests machine learning model to the Swedish data achieved an area under the curve (AUC) statistic of 0.74 (95%CI 0.72-0.76) for the prediction of SUD in an independent validation sample. The strongest predictors of SUD in the random forests model were education scores achieved by the child, social class of the parents, crimes committed by the parents, severity of ADHD and maternal pregnancy complications. We are currently in the process of analyzing the other comorbid disorders in Sweden.

Conclusions: Our results indicate that by combining clinical features, environmental exposures and family history variables, we are able to achieve a level of predictive accuracy that could be useful to identify a subset of patients for clinical monitoring or enrollment in high-risk research studies.

Supported By: This project has received funding from the European Union's Horizon 2020 research and innovation programme grant agreement No 667302

Keywords: ADHD, Machine Learning, Substance Use Disorders, Psychiatric Comorbidities, Prospective Prediction

16. Brain Imaging of ADHD Across the Lifespan – Results of the Largest Study Worldwide From the Enigma ADHD Working Group

Martine Hoogman[1], Ryan Muetzel[2], ENIGMA-ADHD collaboration[3], Generation R[2], Jan Buitelaar[1], Paul M. Thompson[4], Steven Faraone[5], Philip Shaw[6], Henning Tiemeier[7], Janita Bralten[1], and Barbara Franke[1]

[1]Radboud University Medical Center, Donders Institute, [2]Erasmus University Medical Center, [3]Radboud University Medical Center, [4]School of Medicine, University of Southern California, [5]SUNY Upstate Medical University, [6]National Institute of Mental Health, [7]Erasmus University Medical Center-Sophia Children's Hospital

Background: Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD. However, these studies are often underpowered and heterogeneous in their methods. Our aim is to map the characteristics of the brains of people with ADHD across the life span.
Methods: The ENIGMA-ADHD collaboration is the largest collaboration of neural substrates of ADHD, and consist of 37 cohorts, with more than 4000 subjects of all ages. Both cortical and subcortical brain measures are studied for children, adolescents and adults separately. Knowing that ADHD is the extreme of a continuum, the association between cortical measures and ADHD symptom scores of the CBCL in the general population of children aged 9 and 10 years old (Generation R study, n=2900), are also studied. Finally, also a family-based design is used to unravel more characteristics of the ADHD brain.
Results: Differences between cases and controls were only found in the group of children both for subcortical as well as cortical brain measures. Surprisingly, there was an overlap between the affected cortical measures in the case/control study, the results of the population-based study and those of the family-based study.
Conclusions: Subtle differences in the subcortex and cortex were found between children with ADHD and healthy controls, not in the other age groups. The overlap between the affected brain regions in the clinical, population and family-based studies, shows that, besides from a genetic and behavioral perspective, now also from a neuroimaging perspective there is evidence for the ADHD continuum.
Supported By: National Institutes of Health (NIH) Consortium grant U54 EB020403
Keywords: ADHD, Neuroimaging, Cortex, Mega Analysis

SYMPOSIUM
The Distributed Cortical Working Memory Network: Alterations in Schizophrenia and Their Neural Substrate

12:30 p.m. - 2:30 p.m.
Chair: David Lewis

17. Blunted Tuning of Posterior Parietal Cortex Activity is Central to Working Memory Storage Deficits in Schizophrenia

Britta Hahn[1], Molly Erickson[2], Benjamin Robinson[1], Carly Leonard[3], Steven Luck[4], and James Gold[1]

[1]University of Maryland School of Medicine, Maryland Psychiatric Research Center, [2]Rutgers University, [3]University of Denver, [4]University of California Davis

Background: Prefrontal cortex (PFC) dysfunction is believed to underlie working memory (WM) deficits in people with schizophrenia (PSZ), but few studies have focused on WM storage devoid of manipulation.
Methods: Thirty-seven PSZ and 37 healthy control subjects (HCS) completed a visual change detection task with varying set sizes (SSs), emphasizing WM storage with minimal top-down control, during fMRI. Whole-brain analysis (voxel-wise $P<0.001$ with cluster size thresholding, overall $P<0.05$) identified areas in which BOLD activity covaried with the number of items currently maintained (K), derived from task performance. An EEG-derived auditory entrainment index reflecting cortical glutamate-GABA balance was obtained on a separate day.
Results: K values predicted activity in posterior parietal cortex (PPC) and middle occipital gyrus. Whole-brain interaction analysis found significantly less K-dependent signal modulation in PSZ than HCS in left PPC, not explained by narrower K-value ranges. Reduced activity modulation with current storage (a) statistically accounted for 43.4% of between-group differences in broad cognitive function, and (b) partly reflected hyperactivation of PSZ with fewer items maintained, a phenomenon which persisted in subgroups matched for WM capacity. PPC BOLD activation was correlated with 40-Hz auditory entrainment in PSZ but not HCS.
Conclusions: In conclusion, less flexible PPC modulation is central to schizophrenia-related WM storage deficits and may represent the substrate of a core cognitive deficit. No effects emerged in PFC. Blunted PPC activity tuning appears to be a primary deficit, not secondary to WM capacity reduction; it is seen when comparing groups based on items actually maintained, and when groups are matched on WM capacity.
Supported By: R01 MH065034
Keywords: Schizophrenia, Working Memory, fMRI, Posterior Parietal Cortex

18. Molecular Substrate of Impaired Working Memory in Schizophrenia: Differential Contributions of Cortical Regions and Cell Types

David Lewis[1], Gil Hoftman[2], Samuel Dienel[2], Makoto Tsubomoto[3], and Takanori Hashimoto[4]

[1]University of Pittsburgh School of Medicine, [2]University of Pittsburgh, [3]Kanazawa University and University of Pittsburgh, [4]Kanazawa University Graduate School of Medical Sciences

Background: Visuospatial working memory (WM), which is impaired in schizophrenia, depends on a distributed network including primary visual (V1), association visual (V2), posterior parietal (PPC), and dorsolateral prefrontal (DLPFC) cortices. Information is conveyed across these regions via the excitatory projections of glutamatergic pyramidal neurons located in layer 3, whose activity is regulated by subsets of GABAergic neurons that express parvalbumin (PV), somatostatin (SST) or vasoactive intestinal polypeptide (VIP). Here, we sought to determine the potential contributions of alterations in specific cell types and cortical regions to WM impairments in schizophrenia.
Methods: We quantified the expression of markers of GABA neuron subtypes and of glutamate and GABA neurotransmission in total gray matter and layer 3, respectively, in four

cortical regions of the WM network from 20 matched pairs of schizophrenia and unaffected comparison subjects.
Results: In comparison subjects, mRNA levels of PV declined ($p<.001$) and SST levels increased ($p<.001$) from posterior-to-anterior regions, whereas VIP levels did not differ across regions. In schizophrenia subjects, each transcript in PV and SST neurons exhibited similar alterations across all regions (all $p<.02$), whereas VIP neuron transcripts were generally unaltered. Within layer 3 of comparison subjects, markers of glutamate neurotransmission were lowest in V1 and highest in DLPFC ($p<.0001$), whereas GABA neurotransmission markers showed the opposite pattern ($p<.0002$). In schizophrenia subjects, the posterior-to-anterior increase in glutamate markers was blunted and the posterior-to-anterior decline in GABA markers was enhanced.
Conclusions: Differential alterations across cortical regions and cell types may contribute to WM deficits in schizophrenia.
Supported By: NIMH P50 MH103204
Keywords: GABA, Glutamate, Schizophrenia, Working Memory

19. Dorsolateral Prefrontal and Posterior Parietal Networks Supporting Working Memory in a Non-Human Primate Model

Christos Constantinidis[1]

[1]Wake Forest University, School of Medicine

Background: Neurons in both the dorsolateral prefrontal and posterior parietal cortex are active during working memory tasks. The functional specialization of the two areas and the underlying circuit properties responsible for such a specialization are unknown.
Methods: In order to address this question, we trained monkeys to perform tasks requiring memory of stimuli in the presence of distraction and remembering either the initial or final of two stimuli presented in sequence. We then performed neurophysiological recordings with arrays of electrodes in each area.
Results: Subtle but consistent differences were present in the activity between areas. Prefrontal neurons were better able to represent the actively remembered stimulus, whereas the posterior parietal cortex was more driven by distractors. Additionally, task variables were represented more robustly in the activity of prefrontal neurons. In an attempt to understand the functional differences in responses between areas we analyzed the strength and dynamics of effective connectivity in the two areas, examining neurons recorded simultaneously at distances of 0.2 − 1.5 mm apart from each other. The strength of effective connectivity was more localized over short distances in the posterior parietal than the prefrontal cortex, suggesting stronger influences of local inputs.
Conclusions: Our results reveal that systematic circuit differences account for specialization of parietal and prefrontal cortex during working memory and point to the functional consequences of circuit interruptions in mental illnesses.
Supported By: NIH R01EY016773
Keywords: Prefrontal Cortex, Posterior Parietal Cortex, Monkey, Working Memory, Neurophysiology

20. Intrinsic Properties of Layer 3 Pyramidal Neurons From Monkey Prefrontal and Parietal Cortices

Guillermo Gonzalez-Burgos[1], Takeaki Miyamae[1], Yosef Krimer[1], Dominique Arion[1], John F. Enwright[1], and David Lewis[1]

[1]University of Pittsburgh

Background: In primates, working memory depends on activity in a distributed network of cortical areas, including the posterior parietal (PPC) and dorsolateral prefrontal (DLPFC) cortices, interconnected by projections originated from layer 3 pyramidal neurons (L3PNs). Intrinsic properties of L3PNs differ between primate sensory cortex and DLPFC, but whether L3PN properties differ between association areas such as DLPFC and PPC is less clear.
Methods: We assessed morphology, physiology, and gene expression in L3PNs from macaque monkey DLPFC (area 46) and PPC (areas 7a and IPS) using biocytin cell filling during recordings in acute slices, and L3PN laser microdissection combined with DNA microarray analysis of transcripts.
Results: Morphometric analysis of the dendritic tree of DLPFC ($n=21$) and PPC ($n=18$) L3PNs showed that whereas apical dendrite properties are similar ($p>0.491$), L3PN basal dendrites are significantly larger ($p=0.00065$), more complex ($p=0.00018$), and display higher dendritic spine density ($p=0.00042$) in DLPFC than PPC. Patch clamp analysis revealed two physiological classes of L3PNs (regular firing and burst firing cells, RF and BF respectively) that were present in each cortical area but in significantly different proportions (RF:BF) between PPC (94:6, $n=52$) and DLPFC (50:50, $n=44$, $p=7x10-7$). DNA microarray studies showed ~300 genes differentially expressed (FDR=0.05) between DLPFC and PPC L3PNs, including several transcripts that may contribute to the morphological and physiological differences observed between cortical areas.
Conclusions: L3PNs from DLPFC and PPC display different morphological, physiological and transcriptome properties that may contribute to area-specific information processing and to area-specific alterations of L3PNs in schizophrenia.
Supported By: P50 MH103204
Keywords: Pyramidal Neuron, Working Memory, Schizophrenia

SYMPOSIUM
Fine-Scale Mapping of Brain Abnormalities in Psychiatric Disorders: Recent Findings From the Enigma Schizophrenia, Major Depression and Bipolar Working Groups

12:30 p.m. - 2:30 p.m.
Chair: Jessica Turner
Co-Chair: Theo van Erp

21. ENIGMA-Relatives: The Association Between Familial Risk for Schizophrenia or Bipolar Disorder and Brain Abnormalities

Sonja de Zwarte[1], Rachel Brouwer[1], Christopher Ching[2], Ole Andreassen[3], Theo van Erp[4], Jessica Turner[5], Paul Thompson[6], René Kahn[7], and Neeltje van Haren[8], ENIGMA-Relatives Working Group[9]

[1]Brain Center Rudolf Magnus, University Medical Center Utrecht, [2]Keck School of Medicine of USC, University of Southern California; Semel Institute for Neuroscience and Human Behavior, University of California at Los Angeles, [3]NORMENT - KG Jebsen Centre, Institute of Clinical Medicine, University of Oslo, [4]University of California, Irvine, [5]Georgia State University, [6]Keck School of Medicine, University of Southern California, [7]Icahn School of Medicine at Mount Sinai; Brain Center Rudolf Magnus, University Medical Center Utrecht, [8]Erasmus Medical Centre; Brain Center Rudolf Magnus, University Medical Center Utrecht, [9]http://enigma.ini.usc.edu

Background: Schizophrenia and bipolar disorder share genetic liability and some structural brain abnormalities are common to both conditions. Interestingly, imaging studies have indicated that there may be a converse pattern of brain abnormalities in first-degree relatives of schizophrenia patients (FDRs-SZ) and bipolar patients (FDRs-BD), with smaller volumes reported in FDRs-SZ and enlargements in FDRs-BD.
Methods: Here, we meta-analyzed global and subcortical brain measures of 6,008 individuals (1,228 FDRs-SZ, 852 FDRs-BD, 2,246 controls, 1,016 patients with schizophrenia, and 666 patients with bipolar disorder) from 34 schizophrenia and/or bipolar disorder family cohorts, with standardized methods. Analyses were repeated with a correction for intracranial volume (ICV) and for the presence of any psychopathology in the relatives and controls.
Results: FDRs-BD had significantly larger ICV ($d=+0.16$, $q<0.05$ corrected), whereas FDRs-SZ showed smaller thalamic volumes than controls ($d=-0.12$, $q<0.05$ corrected). ICV explained the enlargements of brain measures in FDRs-BD, while in FDRs-SZ, after correction for ICV, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, and thalamus volumes were significantly smaller, the cortex was thinner ($d's<-0.09$, $q<0.05$ corrected), and third ventricle was larger ($d=+0.15$, $q<0.05$ corrected). The findings were not explained by psychopathology in the relatives or controls.
Conclusions: Despite shared genetic liability, FDRs-SZ and FDRs-BD show a differential pattern of structural brain abnormalities, specifically an opposite effect in ICV. This may imply that the neurodevelopmental trajectories leading to brain abnormalities in schizophrenia or bipolar disorder are distinct. As a next step, we are investigating whether IQ/educational attainment might be associated with this divergence.
Keywords: Schizophrenia, Bipolar Disorder, First-Degree Relatives, Structural MRI, Meta-Analysis

22. Meta-Analysis of Hippocampal Subfields: Results From the ENIGMA-MDD Working Group

Philipp Saemann[1], Michael Czisch[1], Neda Jahanshad[2], Christopher D. Whelan[3,4], Laura van Velzen[4], Derrek Hibar[5], Laura Han[6], Ilya M. Veer[7], Henrik Walter[7], Dick Veltman[6], and Lianne Schmaal[8]

[1]Max Planck Institute of Psychiatry, [2]Keck School of Medicine, University of Southern California, [3]University of Southern California, [4]VU University Amsterdam, [5]Janssen Research & Development, [6]VU University Medical Center, [7]Charité – Universitätsmedizin Berlin, [8]Orygen, The National Centre of Excellence in Youth Mental Health

Background: Hippocampal volume reductions in major depressive disorder (MDD) represent a robust finding in retrospective meta-analyses. Subregional specificity of this finding has been suspected from several smaller previous studies. Given the complex role of the hippocampus both for stress response regulation and its vulnerability to chronic disease, we aim at finer mapping of this result using FreeSurfer based, automated subfield segmentation.
Methods: Twenty-three centers with MDD/control samples contributed. Results reported here stem from 2522 patients and 4244 controls. After segmentation and standardized QC, local statistical were run for 25 models in total. Key models were: Cases vs. controls (covarying for age, age squared, sex-by-age, sex-by-age-squared, ICV and scanner/site); recurrent vs. controls, first episode vs. controls, early onset (EO, <22 years) vs. controls, late onset (LO) vs. controls. Eventually, inverse variance-weighted random-effect meta-analysis model in R (metafor package) with FDR correction for 14 phenotypes was performed.
Results: Regional specificity of volume deficits were detected in MDD as a whole (2522 patients, 4244 controls) (CA3>whole>CA1>GC.ML.DG>CA4>molecular layer). No robust effects were found in first episode patients (743 patients, 3812 controls) except for nominal effects. In recurrent MDD, only CA1 effects were robust. EO depression showed unexpectedly strong effects (836 patients, 3472 controls). Similarly, patients with current AD treatment showed strong effects, similarly distributed as in MDD except for CA1. No correlation with depression severity was detected.
Conclusions: Hippocampal structural changes in MDD show subregion specificity. While first episode status seems less critical and first/recurrent episode patients are similar, early onset appears as key predictor of structural abnormalities.
Supported By: None.
Keywords: Depression, Hippocampus, Hippocampal Subfields, Meta-analysis, Morphometry

23. In Vivo Hippocampal Subfield Volumes in Bipolar Disorder – A Multisite ENIGMA Mega-Approach

Tiril P. Gurholt[1], Unn K. Haukvik[1], Stener Nerland[1], Paul M. Thompson[2], Christopher Ching[2], Ole Andreassen[1], Ingrid Agartz[3], and ENIGMA Bipolar Disorder Working Group ENIGMA Consortium[4]

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Background: A previous large-scale ENIGMA study reported hippocampal volume reductions in bipolar disorder (BD). The hippocampus consists of anatomically and functionally distinct

subfields that may be differently involved in the pathophysiology of the disorder. This study aims at mapping hippocampal subfield morphology in BD across subgroups, the relation to clinical characteristics, and effects of medication.
Methods: T1-weighthed MRI scans from 3093 subjects (BD (n=1155, 37.4±11.8 years, 38.4% male), and healthy controls (HC) (n=1938, 33.1±10.5 years, 48.3% male)) from 15 sites were post-processed with the FreeSurfer hippocampal subfield segmentation vs. 6.0. Linear mixed effect models were used to explore diagnostic differences in hippocampal subfield volumes with sex, age, age-squared and intracranial volume as covariates, and scanner and field strength as random variables. Post hoc analyses of differences between BD subgroups and controls (BD1=667/BD2=138) were conducted and a Bonferroni-correction was applied to correct for multiple comparisons.
Results: BD patients had smaller whole hippocampus (Cohen's d=-0.21), CA1 (d=-0.17), CA4 (d=-0.18), dentate gyrus (d=-0.20), molecular layer (d=-0.22), granule cell layer of dentate gyrus (d=-0.2), hippocampal tail (d=-0.14), subiculum (d=-0.16), presubiculum (d=-0.2), and HATA (d=-0.16) volumes, all p-values<0.001, compared to HC. Effect sizes and p-values were significant in both hemispheres, except for the hippocampal tail. Split into subgroups, BD1 but not BD2 patients showed a similar pattern of smaller subfield volume.
Conclusions: BD patients showed lower volumes across the different hippocampal subfields, driven by the BD1 group. Further analyses of associations to psychosis history, and medication use will be presented.
Supported By: The Research Council of Norway (grants number 223273); KG Jebsen Foundation; NIH U54 EB020403
Keywords: Bipolar Disorder, Neuroimaging, Hippocampal Subfields, Mega Analysis, Brain Magnetic Resonance Imaging (MRI)

24. Shape Asymmetry of Deep Brain Structural Structures in 2763 Individuals With Schizophrenia Compared to 3768 Healthy Volunteers in a Prospective Shape Meta-Analysis via the ENIGMA Consortium

Boris Gutman[1] and Lei Wang[2], ENIGMA Schizophrenia Working Group[3]

[1]Armour College of Engineering, Illinois Institute of Technology, [2]Feinberg School of Medicine, Northwestern University, [3]http://enigma.ini.usc.edu/szwg

Background: Shape analysis methods have advanced our understanding of morphometric changes in schizophrenia. However, findings are equivocal, including hemisphere asymmetry. We performed a prospective shape meta-analysis to investigate subcortical shape in 2763 individuals with schizophrenia and 3768 healthy controls, using data from 21 worldwide institutions via the ENIGMA Consortium.
Methods: Harmonized protocols at each individual site included: Parcellation with same-version FreeSurfer for thalamus, caudate, putamen, pallidum, accumbens, hippocampus and amygdala from structural MRI; Surface triangulation and atlas-registration of each structure; Shape computation as vertex-wise radial distance to medial curve and log Jacobian determinant indicating localized tissue change; Effect size, regression parameter, and confidence interval computation. Mass-univariate meta-analysis employed sample weighting as implemented in R. Symmetry index was calculated as absolute value of left-v-right differences.
Results: The hippocampus, amygdala, accumbens, and putamen showed exaggerated leftward asymmetry for schizophrenia compared to controls. The thalamus showed predominantly exaggerated leftward asymmetry for schizophrenia, although small but significant portions of the surface also showed diminished symmetry. The pallidum and caudate showed minimal or no differences in the symmetry indices between groups. Shape asymmetry alterations extended across multiple structures: one pattern encompassed the hippocampus, amygdala, and posterior thalamus, another included the putamen, accumbens and ventral and dorsal thalamus.
Conclusions: We observed patterns of subcortical shape asymmetry alterations previously not detected by volume meta-analysis of overlapping subjects. These patterns were contiguous across multiple, neighboring structures. These results suggest that specific subcortical brain structures may be preferentially affected in schizophrenia but asymmetrically and are potential biomarkers for the disease and its progression.
Supported By: The ENIGMA project is in part supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health (Grant No. U54EB020403). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Keywords: Subcortical Structures, Brain Asymmetry, Structural Neuroimaging

SYMPOSIUM
Epigenome-Wide Association Studies Reveal New Methylation Loci Related to Trauma and Post-Traumatic Stress Disorder

12:30 p.m. - 2:30 p.m.
Chair: Mark Logue

25. Longitudinal Epigenome-Wide Changes From Trauma to PTSD Diagnosis

Shota Nishitani[1], Varun Kilaru[1], Vasiliki Michopoulos[1], Sterling Winters[1], Barbara Rothbaum[1], Kerry Ressler[2], Tanja Jovanovic[3], and Alicia Smith[1]

[1]Emory University School of Medicine, [2]Harvard Medical School and McLean Hospital, [3]Wayne State University

Background: Most individuals who experience a traumatic event exhibit acute, but transient, symptoms over the first week after trauma. However, recovery from trauma occurs much more slowly in those with post-traumatic stress disorder (PTSD). Though advances in epigenetics have identified methylation differences in subjects with PTSD, little is known the longitudinal epigenetic changes after trauma exposure.

Methods: Following the presentation to the emergency department, 26 patients contributed 149 saliva samples longitudinally from the time of the trauma through 3 months and their DNA methylation was assessed (MethylationEPIC). After filtering for variable CpG sites, we compared methylation between those that would and would not develop PTSD at 1 month using the EDGE package, which is optimized for repeated measure microarray data.
Results: After correction for multiple comparisons (FDR<.05), we found 71 CpGs in 56 genes that differ over the first month in a non-linear manner based on whether a subject will develop PTSD (7.5E-6 < p < 3.9E-8). The PTSD-associated CpGs are enriched for binding of multiple transcription factors including hormone-nuclear receptor sites (FDR<.05). Gene Ontology analysis of the nominally-associated CpGs (p<.05) revealed enrichment of 45 biological processes (FDR<.05) including nervous system development (p = 1.0E-4).
Conclusions: In this pilot study, we found significant, non-linear DNA methylation changes that associate with PTSD development following trauma exposure. Our results provide insight into the biological response to trauma and may reveal biomarkers that can be used to delineate those at risk for developing PTSD and those that will be resilient.
Supported By: National Institutes of Health Grants R21MH10692 (A.K.S.).
Keywords: PTSD, DNA Methylation, Genome-Wide Association Data, Saliva, Longitudinal Study

26. Epigenome-Wide Association Study of Posttraumatic Stress Symptoms in 1,135 U.S. Veterans

Janitza Montalvo-Ortiz[1], Joel Gelernter[2], Steven M. Southwick[2], John Krystal[2], and Robert Pietrzak[2]

[1]Yale School of Medicine/VA CT Healthcare Center, [2]Yale School of Medicine/VA CT Healthcare Center/NC-PTSD

Background: Posttraumatic stress disorder (PTSD) is a chronic and often disabling condition that is highly prevalent in military veterans. Epigenetic mechanisms have been implicated in the etiology of PTSD, with DNA methylation being the most studied to identify novel biomarkers associated with this disorder.
Methods: We performed the largest epigenome-wide association study (EWAS) of PTSD to date. Our sample included 1,135 European-Americans (EAs) male U.S. veterans who participated in the National Health and Resilience in Veterans Study (NHRVS). DNA was collected from saliva samples and the Illumina HumanMethylation EPIC BeadChip was used for the methylation analysis. PTSD symptoms were assessed using past-month PTSD Checklist (PCL) scores. EWAS was conducted using linear regression adjusted for age, cell type proportions, first 10 principal components, and smoking status. To adjust for multiple testing, false discovery rate (FDRadj) was set to 0.05.
Results: We identified 27 genome-wide significant (GWS) CpG sites associated with PTSD. These CpG sites map to genes involved in the regulation of NF-kappa-B-activation, a key regulator of inflammation and implicated in synaptic plasticity and memory, G-protein coupled receptor (GPRC) activity, gene regulation, metabolism, estrogen response, and protein binding. Some of these genes have also been previously identified in genome-wide association studies (GWAS) of educational attainment, schizophrenia, and Parkinson's disease.
Conclusions: If replicated, these findings suggest potential epigenetic biomarkers for PTSD that may help inform prevention and treatment strategies of this disorder in veterans and other trauma-affected populations.
Supported By: U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder.; NARSAD
Keywords: Epigenetics, DNA Methylation, PTSD - Posttraumatic Stress Disorder, Veterans, Trauma Exposure

27. Differential Methylation at Glucocorticoid-Relevant Regulatory Regions Associated With PTSD in African Americans

Grace Kim[1], Allison Aiello[2], Karestan Koenen[3], Sandro Galea[4], Derek Wildman[5], and Monica Uddin[5]

[1]University of Illinois at Urbana-Champaign, [2]UNC Chapel Hill, [3]Harvard T.H. Chan School of Public Health, [4]Boston University, [5]University of South Florida

Background: Recent genome-scale work has identified African-ancestry specific genetic contributions to post-traumatic stress disorder (PTSD) risk but integrated analyses of other epigenomic data in individuals of predominantly African ancestry are currently lacking. We sought to identify functionally relevant, differentially methylated (DM) genomic sites that associate with PTSD in African-Americans (AA), focusing specifically on genes in the glucocorticoid receptor regulatory network (GRRN) pathway.
Methods: We conducted CpG-specific DM analysis on GRRN-associated CpGs using leukocyte-derived DNA methylation (DNAm) microarray data from the Detroit Neighborhood Health Study (n = 148 trauma-exposed AA adults, 49 with PTSD). We identified functionally relevant GRRN probes based on UCSC annotation and cis-eQTM (cis-expression quantitative trait methylation loci) analysis of GRRN genes (within 250kb), using a subset of participants with both DNAm and gene expression data (n=91). Analyses were conducted in R (v3.4.4) and DM regression models included sex, age, ancestry, smoking, and estimated proportion of leukocytes as covariates.
Results: Of 64 GRRN-associated eQTMs with nominally significant correlation between expression and DNAm (pval < 0.01), 2 CpGs mapping to FKBP5 (cg16012111) and GATA3 (cg13409449) were significantly associated with PTSD (DM: FDR-adjusted pval < 0.05), such that those with PTSD had lower methylation levels. A CpG mapped to NFATC1 (cg22324981) was positively associated with PTS severity in robust models. All 3 CpGs are found in heavily regulated candidate cis-regulatory elements (ccREs).
Conclusions: Functionally relevant DNAm differences in the GRRN pathway associate with PTSD in AA adults, supporting previous studies in African-ancestry samples. Work is ongoing to replicate these findings in additional AA cohorts.

Supported By: R01MD011728; R01 DA022720; DA022720-S1; RC1MH088283
Keywords: PTSD, Glucocorticoid, DNA Methylation, Leukocyte

28. An Epigenome-Wide Association Study of PTSD in Veterans Implicates Several New DNA Methylation Loci

Mark Logue[1], Erika Wolf[2], Filomene Morrison[3], Zhenwei Zhou[3], Alicia Smith[4], Nikolaos P. Daskalakis[5], Anjanette Stone[6], Steven Schichman[6], Regina McGlinchey[7], William Milberg[7], Traumatic Stress Brain Study Group, Bertrand Huber[3], and Mark Miller[3]

[1]VA Boston Healthcare System, [2]National Center for PTSD at VA Boston Healthcare System, [3]Boston University & VA Boston Healthcare System, [4]Emory University School of Medicine, [5]Mount Sinai School of Medicine, [6]Research Service, Central Arkansas Veterans Healthcare System, [7]Harvard Medical School & VA Boston Healthcare System

Background: Both candidate gene and epigenome-wide association studies (EWASs) have implicated DNA methylation in PTSD. Here, we present an EWAS of PTSD in a cohort of United States veterans (n=378 lifetime PTSD cases and 135 controls) assessed using the Illumina EPIC BeadChip.
Methods: Our model included covariates for ancestry, blood cell heterogeneity, sex, age, and a smoking-score based on 39 smoking-associated CpGs.
Results: Our analysis yielded one genome wide significant association. Locus cg19534438 in the gene G0S2 was associated with PTSD (p=1.19x10-7, FDR q =0.048). This association was not replicated in a smaller cohort of veterans assessed with the Illumina 450K chip (249 PTSD cases and 92 controls). We also noted suggestive association with the smoking-associated locus cg05575921 in AHRR despite the inclusion of the smoking covariate (beta=-0.13, p=9.16x10-6, FDR=0.60). We then examined the top 100 loci from the blood-based EWAS in pre-frontal cortex samples obtained from the National PTSD brain bank (42 cases and 30 controls). One of the top-10 EWAS loci, cg04130728 in CHST11, was also associated in the pre-frontal tissue (in blood, beta=0.15, p=1.19x10-5, FDR=0.60; in brain beta=0.32, p=0.00032, FDR=0.032). Gene set analysis of the top 500 EWAS loci yielded of several significant GO terms involved in pathogen response, including "Response to lipopolysaccharide" (p=6.97x10-6, FDR =0.042).
Conclusions: Our blood-based EWAS of PTSD implicates several new loci in PTSD pathogenesis, some of which may mirror changes in neural tissue, although these associations should be provisional until replicated in larger samples.
Supported By: VA BLR&D Merit Award 1I01BX003477-01 (MWL), National Center for PTSD, and the Translational Research Center for TBI and Stress Disorders (TRACTS), a VA Rehabilitation Research and Development (RR&D) Traumatic Brain Injury Center of Excellence (B9254-C) at VA Boston Healthcare System.
Keywords: PTSD, DNA Methylation, US Veterans, Epigenome-wide Association, Brain Tissue

SYMPOSIUM
Innovative Techniques for the Understanding of Adolescent Alcohol Effects on Brain Function
12:30 p.m. - 2:30 p.m.
Chair: Cindy Ehlers
Co-Chair: Antonio Noronha

29. Prospective Study of Adolescents Reveals Disturbed Trajectories of Frontal Cortical and Cerebellar Volumes Following Initiation of Drinking

Adolf Pfefferbaum[1] and Edith Sullivan[2]

[1]SRI International BN168, [2]Stanford University School of Medicine (MC 5723)

Background: Development of the human brain continues throughout adolescence and into young adulthood and is characterized by declining cortical gray matter. Initiation of heavy drinking alcohol, which commonly occurs during neurodevelopment years, can potentially alter normal brain trajectories. This analysis questioned the effect of initiating heavy drinking on developmental trajectories of supratentorial cortex and the cerebellum.
Methods: Structural MRI data were acquired annually for 3 sessions through the multi-site, prospective National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) study. Using a cohort-sequential design, 634 no-too-low drinking adolescents, ages 12 to 21 years at entry, were recruited. MRI data used longitudinal alignment procedures and were expressed as regional gray matter volumes adjusted for intracranial volume, thereby attenuating sex differences.
Results: Longitudinal volumetric brain data were analyzed using linear mixed effects models in R. The results revealed that adolescents who initiated heavy drinking (N=62), even without meeting criteria for alcohol dependence, showed acceleration of the normal decline observed in the youth who maintained low-to-no drinking (N=356) in cortical gray matter volumes that were salient in frontal (p=.009) and cingulate (p=.021) regions. Accelerated decline of cerebellar gray matter trajectories also occurred in heavy-drinking adolescents (p<.05). Male and female drinkers were similarly affected.
Conclusions: Adolescents who initiate heavy drinking are vulnerable to disturbing trajectories of normal brain development affecting the extensive frontal-cingulate-cerebellar system. Continued regular examination of this cohort has the potential to detect further divergence from normal trajectories with continued drinking and to localize extent of recovery with sustained abstinence.
Supported By: NIAAA: R01AA017347, R01AA010723, R01AA005965, U01AA017923, U01AA021697, K05AA017168
Keywords: MRI, Cortical Volume, Cerebellar Volume, Neurodevelopment, Alcohol Drinking

30. Translational Studies on the Effects of Adolescent Alcohol Exposure on Sleep and Brain Connectivity

Cindy Ehlers[1]

[1]The Scripps Research Institute

Background: Frequent binge drinking during adolescence has been associated with health risk behaviors including alcohol use disorders (AUD), yet few studies have documented its effects on neurophysiological consequences in young adulthood. Two measures, sleep and synchrony of phase (phase-locking, PL) of event-related oscillations (EROs) between frontal and parietal cortex were evaluated.
Methods: The participants were young adults of Mexican American and American Indians (age 18-30 yrs, n=1041), with and without a history of adolescent binge drinking (5 drinks for boys 4 for girls per occasion at least once per month), and 74 young adult rats with and without a history of 5 weeks of adolescent alcohol vapor exposure.
Results: Human binge drinkers were found to have lower PL in the beta ($F=4.4$, $p=0.035$) and theta ($F=3.9$, $p=0.048$) frequencies. PL was also decreased in the rats exposed to ethanol vapor in the theta band ($F=9.0$, $p=0.004$). A history of adolescent regular binge drinking was also associated with: reduced sleep quality as indexed by longer sleep latencies, more problems with breathing, bad dreams and an overall higher Pittsburgh sleep quality index total score (all $p'<0.05$). Adolescent vapor exposure in the rat was found to result in decreases in theta power (4-8 Hz) ($F=7.1$, $p<0.01$), and delta (1-4 Hz) ($F=14.4$, $p<0.001$) and theta (4-8 Hz) ($F=8.0$, $p<0.009$) power during slow wave sleep.
Conclusions: These findings suggest that alcohol exposure during adolescence may result in deficits in sleep quality in humans and slow wave sleep in animals and decreases in synchrony between cortical neuronal networks, in both species.
Supported By: RO1s AA026248, AA010201, AA006059 UO1 AA019969
Keywords: Adolescents, Alcohol Use Disorder, Binge Drinking, Event-Related Potentials, Sleep

31. Persistent Neuroimmune and Epigenetic Signaling in Adult Brain Following Adolescent Alcohol Exposure Mimics Findings in Human Alcoholics

Fulton Crews[1], Leon Coleman[1], and Ryan Vetrino[1]

[1]University of North Carolina

Background: Adolescence is a period of maturation of self-control, consideration of future consequences, planning, and socialization skills, and eventually reductions in risk taking and sensation seeking.
Methods: To determine if adolescent binge drinking caused persistent effects, Wistar rats exposed to adolescent intermittent ethanol (AIE) across puberty were assessed in adulthood. Post-mortem human brain of AUD and control were determined.
Results: AIE increased adult brain expression of innate immune genes HMGB1, CCL2, Toll-like receptors, and RAGE. AIE also increased activation of the transcription factor NFkB and altered microglial morphology in parallel with increased epigenetic marker H3K9me2. AIE also increased adult risky decisions and blunted behavioral flexibility in parallel with reduced adult hippocampal neurogenesis, reduced forebrain cholinergic and midbrain serotonergic neurons as well as increases in markers of neurodegeneration. MRI found altered cortical thickness and myelin and a decrease in rsfMRI cortical-striatal connectivity in adults after AIE. Post-mortem AUD human brain assessments mimicked those found following AIE. Further, increases in human brain gene expression correlated with age of drinking onset and lifetime alcohol consumption. Exercise, indomethacin, donepezil and galantamine were found to prevent and/or reverse AIE pathology.
Conclusions: Adolescent alcohol exposure increases expression of HMGB1, TLR, RAGE, NFkB, neuroimmune genes, and histone gene silencing markers in brain that persist into adulthood long after alcohol exposure ends. Hippocampal, cholinergic, and serotonergic neuron changes could underlie altered PFC connectivity and risk-taking behaviors. Prevention and reversal of these pathologies is consistent with persistent, but not permanent, changes which could be rescued in adulthood.
Supported By: National Institute on Alcohol Abuse and Alcoholism for support through the Neurobiology of Adolescent Drinking in Adulthood (NADIA) consortium (AA020024, AA020023), the Bowles Center for Alcohol Studies (AA011605), and the U54 collaborative partnership between NCCU and UNC (AA019767).
Keywords: Alcohol, Adolescence, Toll-like Receptors, NFkB, Cognition

32. Epigenetic Regulators of Molecular Changes in the Amygdala Caused by Adolescent Alcohol Exposure in Humans and Rodents

Subhash Pandey[1], John Peyton Bohnsack[1], Huaibo Zhang[2], Tara Teppen[2], Evan Kyzar[1], and Svetlana Dzitoyeva[1]

[1]University of Illinois at Chicago, [2]University of Illinois at Chicago; Jesse Brown VA Medical Center

Background: Drinking during adolescence is a primary risk factor for developing alcohol use disorder (AUD) and comorbid anxiety later in life. This study investigated how adolescent drinking effects epigenetic mechanisms mediated by EZH2 (histone methyltransferase) in humans and rodents.
Methods: Human postmortem amygdala from individuals with AUD who began drinking before (n=11) and after the age of 21 (n=11) and control subjects (n=22) was used for mRNA and epigenetic analysis. Additionally, Sprague-Dawley male adolescent rats were exposed with intermittent ethanol (2g/kg) (AIE) or saline (AIS). Adult rats were infused with EZH2 siRNA into the central nucleus of amygdala (CeA) and then evaluated for anxiety-like behaviors. qPCR and ChIP assay were used to examine mRNA levels and epigenetic modifications (n=6-8 per group).

Results: Individuals with early onset drinking had decreased BDNF ($p=0.008$), ARC mRNA ($p=0.012$), and BDNF protein expression ($p=0.04$) but not in late onset drinking ($p=0.30$) in amygdala. ChIP analysis revealed that this decrease was likely caused by increased repressive H3K27me3 deposited ($p<0.05$) by increased EZH2 ($p<0.05$) at BDNF-IX and Arc promoter in early onset AUD. Our results also indicate that AIE caused decreased BDNF and Arc expression ($p<0.001$), increased anxiety ($p<0.001$), increased EZH2 ($p<0.001$) and H3K27me3 ($p=0.01$) associated with the BDNF-IX and Arc promoter, and that this can be prevented by knocking down EZH2 in the CeA of rats in adulthood.
Conclusions: This data suggests that EZH2 is an important epigenetic regulator of AIE-induced molecular changes in the amygdala and could be a potential target for treatment of AUD.
Supported By: Supported by NIH-NIAAA P50AA022538, UO1AA019971, U24AA024605, RO1AA010005 and by the VA Senior Research Career Scientist award to SCP
Keywords: Histone Methylation, Amygdala, BDNF, Epigenetic, Alcohol Addiction

SYMPOSIUM
Personalized Medicine Approaches in Deep Brain Stimulation for Depression - New Data on Network Dysfunctions and Treatment Outcomes

12:30 p.m. - 2:30 p.m.
Chair: Thomas Schlaepfer
Co-Chair: Patricio Riva Posse

33. Quantifying the Axonal Pathways Directly Stimulated in Therapeutic Subcallosal Cingulate Deep Brain Stimulation

Cameron McIntyre[1]

[1]Case Western Reserve University

Background: Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is an emerging experimental therapy for treatment-resistant depression. New developments in SCC DBS surgical targeting are focused on identifying specific axonal pathways for stimulation that are estimated from patient-specific computational models. This connectomic-based biophysical modeling strategy has proven successful in improving the clinical response to SCC DBS therapy, but the DBS models used to date have been relatively simplistic, limiting the precision of the pathway activation estimates.
Methods: We used the most detailed patient-specific foundation for DBS modeling currently available (i.e., field-cable modeling) to evaluate SCC DBS in our most recent cohort of six subjects, all of which were responders to the therapy. We quantified activation of four major pathways in the SCC region: forceps minor (FM), cingulum bundle (CB), uncinate fasciculus (UF), and subcortical connections between the frontal pole and the thalamus or ventral striatum (FP). We then used the percentage of activated axons in each pathway as regressors in a linear model to predict the time it took patients to reach a stable response, or TSR.
Results: Our analysis suggests that stimulation of the left and right CBs, as well as FM are the most likely therapeutic targets for SCC DBS. Additionally, the right CB alone predicted 84% of the variation in the TSR, and the correlation was positive.
Conclusions: The results help to refine the understanding of which axonal pathways are necessary and sufficient for eliciting an antidepressant effect in SCC DBS.
Supported By: NIH R01 MH102238
Keywords: Deep Brain Stimulation, Depression, Subcallosal Cingulate

34. "Shoot First and Call Whatever You hit the Target" - How to Improve Outcomes in DBS for Depression

Patricio Riva Posse[1], Kisueng Choi[2], Allison Waters[2], Andrea Crowell[1], and Helen Mayberg[2]

[1]Emory University, [2]Icahn School of Medicine at Mount Sinai

Background: Deep brain stimulation (DBS) is a promising technique for modulating circuits underlying neuropsychiatric disorders. Since its implementation in mood disorders, multiple case series demonstrated positive results in the subcallosal cingulate cortex. Unfortunately, an industry sponsored clinical trial in the subcallosal cingulate did not replicate these findings. The identification of biomarkers is crucial for the future of this treatment.
Methods: 35 patients with treatment-resistant depression have been implanted since 2007 at Emory University. Tractography guided target selection was analyzed retrospectively in the initial 17 patients to find a pattern of common tractography maps in responders. In the last 18 subjects, tractography has been used prospectively for target selection.

Additionally, several approaches to determine target engagement using electrophysiology, with local field potentials (LFPs) and EEG − evoked potentials (ERPs).
Results: Prospective target selection resulted in 76.4 % of patients (13/17) responding at 24 weeks (50% decline in HDRS-17). Electrophysiologic tests demonstrate LFP and EEG differences between "on-target" and ineffective contacts. Longitudinal measurements of LFPs demonstrate gradual changes that correlate with depression scores. Long-term results (up to 10 years of follow up) in the initial cohorts show that 60% of subjects have sustained antidepressant response.
Conclusions: Deep Brain Stimulation remains a potential treatment for severe depression despite having failed in different trials across different targets. Sustained and robust long-term results, improvements in target selection, dynamic testing of the neural networks after implantation, and biomarker driven parameter selection bring new ways of improving future trials.
Supported By: 1UH3NS103550-01
Keywords: Treatment Resistant Depression, Deep Brain Stimulation, Electrophysiology, White Matter Tractography

35. Frontal White Matter Architectural Network Changes Predict Therapeutic Deep Brain Stimulation for Major Depression

Volker Coenen[1], Thomas Schlaepfer[2], Horst Urbach[2], and Marco Reisert[2]

[1]University of Freiburg, [2]University Hospital Freiburg

Background: Despite therapeutic advances 20% of patients with major depression remain treatment resistant. For a subgroup Deep Brain Stimulation (DBS) might serve as a valid treatment. Two pivotal trials in major depression were stopped. One reason might be the difficult selection of patients. We present results from two trials of DBS to the superolateral medial forebrain bundle (slMFB-DBS; FORESEE I and II). The goal was to identify informed features that allow to predict treatment response.
Methods: N= 24 patients were analyzed. Preoperative imaging including anatomical sequences (T1, T2) and diffusion tensor imaging (DTI) magnetic resonance imaging sequences were used together with postoperative helical CT scans (for DBS electrode position). Patient specific anatomical modeling (PAM) was used to understand connectivity patterns of responders and non-responders. We further performed voxel base morphometric analysis together with statistical evaluation of the outcome (MADRS-response).
Results: PAM does not help to differentiate responders from non-responders. A left fronto-polar and orbito-frontal region was identified that showed increased volume in preoperative anatomical scans. Further statistical analysis shows that this "hub region's" volume is predictive for later MADRS response from DBS. The hub region connects to typical fiber pathways that have been addressed before in effective DBS in major depression.
Conclusions: Left frontal volume growth might indicate intrinsic activity upon disconnection form the main emotional network. The results are significant since for the first time we found an informed feature that might allow to identify and phenotype future responders for slMFB DBS. This is a clear step into the direction of personalized treatments.
Keywords: Major Depression, Deep Brain Stimulation, Diffusion Tensor Imaging (DTI), Brain Magnetic Resonance Imaging (MRI), Medial Forebrain Bundle

36. Long-Term Efficacy of Different Deep Brain Stimulation to Different Targets - What is the True Clinical Benefit?

Thomas Schlaepfer[1], Hannah Kilian[1], Bettina Bewernick[1], and Volker Coenen[1]

[1]University Hospital Freiburg

Background: Several stimulation targets are currently under research for the treatment of otherwise treatment-resistant depression (TRD) with deep brain stimulation (DBS). Rapid antidepressant effects of DBS to the supero-lateral branch of the medial forebrain bundle (slMFB) have been demonstrated in our group.

Long-term data on the antidepressant efficacy are needed to confirm this true clinical utility for the chronically affected population of TRD patients.
Methods: 28 patients suffering from TRD were treated with DBS bilaterally to the slMFB in two pilot studies. Data were pooled for long-term analysis. Primary outcome measure was the antidepressant response measured with the Montgomery-Åsberg Depression Rating Scale (MADRS).
Results: A significant difference in the severity of depression compared to baseline could be seen from the first months of DBS. Specifically, after one month of stimulation mean response measured with the MADRS score reached 52 +/- SD 8 %. After eight years mean response was 73 +/- SD 12%. In general, responders staid in response and the level of response was maintained over the observational period. Global functioning was also improved with stimulation. Main side effect was a transient strabismus at higher stimulation currents.
Conclusions: This study demonstrates long-term antidepressant efficacy of DBS of the slMFB. This confirms previous efficacy data from our first study and data from an independent group on four patients. In addition, it demonstrates the necessity of a careful long-term clinical management and assessment of these patients to minimize dropouts.
Supported By: Medtronic Inc.
Keywords: Deep Brain Stimulation, Major Depressive Disorder (MDD), Treatment Resistance

SYMPOSIUM
Gut and Brain in Motherhood: Perinatal Distress and Neuronimmune, Neuroendocrine and Microbiota Alterations

12:30 p.m. - 2:30 p.m.
Chair: Jennifer Payne

37. The Role of Allopregnanolone in Perinatal Mood and Anxiety Disorders

Lauren Osborne[1], Gayane Yenokyan[2], Abanti Sanyal[2], and Jennifer Payne[1]

[1]Johns Hopkins University School of Medicine, [2]Johns Hopkins School of Public Health

Background: Prior investigations into the relationship between progesterone metabolites and postpartum depression (PPD) have yielded mixed results. We sought to determine the relationship between allopregnanolone during pregnancy and postpartum and concurrent or future symptoms of depression.
Methods: Allopregnanolone (ALLO) levels were measured by ELISA at four time points across pregnancy and postpartum (N=61, all with mood disorders) and replicated (N=64, half healthy controls). PPD was identified by DSM-IV criteria and/or score of >10 on the Edinburgh Postnatal Depression Scale. Generalized linear mixed effects models with random intercept estimated the relationship between ALLO and PPD while accounting for within-person correlation of outcomes over time.

Results: ALLO and concurrent depression were not related. After adjusting for covariates, we found that each additional ng/mL of ALLO in the second trimester (T2) reduced the risk of developing PPD by 63% (95% CI 13% to 84%, $p = 0.022$). Results of the replication cohort confirmed the correlation between lower T2 ALLO and subsequent PPD ($\beta = 0.733$, 95% CI (0.565, 0.951), $p = 0.02$). Results of an additional replication cohort (63 women) are currently being analyzed and will be presented at the conference.
Conclusions: Our principal finding was a significant association between ALLO levels in pregnancy (T2) and the later development of PPD. Our findings differ from previous research, possibly because we measured hormones at several points in pregnancy and in a population with high rates of depression at most points during the study. Our replication cohort included healthy controls and indicates that these results may be more widely applicable.
Supported By: NIH-NIMH R01 MH112704-01 (PI: Payne and Kaminsky)
Keywords: Allopregnanolone, Neuroendocrine, Postpartum Depression, Pregnancy

38. Stress Alterations to the Maternal Microbiome Mediate Sex-Specific Neuroimmune Development

Eldin Jasarevic[1], Christopher Howard[1], and Tracy L. Bale[2]

[1]University of Maryland School of Medicine, [2]University of Pennsylvania

Background: Maternal stress experience during pregnancy produces lasting effects on the developing brain, increasing subsequent risk for neuropsychiatric disorders throughout life. Using our well-established mouse model of early prenatal stress, in which exposed males exhibit lasting reprogramming of hypothalamic circuits controlling neuroendocrine response to stress and metabolism. As newborns acquire the initial community of microbiota from the mother during birth, we transplanted vaginal microbiota from stressed dams into naïve pups delivered by cesarean section and recapitulated key aspects of the prenatal stress phenotype. However, the inability to rescue the prenatal stress phenotype involved transcriptional reprogramming to innate immunity pathways in the fetal gut and brain. Thus, we examined the hypothesis that sex-specific neuroimmune development is influenced by stress effects on the maternal gut microbiome.
Methods: We used an integrated multi-Omic approach to assess the stress-reprogramming of the immune compartment of the fetal brain via the maternal gut microbiome. Reconstitution experiments were used to examine the casual contribution of maternal gut microbiome to rescue aspects of the prenatal stress phenotype in adulthood.
Results: Maternal stress exposure increased presence of inflammation-associated microbiota, disrupted microbiota production of metabolites, and decreased availability microbiota derived metabolites in the fetal brain. Analysis revealed sex-specific changes in the frequency and transcriptional and activation patterns of resident and infiltrating immune cells in the fetal brain.
Conclusions: The current work identifies key mechanistic points whereby changes in inflammation and metabolites produced by the maternal gut microbiota impact fetal brain development and exert lasting outcomes on offspring physiology and behavior and metabolic function.
Supported By: P50-MH099910, MH 104184, MH 091258, MH 087597, MH 073030 and MH 108286, NIH NRSA F32 MH 109298.
Keywords: Neuroimmune, Prenatal Maternal Stress, Neurodevelopment, Microbiome-Gut-Brain Axis, Bioinformatics

39. The Gut Microbiome in Pregnancy: Associations With Adverse Childhood Experiences and Inflammation

Liisa Hantsoo[1], Ceylan Tanes[2], Brendan McGeehan[1], Stephanie Criniti[1], Michal Elovitz[3], Charlene Compher[3], Gary Wu[3], and C. Epperson[4]

[1]University of Pennsylvania Perelman School of Medicine, [2]Children's Hospital of Philadelphia, [3]University of Pennsylvania, [4]University of Colorado School of Medicine

Background: Adverse childhood experiences (ACEs) program a dysregulated neuroimmune response to stress in adulthood, but ACE impact on the gut microbiome is unknown. This study assessed associations among ACE, the gut microbiome, and cytokine response to stress in pregnancy.
Methods: Healthy pregnant women completed the Adverse Childhood Experiences Questionnaire (ACE-Q) and provided a stool sample at 20-26 weeks gestation; DNA was isolated, 16S sequencing was performed. A subset of women completed the Trier Social Stress Test (TSST) at 22-34 weeks gestation; plasma interleukin-6 (IL-6), interleukin-1β (IL-1β), C-reactive protein (CRP), and tumor necrosis factor α (TNF-α) were measured at four timepoints pre and post TSST; area under the curve (AUC) was calculated. Mixed models assessed relationships between gut microbiota, ACE, and cytokine AUCs, controlling for gestational age, BMI, and fiber intake; false discovery rate (fdr) adjusted p-value (q) < 0.05 was considered significant.
Results: Forty-eight women completed the ACE-Q and provided stool; 19 completed the TSST. Women reporting multiple ACEs (high ACE) had greater differential abundance of gut Prevotella than low ACE participants ($q=5.7x10^{-}13$). Regardless of ACE status, Bacteroides was positively associated with IL-6 ($q<0.001$), TNF-α ($q=0.0006$); Megasphaera positively associated with CRP ($q=0.027$), TNF-α ($q=0.015$); Ruminococcaceae positively associated with CRP ($q=0.034$) and negatively with TNF-α ($q=0.0006$); Dialister negatively associated with IL-6 ($q=0.0038$); Prevotella positively associated with TNF-α ($q=0.015$).
Conclusions: Our findings suggest that multiple ACEs are associated with altered gut microbiota composition during pregnancy. Surprisingly, inflammatory response to stress was not associated with ACE, but with abundance of specific gut taxa.
Supported By: March of Dimes Prematurity Research Center Early Career Award
Keywords: Gut Microbiome, Early Life Stress, Adverse Childhood Experiences, Inflammatory Cytokines, Pregnancy

40. Prenatal Stress in Mice Leads to Inflammation and Serotonergic Dysfunction in the Intrauterine Environment

Tamar Gur[1], Helen Chen[1], Adrienne Antonson[1], Therese Rajasekera[1], and Michael Bailey[2]

[1]Ohio State University, College of Medicine, [2]Nationwide Children's Hospital, Ohio State University College of Dentistry

Background: Studies demonstrate that exposure to prenatal stress can have negative consequences on neurodevelopment and has been linked with psychiatric disorders in the offspring. In this study we address the contribution of maternal stress in utero on inflammation and serotonergic (5-HT) function.
Methods: Pregnant C57/BL6 females were randomly assigned to stressed or non-stressed control group. The stressed group was restrained between embryonic day (E) 10-E16. Placentas and fetal brains were collected on E17.5. RT-PCR, HPLC, and multiplex ELISA were used to examine inflammation levels and 5HT-related gene expression. A second cohort of pregnant CCL2-/- females underwent the same treatment as described above.
Results: Prenatal stress leads to increased levels of the chemokine CCL2 in the placenta, and increased expression of the cytokines IL-1β and IL-6 in both the placenta and fetal brain ($p < 0.05$). Additionally, we extended the finding of decreased Monoamine Oxidase A (MAOA) in the cortex of adult male offspring exposed to prenatal stress to the male fetal brain ($p < 0.05$) and placenta ($p = 0.07$). Furthermore, prenatal stress increased expression of tryptophan hydroxylase 1 (TPH1; which synthesizes 5-HT) ($p = 0.10$) and serotonin turnover in the placenta ($p < 0.05$). However, the increase in inflammation and decrease in MAOA was ameliorated in the placenta and fetal brain of CCL2-/- mice.
Conclusions: Utilizing prenatal stress in a rodent model, we have demonstrated disruptions in inflammation and serotonergic function in utero, which may contribute to alterations in adult behaviors and contribute to psychiatric illness.
Supported By: NIMH K08
Keywords: Prenatal Exposure, Placenta, Microbiome, Early Life Stress

SYMPOSIUM
Early-Life and Adult Stress Vulnerability and Innovative Strategies for Prevention
12:30 p.m. - 2:30 p.m.
Chair: Marco Riva
Co-Chair: Rodrigo Grassi-Oliveira

41. Early Nutritional Intervention Protects Against the Early-Life Stress Induced Cognitive Impairments

Aniko Korosi[1], Kit-Yi Yam[1], Eva Naninck[1], Lidewij Schipper[2], Kitty Reemst[1], Eline van der Beek[3], and Paul Lucassen[1]

[1]University of Amsterdam, [2]Nutricia Research, [3]Nutricia Research/University of Groningen

Background: Early-life stress (ES) is a major risk factor for cognitive impairment and psychopathologies in adulthood. The underlying mechanisms are unknown, and the role of nutrition is largely unknown. We hypothesized that ES leads to lack of essential nutrients and that enriching the early-diet might protect against the ES-induced deficits, focusing on micronutrients and polyunsaturated-fatty-acids (PUFA's), key, among others, for neurogenesis and neuroimmune modulation.
Methods: ES induced via the limiting nesting/bedding material between postnatal day (P) P2-P9, resulted in cognitive decline (assessed with object-recognition-OR, object-location-OL and Morris-water-maze-MWM) in adulthood. We studied 1) nutrient levels, 2) if early-dietary intervention with micronutrients (P2-P9) or PUFAs (P2-P42) prevents the ES-induced cognitive impairments and 3) the mechanisms mediating these effects (i.e. HPA axis, neurogenesis, microglia). N=7-12; Data analyses: two-way ANOVA, corrected for multiple comparisons where needed and considered significant when $P<0.05$-0.01 or FDR <0.1.
Results: ES leads in P9 offspring to reduction in methionine ($F1,51=26.25$; $p=0.0001$ in plasma and $F1,35 = 7.73$; $p =0.009$ in hippocampus) and omega3-PUFAs levels (in hippocampus; FDR=0.08).

Micronutrient supplementation partially protects against the ES-induced cognitive impairments (OR; $F1,41 = 5.432$; $p=0.0248$) and blunts the ES-induced rise in corticosterone ($F1,45 = 4.186$; $p= 0.047$).

Increasing omega3-PUFA availability prevents the ES-induced cognitive impairments (OR: $F1,56=7.24$, $p=0.01$, OL: $F1,22=5.38$, $p=0.03$, MWM probe: condition: $F1,64=4.08$, $p=0.048$ and diet $F1,64=4.81$, $p=0.03$) and restores the ES-induced reductions in neurogenesis ($F1,26=4.12$, $p=0.05$) and increase in microglial-CD68expression ($F1,16=4.94$, $p=0.04$).
Conclusions: These studies give new insights for the development of targeted dietary interventions for vulnerable populations exposed to ES.
Supported By: NWO-Meerwoud; NWO-Food Cognition and Behavior; JPI-NutriCog
Keywords: Early-Life Stress, Micronutrients, Fatty Acids, Cognition, Microglia

42. Inhibiting Ventral Dentate Gyrus Activity Can Prevent Stress-Induced Psychopathology in Mice

Christoph Anacker[1], Victor Luna[2], Amira Millette[2], Gregory Stevens[2], and Rene Hen[2]

[1]Columbia University, [2]Columbia University & New York State Psychiatric Institute

Background: We have shown that hippocampal neurogenesis can confer stress resilience by inhibiting ventral dentate gyrus (vDG) activity. How inhibition affects information processing in the vDG, and whether inhibition could prevent the development of psychiatric disorders is unknown.
Methods: We used cfos immunohistochemistry and in vivo calcium (Ca2+) imaging during 10 days of social defeat stress to investigate correlated activity of vDG neurons in susceptible mice with normal neurogenesis and in resilient mice with 2±0.2

fold increased neurogenesis. To identify new pharmacological targets to inhibit vDG activity, we treated mice with a knockout or overexpression of the serotonin 1A receptor (5HT1aR) in the DG with the 5HT1aR agonist, 8-OH-DPAT, to test if 5HT1aR activation can silence vDG activity and confer stress resilience.
Results: Social defeat increases vDG activity in susceptible mice, as indicated by increased numbers of cfos+ cells (control: 7.6±0.4; defeat: 28.8±2.3, n=3-12, ***p=0.0007). In vivo Ca2+ imaging revealed that defeat also increases correlated activity of vDG neurons (Defeat Day 1: 0.07±0.01, n=21; Day 10: 0.12±0.01, n=90, *p=0.04). These effects are absent in resilient mice with increased neurogenesis (p=0.4). In mice that express 5HT1aR only in the DG, 8-OH-DPAT decreased vDG activity, as indicated by decreased numbers of cfos+ cells (vehicle: 31±4.3, DPAT: 17±3.2, n=5, **p=0.04). 8-OH-DPAT also increased social interaction time after stress, indicating resilience (vehicle: 51±9.1sec, DPAT: 87±10.5sec, n=19, **p=0.008). These pro-resilience effects of 8-OH-DPAT were absent in 5HT1aR knockout mice.
Conclusions: Our results suggest that inhibiting correlated activity in the vDG may be a promising strategy to treat or prevent stress-induced psychopathology.
Supported By: K99 MH108719-02; 2P50 MH090964-06; Hope for Depression Research Foundation
Keywords: Ventral Hippocampus, Neurogenesis, Serotonin 1A Receptor, Chronic Stress, Resilience and Vulnerability

43. Role of miR-19 in the Vulnerability or Resilience to Stress: Novel Target for Preventive Strategies

Annamaria Cattaneo[1]

[1]Biological Psychiatry Lab, IRCCS Fatebenefratelli Brescia

Background: Recent studies have identified miR-19 as a key regulator of brain neurodevelopmental trajectories, since it drives the differentiation of neurons [3-5] and of the development of the immune system. However, up to now, no findings are available on how stressful life experiences, can modulate miR-19 and its target genes and pathways, influencing the vulnerability or resilience for several psychiatric disorders.
Methods: We measured miR-19 in different tissues and models, represented by: i) hippocampus of prenatal stressed animals; ii) hippocampus of rats exposed to chronic mild stress (CMS) and characterized for resilience or vulnerability; iii) human hippocampal progenitor stem (HPS) cells treated with cortisol; iv) blood samples of controls or patients with psychiatric disorders and characterized for childhood trauma.
Results: MiR-19 levels were downregulated in the hippocampus of rats exposed to PNS (FC = -1.4, p-value < 0.01) as well as in HPCs treated with cortisol (p<0.05), an effect that in cells was associated with a reduction in neurogenesis. The CMS paradigm caused a down-regulation in the miR-19 levels, but only in vulnerable rats (FC = -1.7, p-value < 0.005). Alterations in miR-19 levels were also observed in blood of controls and in patients with psychiatric disorders with a history of childhood trauma. We are now evaluating how targeted and untargeted manipulations of the miRNA-19 can also reverse neurogenesis alterations induced by stressful conditions.
Conclusions: Stress is associated with a down-regulation of miR-19, which may cause alterations in neurodevelopment and immunity/inflammation pathways, leading to an enhanced vulnerability for several psychiatric disorders later in life.
Keywords: Stress, Vulnerability, Resilience, In Vitro Models, Biomarkers

44. Resilience is Associated With Larger Hippocampal Dentate Gyrus

Maura Boldrini[1], Hanga Galfalvy[1], Andrew J. Dwork[1], Gorazd B. Rosoklija[1], Rene Hen[2], Victoria Arango[1], and J. John Mann[2]

[1]Columbia University, [2]Columbia University & New York State Psychiatric Institute

Background: Early life adversity (ELA) increases the risk for major depressive disorder (MDD) and suicide, and potentially affects dentate gyrus (DG) plasticity. We reported smaller DG and fewer granular neurons (GNs) in MDD. ELA effects on DG plasticity in suicide decedents with MDD (MDDSui) and in resilient subjects (ELA history without MDD or suicide) are unknown.
Methods: We quantified neural progenitor cells (NPCs), GNs, glia, and DG volume in whole hippocampus postmortem in four groups of drug-free, neuropathology-free subjects (n=52 total): psychological autopsy-defined MDDSui and non-psychiatric, non-suicide controls, with and without ELA (before age 15).
Results: ELA was associated with larger DG (p<0.0001) and trending fewer NPCs (p=0.0190) only in controls in whole DG, showing no effect on NPCs and DG volume in MDDSui. ELA exposure was associated with more GNs (p=0.0003) and a trend for more glia (p=0.0160) in whole DG, in MDDSui and controls. MDDSui without ELA had fewer GNs in anterior-mid DG (p<0.0001), fewer anterior DG NPCs (p<0.0001), and smaller whole DG volume (p=0.0005) compared with controls without ELA. In MDDSui, lower Global Assessment Scale (GAS) score correlated with fewer GNs and smaller DG.
Conclusions: Resilience to ELA involves a larger DG perhaps related to more neurogenesis depleting NPCs and since mature GNs and glia numbers do not differ in the resilient group, perhaps there are effects on process extension and synaptic load that can be examined in future studies. In MDDSui without ELA, smaller DG volume, with fewer GNs and NPCs, suggest less neurogenesis and/or more apoptosis and dendrite changes.
Supported By: MH83862, MH64168, MH40210, NS090415, MH94888, MH090964, MH098786, American Foundation for Suicide Prevention Standard Research Grant SRG-0-129-12, Brain and Behavior Research Foundation Independent Investigator Grant 56388, New York Stem Cell Initiative (NYSTEM) C029157 and C023054
Keywords: Suicide, Early Life Adversity, Neural Progenitors, Granule Cells, Hippocampus

SYMPOSIUM
Genetic Approaches to Etiologic and Clinical Heterogeneity
3:00 p.m. - 5:00 p.m.
Chair: David Glahn

45. The Effect of Sex and BMI on the Genetic Overlap Between Plasma-Based Interleukins (-6 and -8) and Suicide Attempt

Emma Knowles[1], Joanne Curran[2], Harald Göring[2], Samuel Mathias[1], Josephine Mollon[1], Amanda Rodrigue[1], Rene Olvera[3], Ana Leandro[2], Ravi Duggirala[2], Laura Almasy[4], John Blangero[2], and David Glahn[1]

[1]Boston Children's Hospital, Harvard Medical School, [2]University of Texas of the Rio Grande Valley School of Medicine, [3]UT Health San Antonio, [4]University of Pennsylvania, Children's Hospital of Philadelphia

Background: Suicide is major public health concern. It is imperative to find robust biomarkers so that at-risk individuals can be identified in a timely and reliable manner. Previous work suggests mechanistic links between increased inflammation and risk for suicide, but questions remain regarding the etiology of this association, as well as the roles of sex and BMI.
Methods: Analyses were conducted using a randomly-ascertained extended-pedigree sample of 1884 Mexican-American individuals (60% female, mean age=42.04, range=18-97). Genetic correlations were calculated between IL-6 and IL-8, and lifetime risk for suicide attempt. The potentially confounding effects of sex and BMI were considered.
Results: 159 individuals endorse a lifetime suicide attempt. IL-8 and IL-6 shared significant genetic overlap with risk for suicide attempt shared significant genetic overlap (ρg=0.49, pFDR=7.67x10-03; ρg=0.53, pFDR=0.01), but for IL-6 this was attenuated when BMI was included as a covariate (ρg=0.37, se=0.23, pFDR=0.12). Suicide attempts were significantly more common in females (pFDR=0.01) and the genetic overlap between IL-8 and risk for suicide attempt was significant in females (ρg=0.56, pFDR=0.01), but not in males (ρg=0.44, pFDR=0.30).
Conclusions: These results demonstrate that: IL-8 shares genetic influences with risk for suicide attempt; females drove this effect; and BMI should be considered when assessing the association between IL-6 and suicide. This finding represents a significant advancement in knowledge by demonstrating that inflammation alterations are not simply a secondary manifestation of suicidal behavior, but rather, the pathophysiology of suicide attempts is, at least partly, underpinned by the same biological mechanisms responsible for regulating inflammatory response.
Supported By: MH078143, MH078111, MH083824; MH059490
Keywords: Inflammation, Suicide, Mood, Sex, Genetic Correlation

46. Association of Inflammatory Genes in Treatment Response in Major Depressive Disorder

Maria Portella[1], David Glahn[2], Heather Whalley[3], Emma Sprooten[4], and Emma Knowles[5]

[1]Institut de Recerca del Hospital de la Santa Creu i Sant Pau, [2]Yale University School of Medicine, [3]University of Edinburgh, [4]Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, [5]Yale University

Background: Many polymorphisms have been associated with response to treatment in major depression, particularly in genes of the monoaminergic system. Recent imaging findings on white matter alterations have revealed the involvement of inflammatory pathways in treatment response. There are few studies that investigate the association of inflammatory genes with treatment response.
Methods: 160 subjects were included. 61 Taq single nucleotide polymorphisms (SNPs) in 9 inflammatory genes (IL-1b, IL-2, IL-6, IL-6R, IL-8, IL-10, IL-18, TNF-alpha and IFN-γ) were genotyped with HapMap programme (www.hapmap.org, parameters: maf=0.05 and r2=0.8).

Severity of depression was assessed by the Hamilton Depression Rating Scale (HRSD-17). Illness stage was evaluated with the Maudsley Staging Method (MSM), including duration of index episode, symptom severity and treatment failures.

Linear regression analyses were conducted considering MSM as the dependent variable (including covariates).
Results: The allelic distribution of an IL6R rs57569414 polymorphism was clearly associated with MSM total scores (p=0.002). Marginal associations were also found between MSM total scores and IL18 (rs543810), IL1-β (rs1143643), IL6 (rs2069824) and IFN-γ (rs2069718) ($p<0.05$). Analyses of genotype frequencies revealed nominal associations between the IL6 rs2069824, IL6R rs4075015, IL2 rs1479923 and IL10 rs3021094 polymorphisms and MSM scores ($p<0.05$).
Conclusions: The current study suggests the involvement of several inflammation-related genes with treatment response in depression. If confirmed, these results may provide information on further genetic response biomarkers and putative new targets for future novel therapies. Our study should be considered as preliminary, and a considerably larger sample would be necessary to validate our findings.
Supported By: Intramural (IR16/007)
Keywords: Treatment Response, Major Depressive Disorder (MDD), Inflammatory Markers, Psychiatric Genetics, Pharmacogenetics

47. Associations of Polygenic Risk for Major Psychiatric Disorder With Brain Structure in Depression and Application to Stratification

Heather Whalley[1], Mathew Harris[1], Xueyi Shen[1], Jude Gibson[1], Mark Adams[1], Toni Clarke[1], Stephen Lawrie[1], and Andrew McIntosh[1]

[1]University of Edinburgh

Background: The clinical heterogeneity of major depressive disorder (MDD) suggests it may group together individuals with diverse aetiologies. Genetic and clinical overlap between MDD and other psychiatric disorders e.g. schizophrenia (SCZ) may highlight potential subtypes that share underlying mechanisms.

Polygenic risk scores (PGRS) have proven an effective way to convey such risks and can be used to examine the impact of genetic risk on underlying neurobiology. Here, we examine associations between psychiatric PGRSs and imaging phenotypes, and explore differential effects in the presence/absence of MDD.
Methods: We assessed associations and interactive effects (e.g SCZ PGR x MDD case/control status) on a range of cortical, subcortical and white matter metrics among 3,618 male and 3,918 female UK Biobank participants. All p values FDR corrected.
Results: There were significant SCZ PGR by MDD interactions for rostral anterior cingulate cortex thickness (β=.191, q=.004) and parahippocampal cingulum fractional anisotropy (β=.141, q=.039). Interactions were driven by positive associations between SCZ PGR and these brain measures among cases (β=.098, p=.026; β=.148, p=.001), compared to negative or zero associations among controls (β=−.087, p=.002; β=−.002, p=.854). MDD cases with low SCZ PGR showed thinner cortex and lower fractional anisotropy, high-SCZ-PGR cases were indistinguishable from controls.
Conclusions: Our results indicate that MDD case-control differences in specific brain metrics vary as a function of SCZ PGR. Our findings provide some evidence that MDD in the presence of high SCZ PGR may represent a distinct form of the disorder.
Supported By: This study was supported by a Wellcome Trust Strategic Award, "Stratifying Resilience and Depression Longitudinally" (STRADL; ref. 104036/Z/14/Z) and conducted using the UK Biobank Resource (application no. 4844).
Keywords: Neuroimaging, Depression, Polygenic Risk Score

48. A Polygenic Score for Course of Illness in ADHD

Emma Sprooten[1], Sourena Soheili-Nezhad[1], Nina Roth Mota[1], Janita Bralten[1], Paula Rovira[2], Maria Soler Artigas[2], Jan Buitelaar[1], and Barbara Franke[1]

[1]Radboud University Medical Center, [2]Universitat Autònoma de Barcelona

Background: Twin studies indicate that genetic factors contributing to ADHD onset are partly distinct from those underlying symptom persistence into adulthood. This genetic heterogeneity, where genetic effects on a diagnosis change over time, is poorly characterized so far. To address this, we derived a new polygenic score that captures genetic variation underlying course of illness in ADHD.
Methods: Two polygenic scores were calculated for each individual in a longitudinal cohort of patients with ADHD (NeuroIMAGE). First, a standard "polygenic onset score" was based on the children-only ADHD case-control GWAS of the psychiatric genomics consortium (excluding NeuroIMAGE). Second, a "polygenic persistence score" was derived by subtracting the children-only effect-sizes from those of a case-control GWAS of adults with persistent ADHD conducted by the IMpACT Consortium. Generalized mixed linear models were run with ADHD remission versus persistence as outcome, and both polygenic scores as predictors, adjusting for family relationships.
Results: The newly derived persistence score significantly (P=0.016) predicted NeuroImage patients who remitted at a later timepoint (N=75) from those who did not (N=297), independent of the polygenic onset score (P=0.048). The persistence score explained 1.7% of variance in remission-persistence likelihood among patients. Covarying for sex and age at last assessment did not change the results.
Conclusions: Polygenic effects on ADHD persistence over time can be isolated from genetic effects underlying ADHD onset by contrasting case-control GWAS of different age-groups. The derived polygenic persistence score can be used for stratification and combined with other clinical and biological measurements to give new insights in the processes behind course of illness in ADHD.
Supported By: Hypatia Fellowship
Keywords: Course of Illness, Polygenic Risk, ADHD, Remission, Adult ADHD

SYMPOSIUM
Central and Peripheral Actions of Insulin: Implications for Psychiatric Disorders

3:00 p.m. - 5:00 p.m.
Chair: Zachary Freyberg
Co-Chair: Michael McCarthy

49. Central Insulin Resistance: Potential Mechanistic Link for Neuropsychiatric Disorders

Lawrence Reagan[1]

[1]University of South Carolina School of Medicine/WJB Dorn VAMC

Background: It is becoming increasingly clear that the complications of insulin resistance (IR) extend to the central nervous system (CNS) and include increased risk for the development of neuropsychiatric disorders. A major goal of our ongoing studies is to more selective identify the mechanistic links between brain IR and neuropsychiatric disorders.
Methods: Our current studies are using a lentivirus approach to examine the effects of hippocampal-specific IR on neuroplasticity measures, including cognitive/behavioral measures.
Results: Hippocampal-specific insulin resistance, independent of peripheral IR, elicits deficits in stimulus-evoked LTP that are accompanied by decreases in the expression and phosphorylation state of hippocampal glutamate receptor subunits, as well as decreases in neurotrophic factor expression. Hippocampal-specific IR also induces deficits in morphological plasticity, including decreases in neurogenesis in the dentate gyrus, as well as synaptic re-organization and dendritic atrophy of hippocampal neurons. These neuroplasticity deficits likely contribute to deficits in spatial learning and memory, as well as development of depressive-like behaviors.

These studies were performed in adult male rats, with at least 12 rats/group. Statistical analysis: simple comparisons were analyzed using a two-tailed unpaired t-test. For multiple

comparisons, two-way ANOVA followed by Bonferroni post hoc test. Significance was set at $P < 0.05$.
Conclusions: These observations support the concept that CNS insulin activity acts independently of peripheral insulin to facilitate hippocampal synaptic plasticity. Additionally, these findings support the concept that hippocampal IR, alone and in combination with peripheral IR, are responsible for the neurological complications observed in patients with metabolic disorders that include increased risk of neuropsychiatric disorders.
Supported By: Department of Veterans grant numbers IO1 BX001804 and I21 BX002085
Keywords: Major Depression, Insulin-Resistance, Hippocampus, Neuroinflammation, Neuroplasticity

50. New Roles for Peripheral Dopamine D2-Like Receptors in Antipsychotic Drug-Induced Metabolic Dysfunction

Zachary Freyberg[1], Zachary Farino[1], Travis Morgenstern[2], Antonella Maffei[2], Matthias Quick[2], Alain De Solis[2], Pattama Wiriyasermkul[2], Robin Freyberg[1], Despoina Aslanoglou[1], Denise Sorisio[1], Benjamin Inbar[2], R. Benjamin Free[3], Prashant Donthamsetti[2], Eugene Mosharov[2], Christoph Kellendonk[2], Gary Schwartz[4], David Sibley[3], Claudia Schmauss[2], Lori Zeltser[2], Holly Moore[2], Paul Harris[2], and Jonathan Javitch[2]

[1]University of Pittsburgh, [2]Columbia University, [3]National Institutes of Health, [4]Albert Einstein College of Medicine

Background: Antipsychotic drugs (APDs) are some of the most widely used medications today. However, APDs also share prominent metabolic side effects, including weight gain, insulin resistance, and increased diabetes risk. The unifying property of all APDs is their blockade of dopamine D2-like receptors including D2 (D2R) and D3 receptors (D3R), suggesting the receptors' roles in metabolic disturbances. Besides brain expression, D2R and D3R are expressed in insulin-secreting pancreatic beta cells. Thus, we investigated D2R/D3R-mediated effects on glucose-stimulated insulin secretion (GSIS) and APD action directly in mouse pancreatic islets and INS-1E cells, a well-established rodent beta cell-derived cell line.
Methods: INS-1E cells and C57Bl/6J mouse pancreatic islets were cultured in RPMI 1640. Cells or islets were glucose-starved and then stimulated with 20 mM glucose +/- additional drugs. Secreted insulin was measured following drug incubation. Glucose-stimulated DA secretion was measured after cells were pre-incubated with 30 micromolar L-DOPA and quantified by HPLC.
Results: We show that beta cells rely on L-DOPA uptake to generate intracellular DA stores and glucose stimulation enhances subsequent DA release. We demonstrate that beta cell D2R and D3R work together to modulate glucose-stimulated insulin and DA secretion. Significantly, we describe the first beta cell-selective D2R KO mouse to elucidate D2R's specific contributions to beta cell function without confounds from D2R deletion in metabolically-relevant CNS regions.
Conclusions: Our work reveals that peripheral DA and D2R/D3R receptors play important metabolic roles via inhibitory effects on GSIS. By blocking pancreatic D2R/D3R, APDs override this negative feedback mechanism, providing a mechanism for their clinically-relevant metabolic disturbances.
Supported By: DoD Investigator-Initiated Award PR141292; The Pittsburgh Foundation Rising Star Award
Keywords: Dopamine, Antipsychotics, Diabetes, Insulin, Dopamine D2 Receptors

51. D2 Dopamine Receptors Alter Circadian Rhythms in Pancreatic Islet Cells: Implications for the Metabolic Side Effects of Antipsychotic Drugs

Danielle Chipchura[1], Heather Wei[1], Zachary Freyberg[2], Susan Leckband[1], and **Michael McCarthy**[3]

[1]VA San Diego Healthcare System, [2]University of Pittsburgh, [3]UCSD School of Medicine

Background: Antipsychotic drugs cause metabolic abnormalities through the antagonism of D2 dopamine receptors (D2R). In addition to functions in the brain, D2Rs negatively regulate insulin release in pancreatic beta cells. Beta cells have circadian rhythms, and insulin release is temporally regulated, with peaks during the day and lowest at night. Antipsychotics are commonly dosed at night. The resulting inhibition in overnight D2R activity may disrupt 24-h rhythms in insulin release and exacerbate metabolic dysfunction. The cellular mechanism of this process could involve disruption of circadian rhythms in beta cells.
Methods: We examined clinical data from patients treated over approximately 1 year with aripiprazole (ARPZ), a D2R partial agonist. To identify effects of timing on metabolic risk, we identified cases treated either in the morning (n=90) or bedtime (n=53), and compared hemoglobin A1c, and six secondary metabolic parameters across groups. Next, we examined the effects of D2R antagonists and agonists on circadian gene expression and insulin release in INS1E cells.
Results: Patients treated with ARPZ at night had a significant decrease in HDL cholesterol ($p<0.05$), while patients who took ARPZ in the morning had no change. The D2R agonists Bromocriptine and L-DOPA potently reduced the amplitude of gene expression rhythms in INS1E cells. Sulpiride, a D2R antagonist reversed these effects. INS1E cells show rhythmic insulin release. Sulpiride disrupts the temporal release pattern, and increased trough levels of insulin.
Conclusions: The metabolic liability of antipsychotic drugs could be due in part to effects on D2R and subsequent disruption of circadian rhythms pancreatic beta cells.
Keywords: Circadian Rhythms, Dopamine, Antipsychotics, Insulin-Resistance, METABOLIC Side Effects

52. Antipsychotics Perturb Glucose Homeostasis by Inhibiting Hypothalamic KATP Channel Activation

Chantel Kowalchuk[1], Laura Castellani[1], Celine Teo[1], Pruntha Kanagasundaram[1], William Brett McIntyre[2], Gary Remington[1], Adria Giacca[3], and **Margaret Hahn**[1]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]McMaster University, [3]University of Toronto

Background: Antipsychotics are associated with high rates of obesity and type 2 diabetes. Moreover, these agents can immediately and independently of weight gain induce insulin resistance via the central nervous system (CNS). We recently demonstrated that olanzapine abolishes the ability of a CNS insulin infusion to restrain hepatic glucose production and to suppress feeding in rodents. Across rodents and humans, the ATP-sensitive potassium (KATP) channel is a critical metabolic sensor downstream of hypothalamic insulin signaling in maintenance of energy and glucose homeostasis. Here, we examined whether olanzapine inhibits central KATP channels to disrupt glucose metabolism.
Methods: Sprague Dawley rats underwent pancreatic euglycemic clamps to measure glucose-kinetics. Rats were pre-treated with a subcutaneous injection of olanzapine (OLA-3mg/kg) or vehicle (VEH). A continuous intracerebroventricular (ICV) infusion of the KATP channel activator Diazoxide (DIAZ-1.5nmol) or VEH was administered throughout the clamp. Based on lack of effects of OLA alone (in absence of a central energy stimulus) on glucose kinetics during pancreatic clamps, VEH-VEH and OLA-VEH groups were pooled into a single control group. Groups included (central-peripheral): VEH-VEH and VEH-OLA (controls) (n=8); DIAZ-VEH (n=10); DIAZ-OLA (n=6).
Results: The glucose infusion rate (GIR) needed to maintain euglycemia during the clamp, a measure of whole body insulin sensitivity, was higher in DIA-VEH rats compared to VEH-VEH/VEH-OLA controls (2.58 mg/kg/min +/- 0.96) (p=0.0009), while DIA-OLA (5.65 mg/kg/min +/- 1.08) rats had a decreased GIR compared to DIA-VEH (12.20 mg/kg/min +/- 2.11) (p=0.0254).
Conclusions: Olanzapine may be acting via hypothalamic KATP channel inhibition to perturb whole body insulin sensitivity.
Supported By: Banting and Best Diabetes Centre New Investigator Award
Keywords: Antipsychotics, Diabetes Mellitus, Central Insulin Action, Insulin Resistance, Schizophrenia

SYMPOSIUM
New Biological Research on Trauma-Related Dissociation

3:00 p.m. - 5:00 p.m.
Chair: Lauren Lebois
Co-Chair: Milissa Kaufman

53. Potential Biological Mechanisms of Sex-Dependent Associations Between Peritraumatic Dissociation and Risk for Posttraumatic Stress Disorder

Jennifer Stevens[1], Vasiliki Michopoulos[2], Lauren Lebois[3], Rebecca Hinrichs[2], Sterling Winters[2], Isaac Galatzer-Levy[4], Katharina Schultebraucks[5], Eléonore Beurel[6], Charles Nemeroff[7], and Kerry Ressler[3]

[1]Emory University School of Medicine, [2]Emory University, [3]Harvard - McLean, [4]Mindstrong Health, New York University School of Medicine, [5]New York University Langone Medical Center, [6]Miller School of Medicine, University of Miami, [7]Dell Medical School at The University of Texas at Austin

Background: Prospective cohort studies indicate that peritraumatic dissociation may partly explain women's greater risk for posttraumatic stress disorder (PTSD; estimated to affect twice as many women as men), but the underlying biological risk mechanisms remain unclear.
Methods: N=83 women and N=103 men were enrolled within 24 hours of trauma and completed the Peritraumatic Dissociative Experiences Questionnaire (PDEQ). Blood samples for steroid hormone and inflammatory cytokine panels were gathered 3.8±0.4 hours post-trauma. PTSD symptoms were assessed 1, 3, 6, and 12 months post-trauma and modeled using latent growth mixture modeling.
Results: Consistent with prior studies, women were more likely to be assigned to a chronic non-remitting PTSD symptom trajectory than men, p=.04. Women and men did not differ in levels of peritraumatic dissociation, but dissociation was differentially associated with the chronic PTSD symptom trajectory in women (r=.28, p=.02) versus men (r=.18, p=.14). Dissociation was negatively associated with interleukin 4 in women (r=-.44, p-FWE=.05) but not men (r=-.33, p-FWE>.05). Women with lower estradiol and higher cortisol levels showed greater peritraumatic dissociation (high vs. low estradiol: t=-2.2, p=.03, M=13.5% difference in dissociation; high vs. low cortisol: t=2.6, p=.01, M=15.6% difference).
Conclusions: Findings suggest that peritraumatic dissociation predicts poorer long-term mental health outcomes in women but not men. In women, dissociation coincided with lower estradiol and greater cortisol, which may reflect a greater HPA-axis response to trauma. Surprisingly, dissociation was not linked with a corresponding increase in inflammatory cytokines (typically stimulated by HPA activation). Women experiencing peritraumatic dissociation may show abnormal interactions between the HPA-axis and immune system.
Supported By: R01 MH094757; K01 MH102415
Keywords: PTSD - Posttraumatic Stress Disorder, Longitudinal Study, Inflammation, Dissociation, Sex Differences

54. Sensory Overload and Imbalance: Resting-State Vestibular Connectivity in PTSD and its Dissociative Subtype

Sherain Harricharan[1], Andrew A. Nicholson[1], Maria Densmore[1], Jean Théberge[1], Margaret C. McKinnon[2], Richard W.J. Neufeld[1], and Ruth A. Lanius[1]

[1]Western University, [2]McMaster University

Background: The vestibular system integrates interoceptive and exteroceptive signals to monitor one's bodily orientation in space. Post-traumatic stress disorder (PTSD) involves typically alterations in interoceptive and bodily self-awareness evidenced by symptoms of hyperarousal and emotional detachment. These symptoms may be associated with disruptions in vestibular multisensory processing between the brainstem (vestibular nuclei) and key vestibular cortical regions [parieto-insular vestibular cortex (PIVC), dorsolateral prefrontal cortex

(dlPFC)]. Accordingly, this study examined functional connectivity of the vestibular system in PTSD and its dissociative subtype (PTSD+DS).
Methods: Using SPM12 and PickAtlas, we implemented a seed-based approach to examine resting-state vestibular nuclei functional connectivity patterns among PTSD (n=60), PTSD+DS (n=41) and healthy controls (n=40).
Results: Decreased vestibular nuclei functional connectivity with the PIVC and the dlPFC was observed in PTSD+DS as compared to PTSD and healthy controls. In addition, PTSD showed decreased vestibular nuclei connectivity with the posterior insula as compared to controls.
Conclusions: These findings suggest that PTSD patients display differing multisensory integration patterns that may compromise vestibular function and contribute to the neurophenomenology of the unique symptom profiles observed in PTSD and its dissociative subtype. Further research will be critical to identify treatments that target vestibular dysfunction in relation to PTSD and PTSD+DS.
Supported By: Canadian Institutes of Health Research [grant numbers 137150, 97914].
Keywords: PTSD - Posttraumatic Stress Disorder, Dissociation, Functional Neuroimaging, Vestibular System

55. Large-Scale Brain Network Architecture Changes Associated With a Trauma-Related Dissociative Syndrome

Lauren Lebois[1], Meiling Li[2], Jonathan Wolff[1], Danhong Wang[2], Liz Grinspoon[1], Sherry Winternitz[1], Jianxun Ren[2], Justin Baker[1], Kerry Ressler[1], Hesheng Liu[2], and Milissa Kaufman[1]

[1]McLean Hospital, [2]Harvard Medical School & Massachusetts General Hospital

Background: Seminal research has identified differential brain activation in individuals with PTSD and depersonalization/derealization symptoms in task-based and seed-based resting state functional connectivity analyses. However, trauma-related dissociation encompasses a wider array of symptoms. Furthermore, interrogation of large-scale intrinsic brain network connectivity related to the full spectrum of dissociative experiences could reveal a novel network of brain abnormalities.
Methods: To examine this, women with histories of childhood abuse, PTSD, and various levels of dissociative symptoms including some with dissociative identity disorder, completed the Multidimensional Inventory of Dissociation (MID), and underwent an fMRI protocol, which included ~22 min of BOLD under both resting state and task conditions. Analysis of functional connectivity was estimated using an individualized parcellation approach. Support vector regressors were then trained using a subset of network edges to estimate participant MID, using a leave one subject out approach (n=1000 permutations), yielding patterns of brain network changes associated with dissociation scores at the individual participant level.
Results: We found that MID severe dissociation scores could be estimated from weighted, individualized functional connectivity, after controlling for motion, age, and PTSD severity (N=44, r=0.489, p=0.002, 1000 permutation tests), whereas models performed at chance using a conventional group-based network parcellation.
Conclusions: Findings indicate that dissociative symptoms have a neurobiological substrate, distinct from PTSD or trauma-history, and that network connectivity can be used to estimate dissociation severity. Based on the pattern of network edges that allowed for this prediction, we surmise that dissociation may be caused by changes in between-network connections primarily involving the default and salience networks.
Supported By: R21MH112956, F32MH109274
Keywords: PTSD - Posttraumatic Stress Disorder, Dissociation, Brain Imaging, fMRI, Intrinsic Connectivity Networks

56. Aiding the Diagnosis of Dissociative Identity Disorder: A Pattern Recognition Study of Brain Structural Biomarkers

Antje Reinders[1], Andre Marquand[2], Yolanda Schlumpf[3], Sima Chalavi[4], Eline Vissia[5], Ellert Nijenhuis[6], Paola Dazzan[1], Lutz Jäncke[3], and Dick J. Veltman[7]

[1]Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, [2]Donders Institute for Brain, Cognition and Behaviour, Radboud University, [3]University of Zurich, [4]KU Leuven, [5]Top Referent Trauma Centrum, Ermelo, [6]Clienia Littenheid AG, Private Clinic for Psychiatry and Psychotherapy, [7]VU University Amsterdam

Background: A diagnosis of Dissociative identity disorder (DID) is controversial and prone to under- and misdiagnosis. From the moment of seeking treatment for symptoms to the time of an accurate diagnosis of DID individuals received an average of four prior other diagnoses and spent seven years, with reports of up to twelve years, in mental health services.
Aim: To investigate whether data-driven pattern recognition methodologies applied to structural brain images can provide biomarkers to aid DID diagnosis.
Methods: Structural brain images of 75 participants were included; 32 female individuals with DID and 43 matched healthy controls. Individuals with DID were recruited from psychiatry and psychotherapy outpatient clinics. Probabilistic pattern classifiers were trained to discriminate cohorts based on measures of brain morphology.
Results: The pattern classifiers were able to accurately discriminate between individuals with DID and healthy controls with high sensitivity (72%) and specificity (74%) on the basis of brain structure. These findings provide evidence for a biological basis for distinguishing between DID affected and healthy individuals.
Conclusions: We propose a pattern of neuroimaging biomarkers that could be used to inform the identification of individuals with DID from healthy controls at the individual level. This is important and clinically relevant because the DID diagnosis is controversial and individuals with DID are often misdiagnosed. Ultimately, the application of pattern recognition methodologies could prevent unnecessary suffering of individuals with DID because of an earlier accurate diagnosis, which will facilitate faster and targeted interventions.

Supported By: This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. A.A.T.S. Reinders was supported by the Netherlands Organization for Scientific Research (www.nwo.nl), NWO-VENI grant no. 451-07-009. S. Chalavi is supported by a David Caul graduate research grant from the International Society for the Study of Trauma and Dissociation (ISSTD) (http://www.isst-d.org/about/awards.htm). Andre F. Marquand gratefully acknowledges support from the King's College London Centre of Excellence in Medical Engineering, funded by the Wellcome Trust and EPSRC and from a VIDI fellowship from the NWO (grant no. 016.156.415).
Keywords: PTSD - Posttraumatic Stress Disorder, Dissociative Disorder, Structural MRI, Pattern Classification

SYMPOSIUM
Elucidating the Risk of Depression in Youth and Adolescence: From Suicidality to Resilience
3:00 p.m. - 5:00 p.m.
Chair: Madhukar Trivedi

57. Dysfunctional Th2-Cell Mediated Adaptive Immune Response is Associated With Suicide Behavior in Adolescents and Young Adults

Manish Jha[1], Madhukar Trivedi[2], Ling Cai[2], Jennifer Furman[2], Tracy Greer[2], Jennifer Hughes[2], and Taryn Mayes[2]

[1]Icahn School of Medicine at Mount Sinai, [2]U.T. Southwestern Medical Center

Background: Aberrant immune response is implicated in the pathophysiology of suicide behavior. In this report, we conducted an exploratory analysis of immune profile differences between adolescent and young adult participants at risk of major depressive disorder (MDD; at-risk) and adolescents with diagnosis of MDD plus recent suicide behavior/severe ideation (suicide behavior).
Methods: Plasma samples from at-risk (n=72) and suicide behavior (n=38) participants (ages 10-25 years) were assayed for chemokines and T helper (Th)1- [Interferon gamma (IFN-γ) and interleukin (IL) 2], Th2- (IL-4 and IL-10), and non-T- (IL-1β, IL-6, tumor necrosis factor alpha or TNF-α) cell-related cytokines using a Bio-Rad multiplex (Bio-Plex Pro Human Chemokine 40-plex Panel) assay. Cytokine and chemokine levels (after log transformation of variables with skewed distribution) were compared between the two groups.
Results: Only levels of IL-4 (adjusted p=0.0026) differed significantly between the two groups after controlling for age, gender, body mass index, race and ethnicity and false discovery rate (FDR) correction. Participants with suicide behavior had lower IL-4 (median=16.7 ng/ml, IQR=7.9) levels than those at-risk (median=27.7 ng/ml, IQR=18.4). Levels of IL-10 were also lower in those with suicide behavior (median=18.1 ng/ml, IQR=8.9) than those at risk (median=23.3 ng/ml, IQR=8.2, unadjusted p=0.049). However, this was not significant after FDR correction (p=0.39). There was no significant association between self-reported depression severity and either IL-4 (p=0.45) or IL-10 (p=0.46) levels.
Conclusions: Adolescent and young adult patients with recent suicide behavior exhibit lower Th2-cell related cytokines, suggesting an autoimmune process. Targeting inflammation presents a promising avenue to reduce suicide behavior.
Supported By: Center for Depression Research and Clinical Care, UT Southwestern; Hersh Foundation; Jordan Harris Foundation
Keywords: Immune Dysfunction, Major Depressive Disorder (MDD), Interleukin-4, Depression and Suicide, Suicidal Behavior

58. Child Abuse, Depression, and Methylation in Myelin-Related Genes

Joan Kaufman[1], Janitza Montalvo-Ortiz[2], Nicholas Wymbs[3], Catherine Orr[4], Matthew D. Albaugh[4], Kerry O'Loughlkin[4], Hannah Holbrook[4], Robert Althoff[4], Hugh Garavan[4], Stewart Mostofsky[3], Joel Gelernter[5], and James Hudziak[4]

[1]Kennedy Krieger Institute/Johns Hopkins Medical Institute, [2]Yale School of Medicine/VA CT Healthcare Center, [3]Kennedy Krieger Institute, [4]University of Vermont, [5]Yale University School of Medicine

Background: In postmortem brain tissue studies of psychiatrically healthy controls and depressed individuals who died by suicide, with or without a history of severe child abuse, through unbiased genome-wide DNA methylation analyses it was suggested that vulnerability to depression and suicide in individuals with a history of child abuse is mediated by epigenetic changes in the myelin related genes LINGO3 and POU3F1. To test the translational applicability of these postmortem results we examined peripheral markers of LINGO3 and POU3F1 in youth participating in a study examining risk and resilience in maltreated children.
Methods: The sample included 141 children (Ages: 8-15 years old; X=11.4, SD=1.9). DNA specimens were derived from saliva samples and processed using the Illumina 450K beadchip. A subset of the children (N=46) with DNA specimens also had neuroimaging data, with rsfMRI data processed using SPM12 and custom MATLAB scripts, DKI data processed with FSL and DKE for tensor estimation.
Results: After controlling for demographic factors, cell heterogeneity, and three principal components, maltreatment history and methylation in LINGO3 and POU3F1 significantly predicted depression in the children (p<.05, all comparisons). In terms of the imaging data, increased LINGO3 methylation was associated with reduced functional connectivity between the left amygdala and right mPFC (FEW correction, p<.05), and increased POU3F1 methylation was associated with reduced right uncinate fasciculus fractional anisotropy (p<.03).

Conclusions: The data presented support a role of myelin-related genes in the pathophysiology of depression in maltreated children and suggest the potential utility of LINGO3 and POU3F1 as biomarkers for stress-related disorders.
Supported By: Zanvyl and Isabelle Krieger Fund (JK), the NIH R01MH098073 (JK, JH), R01 MD011746-01 (JK); the National Center for Posttraumatic Stress Disorder – Veterans Affairs Connecticut (JG, JK); the VA Cooperative Study #575B, Genomics of Posttraumatic Stress Disorder in Veterans (JG, JK); and the Biological Sciences Training Program through 5T32 MH14276 (JLMO).
Keywords: Child Abuse, Epigenetics, Suicide, Depression, Brain Magnetic Resonance Imaging (MRI)

59. LCM-Seq: Pyramidal Neuron Transcriptomic Profiling in the Prefrontal Cortex of Abused Suicides

Daniel Almeida[1], Gang Chen[1], Jean-Francois Theroux[1], Zahia Aouabed[1], Maria Antonietta Davoli[1], Naguib Mechawar[1], and **Gustavo Turecki**[1]

[1]McGill University

Background: The transcriptome of a cell constitutes an essential piece of cellular identity and accounts for the heterogeneity of cell types within the mammalian brain. Thus, while some studies have investigated transcriptomic alterations underlying the neurobiology of childhood abuse and suicide, the use of bulk-tissue homogenates may have masked their ability to determine cell-type specific molecular dysfunctions. Here we employ a cell type specific investigation of transcriptomic alterations, in prefrontal layer V pyramidal neurons, associated specifically with a history of childhood abuse (CA).
Methods: Laser captured microdissection was used to isolate prefrontal layer V pyramidal neurons from post-mortem human brain. Subject groups included individuals who died by suicide with and without a history of severe CA and non-psychiatric controls. RNA sequencing libraries were constructed using the SMARTseq v4 cDNA synthesis kit followed by Illumina indexing. Fifty libraries were sequenced on the HiSeq 4000 platform using PE 100bp sequencing at a depth of ~40M reads per subject.
Results: We achieved a mapping efficiency of ~80% and captured a wide distribution of transcripts. Differential gene expression analysis revealed 44 upregulated and 77 downregulated protein coding genes in abused suicides compared to controls. Weighted Gene Co-Expression Network Analysis identified a module negatively associated with CA. Gene ontology analysis of this module resulted in terms related to nervous system development. Within the module, 9 of the most interconnected hub genes were amongst those differentially expressed in abused suicides.
Conclusions: By employing LCM RNA sequencing we were able to identify pyramidal specific alterations associated with a history of CA.
Supported By: CIHR Foundation Grant
Keywords: Laser Capture Microdissection, Human Postmortem Brain, Childhood Adversity, Depression and Suicide, Transcriptomics

60. Impact of Childhood Trauma on Depression Features and Immunometabolic Dysregulation at Adult age

Brenda Penninx[1]

[1]Amsterdam UMC

Background: Childhood trauma is a profound risk factor for depression in adult life. However, precise underlying neurobiological dysregulations for this impact remain unclear. We examined the impact of childhood trauma on depression features, various stress system and metabolic dysregulations and biological aging.
Methods: Data were used from 2981 respondents (652 healthy controls, 2329 patients) of the longitudinal Netherlands Study of Depression and Anxiety. Childhood trauma was based on a face-to-face interview examining emotional, physical and sexual neglect and/or abuse. Depression characteristics include symptomatology and 6-year course. Also, serum inflammation and metabolic syndrome markers, and sequence-based genome-wide epigenetic aging were assessed.
Results: Emotional neglect (38.3%) and psychological abuse (25.2%) were the most prevalent types of childhood trauma, but also sexual abuse (18.5%) and physical abuse (14.4%) were common. Persons with childhood trauma reported higher depression severity, more comorbid anxiety, suicidal ideation and attempts (all $p<.001$). Depressed patients with a higher childhood trauma score also reported higher inflammation markers (CRP: $b=0.07$, $p=.01$; IL-6: $b=0.08$, $p=.02$), higher metabolic syndrome abnormalities ($b=0.04$, $p=.04$) which were mainly driven by higher waist circumference, triglycerides and lower HDL cholesterol. Finally, more advanced epigenetic aging ($b=0.09$, $p=.02$) was found among those with higher childhood trauma. These biological dysregulations were found to be linked to more chronicity of depression over six years.
Conclusions: Childhood trauma results in more immunometabolic dysregulation and more advanced biological aging, which may partly contribute to the more profound chronic and severe depression profile seen in those with early-life adversity.
Supported By: Dutch Scientific Organization (NWO)
Keywords: Depression, Childhood Trauma, Inflammation, Metabolic Dysregulation, Epigenetic Aging

SYMPOSIUM
Innovative Analytical Tools and Methodologies for Improving Psychiatric Disorder Classification

3:00 p.m. - 5:00 p.m.
Chair: Poornima Kumar

61. Defining and Dissociating Transdiagnostic Psychiatric Traits

Claire Gillan[1] and Xing Fang Tricia Seow[1]

[1]Trinity College Dublin

Background: Prior work has suggested that a recently identified 'social-withdrawal' dimension of psychopathology may be associated with an enhancement in model-based planning, which

is a core deficit associated with OCD and more broadly, 'compulsivity'. The present study tested this idea using a task that dissociates one's ability to form and update a meta-model of the environment from the extent to which that model is used to guide choice.
Methods: We collected data from 92 individuals and related their cognitive profiles to self-report psychiatric symptoms, either expressed in terms of their classic DSM distinctions, or as trans-diagnostic dimensions. We tested the hypothesis that (i) the latter approach would yield stronger results and that (ii) we would observe a double dissociation between compulsivity and social withdrawal in terms of how they are able to use a meta-model to guide behavior.
Results: Consistent with prior work, OCD symptoms were related to a tendency to shift behavior excessively in response to noise ($p<.01$), and also lower behavioral sensitivity to state changes ($p<.001$). We found a trend for social anxiety in the opposite direction ($p<.001$ and $p<.01$, respectively). When we refactored subjects' data into transdiagnostic dimensions using previously defined factor loadings, these effects became significantly stronger (all $p<.001$).
Conclusions: Compulsivity is linked to a deficit in the ability to use formal models of the world to guide behavior, while an enhancement was observed for those high in social-withdrawal. These data highlight a rare instance where enhanced cognitive performance may put one at risk for a mental health disorder.
Supported By: Wellcome
Keywords: Compulsivity, Social Anxiety Disorder, Transdiagnostic, Model-Based and Model-Free Decisions, Confidence

62. Multimodal Assessment of Frontostriatal Circuitry as a Tool for Parsing Motivational Impairments

Alexis Whitton[1], Poornima Kumar[2], Michael Treadway[3], Daniel Foti[4], Ashleigh Rutherford[5], Manon L. Ironside[5], Fei Du[5], and Diego Pizzagalli[5]

[1]The University of Sydney, [2]Harvard Medical School, [3]Emory University, [4]Purdue University, [5]McLean Hospital/Harvard Medical School

Background: Although highly correlated, different motivational deficits do not respond equally to the same interventions, suggesting that they have separable pathophysiological underpinnings. This talk will highlight the ways in which multimodal assessment of frontostriatal circuitry can improve our understanding of the divergent mechanisms underpinning different motivational disturbances.
Methods: New findings from two studies will be presented, including data from healthy controls, individuals with major depressive disorder and individuals with bipolar disorder. Frontostriatal circuitry was measured using a multi-unit approach that incorporated measures of dorsal anterior cingulate cortex prediction errors (dACC PEs), ventral striatal reward prediction errors (VS RPEs) and ratios of medial prefrontal cortex glutamate/glutamine. Hierarchical regression was used to determine whether these units of analysis explained significant variance across five different motivational domains: reward learning, self-reported state anhedonia, trait pleasure, trait impulsivity, and clinician-rated mania severity.
Results: In controls ($n=32$), better reward learning was predicted by greater differentiation of dACC PEs across reward contexts (Δ dACC PE; $p=0.02$) and stronger right VS RPEs ($p=0.01$). Elevated state anhedonia, but not trait pleasure or impulsivity, was predicted by blunted Δ dACC PEs ($p=0.02$). In the clinical sample ($n=80$), elevated state anhedonia, but not mania severity, trait pleasure or impulsivity, was predicted by reduced Δ dACC PE, regardless of diagnosis ($p=0.04$).
Conclusions: This work shows that divergent neurobiological mechanisms contribute to individual differences in reward learning and state anhedonia, relative to mania, trait pleasure and impulsivity. The utility of these methods for parsing the pathophysiology of motivational deficits in other diseases (e.g., dementia) will be discussed.
Supported By: NIMH R01MH101521; NIMH R37MH068376; NHMRC APP1110773; NARSAD
Keywords: Motivation, Reward Learning, Anhedonia, Frontostriatal Circuits, Mood Disorders

63. Multimodal Fusion: An Effective Approach to Identify Translational Biomarkers of Psychiatric Disorders

Jing Sui[1] and Vince D. Calhoun[2]

[1]Institute of Automation, Chinese Academy of Sciences, [2]The Mind Research Network & The University of New Mexico; Yale University, School of Medicine

Background: Recent years have witnessed a rapid growth of multimodal imaging approaches to brain imaging. It is becoming increasingly clear that multi-modal fusion is able to provide more information for individual subjects by exploiting the rich multimodal information that exists, rather than an analysis of each modality alone. An increasing number of studies are using multimodal data in the context of the study of mental illness. However, the number of studies that do true multimodal fusion (i.e. capitalizing on joint information among modalities) is still remarkably small given the known benefits.
Methods: In this talk, we start by introducing the basic reasons why multimodal data fusion is important and what it can do and help compensate for imperfect brain imaging studies. Then we introduce several effective fusion approaches, such as multimodal MRI fusion with reference, and individualized prediction with ensemble multimodal features.
Results: We provide examples of using the multimodal information to 1) guide detection of potential cognitive neuromarkers of schizophrenia in 3 sites and 2) to realize individualized prediction of ECT treatment outcome of major depression in 3 sites. 3) to differentiate first-episode of major depression and bipolar disorders by machine learning at ~90% accuracy.
Conclusions: Multimodal fusion is an effective tool that provide more clues by exploiting links among enriched types of imaging, cognitive and behavioral information for individuals, which will benefit identification of potential imaging biomarkers for psychiatric disorders.
Supported By: NSFC, NIH R01
Keywords: Treatment Predictions, Multimodal Fusion, Schizophrenia, Mood Disorders, MRI

64. Identifying Depressive Biotypes Based on Structural Covariance Networks Using Clustering Algorithms

Poornima Kumar[1], Lisa Nickerson[1], and Diego Pizzagalli[1]

[1]McLean Hospital Harvard Medical School

Background: Major depressive disorder (MDD) is a heterogeneous syndrome with several hundred unique combinations of symptoms. However, the underlying neurobiology of this heterogeneity remains poorly understood. A promising approach is to cluster individuals based on their shared biology and map them onto clinical phenotypes. Assessing structural covariance grey matter networks is a useful approach, as they provide information about the cortical organization in the brain.
Methods: 3T structural MRI data were collected from 104 MDD unmedicated patients and 194 healthy controls. Grey matter volumetric maps were generated using FSL-VBM. MELODIC was used to identify independent components that reflect sources of shared spatial covariance. We then used K-means clustering on these structural covariance networks to discover clusters of patients, by assigning them to nested subgroups with similar patterns of structural covariance alterations. Follow-up tests were conducted to identify the clinical phenotypes differentiating the emerged clusters.
Results: Across the entire group, we identified 25 structural covariance networks that were spatially meaningful and relevant to MDD, including the anterior and posterior dorsal medial, ventromedial prefrontal, basal ganglia, amygdala/hippocampal networks. K-means clustering revealed two unique MDD subgroups that had significantly different clinical profiles. Individuals in subgroup one were more anhedonic than in subgroup two. Other differences in clinical symptoms will be discussed.
Conclusions: By reducing diagnostic heterogeneity, clustering could be leveraged to parse out the heterogeneity of MDD solely on the basis of structural networks. I will discuss further on capitalizing machine learning approaches to map clinical phenotypes with the underlying biology.
Supported By: NIMH ROI, NIMH R21, NARSAD
Keywords: Machine Learning, Depression., Structural Covariance, K-Means Clustering

3:00 p.m. - 5:00 p.m.

SYMPOSIA
Transdiagnostic Theta Burst Stimulation – The Future is Now

3:00 p.m. - 5:00 p.m.
Chair: Noah Philip
Co-Chair: Rebecca Price

65. The Frontal Pole: A New Transdiagnostically Relevant Target to Change for Brain Stimulation Research

Colleen Hanlon[1]

[1]Medical University of South Carolina

Background: Cue-reactivity is a powerful predictor of relapse among multiple addiction phenotypes. We have performed a series of sham-controlled, multiday clinical trials which have evaluated the efficacy of continuous theta burst stimulation as a tool to dampen cue reactivity in cocaine users, alcohol users, smokers, and compulsive eaters.
Methods: 76 treatment seeking individuals (cocaine, alcohol, nicotine users, compulsive eaters) participated in 1 of 4 clinical trials wherein they received a functional MRI assessment of cue-reactivity (tailored to their drug of choice) before and after a 5- or 10-day course of real or sham continuous theta burst stimulation (120% RMT, 3600 pulses;132 fMRI scans total). Brain reactivity to cues was quantified in apriori defined nodes of the salience and executive control networks. Multiple regression was used to assess the impact of time, treatment, and addiction-phenotype on cTBS related changes in cue-reactivity.
Results: There was a significant interaction between treatment and time in the dorsolateral prefrontal cortex ($F(1,142)=7.38;p=0.007$), vMPFC ($F(1,142)=6.43;p=0.012$), Insula ($F(1,142)=6.97;p=0.009$), and ACC ($F(1,142)=5.42;p=0.023$). There was no significant effect of addiction-phenotype on these regions other than the ACC ($F=5.24;p=0.023$) wherein the effect was largest in the alcohol users. There was also no significant interaction with the Occipital cortex response to cues (control region).
Conclusions: These data demonstrate, for the first time, that a multiday course of real versus sham cTBS to the left frontal pole has a significant effect cue-reactivity in multiple classes of patients. The feasibility and efficacy this approach opens a de novo therapeutic possibility for changing cue reactivity with TBS.
Funding Source: R01DA036617, R01DA044471, P50AA010761
Keywords: TMS, Brain Imaging, fMRI, Addiction, Alcohol

66. Theta-Burst Stimulation in Major Depression: Clinical and Neuroimaging Results

Jonathan Downar[1]

[1]University of Toronto

Background: For therapeutic rTMS, there have been recent advances in developing new stimulation protocols that may offer more rapid, more robust, or more cost-effective treatment compared to conventional protocols.
Methods: Here we will review clinical and neuroimaging findings emerging from a series of randomized controlled trials using 3-minute intermittent theta-burst stimulation (iTBS) protocols for major depression, including a non-inferiority study comparing iTBS to 37.5 min conventional stimulation (the THREE-D trial), and a more recently completed study comparing trajectories of outcome for twice-daily iTBS delivered either at a 0 minute or a 60-minute interval.
Results: Clinical results suggest that 3 min iTBS sessions match the efficacy of conventional 37.5 min 10 Hz sessions for treating major depression, and that 2 sessions of iTBS may accelerate the trajectory of improvement for a subset of patients when given at a 60-minute interval but not with a 0-minute interval. Neuroimaging predictors and correlates of improvement implicate the salience network (SN), although the

specific regions appear to be distinctly different for theta-burst than for 10 Hz rTMS, despite the similar clinical outcomes for these two treatments.
Conclusions: Theta-burst treatments appear non-inferior in efficacy to conventional rTMS protocols and offer shorter session duration, greater cost-effectiveness, and the potential to facilitate multi-site or multi-session daily regimens. These implications may enhance both the remission rates and the accessibility of rTMS in routine clinical practice.
Funding Source: Canadian Institutes of Health Research
Keywords: rTMS, Theta Burst,fMRI.

67. Stanford Accelerated Intelligent Neuromodulation Therapy for Suicidal Ideation (SAINT-SI)

Nolan Williams[1]

[1]Stanford University

Background: There are no procedures currently approved for the treatment of suicidal thinking during an inpatient psychiatric hospitalization. Recent studies have demonstrated both the safety and possible increased efficacy of accelerated iTBS (aiTBS). The shorter duration of aiTBS protocols could allow treatment to be delivered during an acute psychiatric hospitalization. The study intends to evaluate the preliminary safety and efficacy of inpatient aiTBS targeting the L-DLPFC for the treatment of suicidal thinking.
Methods: Six psychiatric inpatients with suicidal thinking completed a treatment course of aiTBS targeting the L-DLPFC. Patients received treatment on five consecutive days, each day consisting of 10 sessions of iTBS (1800 pulses per session) delivered over the course of 10 minutes at 80% resting motor threshold with 50-minute inter-session intervals. In total, patients received 50 iTBS sessions and 90,000 pulses over the course of the five days. Suicidal thinking was assessed before and immediately after with the Scale for Suicidal Ideation (SSI).
Results: The average entry SSI score was 13.3. All six patients experienced an average reduction of 86.27% in their level of suicidal thinking ($p=0.031$) with a group average of 1.83 on the SSI after completion of the 5-day course. No one experienced worsening suicidality after completing the course and there were no serious adverse events.
Conclusions: aiTBS shows promise as a highly effective treatment option for acute suicidality in psychiatric inpatients. Randomized controlled trials will be necessary to further assess the efficacy of this intervention for suicidal crises.
Funding Source: NARSAD
Keywords: TMS, Brain Stimulation, Neuromodulation, Suicidal Ideation

68. Intermittent Theta Burst Stimulation for Posttraumatic Stress Disorder

Noah Philip[1], Jennifer Barredo[2], Emily Aiken[2], Victoria Larson[2], Richard Jones[3], M. Tracie Shea[3], Benjamin Greenberg[4], and Mascha van 't Wout-Frank[1]

[1]Alpert Medical School of Brown University/Center for Neurorestoration and Neurotechnology Providence VA, [2]Center for Neurorestoration and Neurotechnology, Providence VAMC, [3]Providence VA Medical Center, [4]Butler Hospital, Providence VA Medical Center

Background: Posttraumatic Stress Disorder (PTSD) is a chronic psychiatric disorder associated with disruption in social and occupational function (SOF). Available treatments for PTSD are less effective at reducing symptoms and improving function in military veterans. To this end, transcranial magnetic stimulation represents a novel approach to PTSD. Intermittent theta-burst stimulation (iTBS) is a new, more rapid protocol with emerging data supporting efficacy in depression.
Methods: Fifty Veterans with PTSD received ten days of sham-controlled iTBS (1800 pulses/day), followed by ten unblinded sessions. Outcomes included feasibility and acceptability, changes in PTSD symptoms, SOF, and depression. Mixed models evaluated efficacy up to one-month post-treatment. We acquired resting state fMRI on an eligible subset to identify predictors of improvement.
Results: At two weeks, active iTBS significantly improved SOF (Cohen's $d=.39$; $p=.04$), and a trend towards depression ($d=-.45$; $p=.07$). Mixed model analyses indicated superiority of active iTBS on PTSD ($d=-.74$; $p<.001$), SOF ($d=.93$, $p<.001$), and depression ($d=-.47$; $p<.001$). Improvements generally occurred in the first week. Side effects were consistent with standard TMS, and blinding was successful. Clinical improvement was predicted by stronger (greater positive) connectivity within the default mode network (DMN), particularly between DMN subsystems, and by anticorrelated (greater negative) cross-network connectivity (FDR-corrected $p<.05$).
Conclusions: This is the first sham-controlled study of iTBS for PTSD. Stimulation was safe, feasible, and indicated efficacy. Clinical improvements occurred early, thus necessitating further study of optimal iTBS time course and duration. Consistent with prior TMS neuroimaging studies, these results implicate an important role of DMN and multinetwork connectivity relationships in response prediction.
Funding Source: VA RR&D I21 RX002032
Keywords: Theta Burst, Transcranial Magnetic Stimulation (TMS), PTSD - Posttraumatic Stress Disorder, Functional Brain Imaging

SYMPOSIUM
Weight Suppression and Reward Processing: Biobehavioral Predictors of Illness Maintenance in Eating Disorders

3:00 p.m. - 5:00 p.m.
Chair: Pamela Keel

69. Damned if They Do and Damned if They Don't: Weight Suppression as a Maintenance Factor in Eating Disorders

Michael Lowe[1]

[1]Drexel University

Background: Eating disordered (ED) individuals are typically in a state of weight suppression (WS; a considerable gap

between their highest past and current weight). WS predicts ED maintenance, perhaps because WS strongly predicts future weight gain, a feared outcome.
Methods: Research reviewed includes: WS as a prospective predictor of weight change; WS and current BMI as predictors of treatment outcome in AN; treatment outcome and length of disorder as a function of WS. We also report recent data on WS's relation to resting metabolic rate and leptin in those with BN.
Results: WS consistently predicts future weight gain. In AN, a WS X Current BMI interaction most consistently predicts outcome; higher WS/lower BMI showed the best outcomes, higher WS/higher BMI showed the worst outcomes; higher WS/lower BMI gained the most weight. In our recently collected data, controlling for lean body mass and study site, WS was not related to RMR. A regression found a significant inverse relationship between WS and leptin (β = -0.14, p = .01, N=89) with fat mass (β = 0.15, p < .001) controlled.
Conclusions: Existing theories of ED psychopathology primarily focus on behavioral, cognitive and affective disturbances. However, because elevated WS consistently predicts weight regain that is vigorously resisted, a vicious cycle is created that helps maintain the disorder. The absence of a WS/RMR relationship, together with an inverse WS/leptin relationship, suggests that WS may increase appetitive drive and the reward value of food, contributing to the weight gain to which weight suppressed individuals are susceptible.
Supported By: R01 MH095982
Keywords: Weight Loss, Eating Disorders, Outcome

70. Examining Reward Value in Bulimic Syndromes: Novel Insights Into Weight Suppression as a Biobehavioral Predictor of Illness Trajectory

Pamela Keel[1], Lindsay Bodell[2], Grace Kennedy[1], Jonathan Appelbaum[1], and Diana Williams[1]

[1]Florida State University, [2]University of Western Ontario

Background: Reward valuation/effort represents a centrally-mediated RDoC construct posited to influence responsiveness to a range of rewarding stimuli, increase risk for binge eating, and could explain why weight suppression (WS) predicts illness maintenance (Bodell & Keel, 2015). We hypothesized women with bulimic syndromes (BN-S) would demonstrate greater WS and reward value for non-food and food rewards and lower reward satiation compared to controls and tested associations among WS, food and non-food reward value and reward satiation.
Methods: Participants (N=76) completed clinical assessments and a novel progressive ratio (PR) task for 2 min of playing Angry Birds in both a fasted and fed condition at 9:00 AM on separate days. Participants completed the M&Ms PR task in the afternoon of the fasted Angry Birds day and an ad lib meal in the afternoon of the fed Angry Birds day.
Results: BN-S (n=68) had significantly higher WS and breakpoint (BP) on all PR tasks and lower reward satiation compared to controls (n=8) (all p-values<.05). Positive associations were found for BP across conditions/rewards (Angry Birds fasted-fed: r=.57, p<.001; M&Ms-Angry Birds fasted/fed: r=.30/r=.42, p=.005/p<.001). Finally, ad lib reward satiation was associated with WS (r=-.26, p=.03), M&Ms (r=-.50, p<.001), and Angry Birds fasted BP (r=-.25, p<.05), with unique contributions of WS (b=-.29, p=.04) and food reward value (b=-.53, p<.001) but not non-food reward value (b=-.06, p=.68) in predicting reward satiation.
Conclusions: Findings support increased reward value in BN-S that may increase risk for binge eating and contribute to the link between WS and BN-S maintenance.
Supported By: NIMH R01 MH111263
Keywords: Bulimia Nervosa, Weight Loss, Reward Valuation, Satiation

71. Associations Between Neural Reward Processing and Binge Eating in Adolescent Girls

Lindsay Bodell[1], Jennifer Wildes[2], Andrea Goldschmidt[3], Rachel Lepage[4], Kate Keenan[2], Amanda Guyer[5], Alison Hipwell[4], Stephanie Stepp[4], and Erika Forbes[4]

[1]University of Western Ontario, [2]University of Chicago, [3]Warren Alpert Medical School of Brown University/The Miriam Hospital, [4]University of Pittsburgh, [5]University of California, Davis

Background: Neuroimaging studies suggest that altered brain responses to food-related cues in reward-sensitive regions characterize individuals who experience binge-eating episodes. However, the absence of longitudinal data limits understanding of whether such alterations increase vulnerability to binge eating, as theorized in models of the development of this behavior. The purpose of the current study was to examine the role of "Reward Responsiveness" constructs of the Positive Valence Systems of the Research Domain Criteria in the development of binge eating using a longitudinal design.
Methods: Adolescent girls (n=122) completed an fMRI monetary reward task at age 16 years and completed self-report assessments of binge eating and depression at ages 16 and 18 years. Regression analyses examined concurrent and longitudinal associations between BOLD response to anticipating and winning monetary rewards and severity of binge eating while controlling for depressive symptoms.
Results: Greater ventromedial prefrontal cortex (PFC) and caudate response to winning money ("initial response to reward") were correlated with greater severity of binge eating concurrently (β = .60, t = 3.71, p = .001; β = .39, t = 2.09, p < .05) but not prospectively (p >. 05). There were no significant associations between reward anticipation and binge eating after accounting for covariates (ps > .10).
Conclusions: This study is the first to examine longitudinal associations between reward responding and binge eating in community-based, adolescent girls. Ventromedial PFC response to reward outcome—possibly reflecting enhanced subjective reward value—appears to be a state marker of binge eating severity rather than a predictor of future severity.
Supported By: R01MH56630; R01MH66167; R01MH093605; T32MH082761; K23DK105234

Keywords: Binge Eating, Reward, Adolescents, Disordered Eating

72. Toward a Model for Illness Maintenance in Anorexia Nervosa

Guido Frank[1]

[1]University of Colorado Denver

Background: Adolescent anorexia nervosa (AN) is an eating disorder associated with intense fear of weight gain, food refusal, and severe weight loss. AN is the third most common chronic illness among adolescent females with a mortality rate 12 times higher than expected for females 15-24 years old. Little is known about biomarkers that could be used to predict treatment outcome in AN. Here we wanted to test whether brain taste reward learning response in AN is altered and related to treatment response.
Methods: We recruited adolescent girls with AN and matched healthy controls who underwent a sucrose-taste classical conditioning paradigm that elicits the dopamine-related prediction error (PE) during functional magnetic resonance imaging. We extracted brain response parameter estimates from anatomical regions of interest and used MANCOVA to analyze group contrasts, including comorbid conditions and medication use as covariates. Results were multiple comparisons corrected.
Results: Fifty-six female adolescents with AN (mean age=16.6±2.5 years, mean body mass index, BMI=15.9±0.9 kg/m2) and fifty-two control adolescents (mean age=16.0±2.8 years, mean BMI=20.9±2.1 kg/m2) participated in the study. PE response was elevated in adolescents with AN in caudate head, nucleus accumbens and insula (MANCOVA, Wilk's lambda 0.707, $p<0.023$, partial eta2=0.296), which correlated negatively with sucrose taste pleasantness. Bilateral AN orbitofrontal gyrus rectus PE response correlated positively with harm avoidance (rho=0.317 to 0.336, $p<0.02$), but negatively with treatment BMI change (rho=-0.268 to -0.282, $p<0.05$).
Conclusions: These results support elevated PE signal in AN and suggest a link between PE and weight gain and harm avoidance in AN.
Supported By: NIMH
Keywords: Anorexia Nervosa, Brain Imaging, fMRI, Reward Learning, Dopamine, Computational Modeling

SYMPOSIUM
Neurochemical Circuits and Molecular Mechanisms of Panic and Agoraphobia
3:00 p.m. - 5:00 p.m.
Chair: Anantha Shekhar

73. Using Opto-Chemogenetics to Assess the Role of Orexin/Glutamate Hypothalamic System in Panic/Phobia and to Identify Panic/Phobia Off/On Inputs

Philip Johnson[1], Cristian Bernabe[1], Izabela Caliman[1], Stephanie Fitz[1], Aline Abreu[1], Andrei Molosh[1], Seema Bhatnagar[2], Pascal Bonaventure[3], and Anantha Shekhar[1]

[1]Indiana University School of Medicine, [2]University of Pennsylvania, [3]Johnson and Johnson Pharmaceutical Research and Development LLC

Background: Discovered in 1998, it was not initially appreciated that orexin neurons (colocalized with glutamate) are almost exclusively concentrated in the perifornical hypothalamus (PeF) region, which when stimulated elicits panic-associated behavior and cardiovascular responses in rodents and induces core symptoms of panic attacks in humans.
Methods: In order to determine the role of orexin/glutamatergic neurons in regulating panic and place avoidance we first used chemo and wireless optogenetics. We then used retrograde tracing from PeF to identify potential panic/phobia on or off inputs. To confirm their role, we injected a canine adeno associated virus with a nonspecific neuronal promoter into the PeF, which is retrogradely transported and induces expression of Cre-recombinase (Cre-R) in all neurons that project to the PeF. We then injected an adeno associated virus into these inputs with a neuronal promoter to induce a double floxed inverted sequence of either an excitatory human muscarinic 3 receptor for chemogenetic or channelrhodopsin for optogenetics which is expressed in the presence of Cre-R.
Results: Chemogenetic or optogenetic excition of orexin or glutamatergic neurons in the PeF induced panic associated behavior and cardiovascular responses in rodents with optogenetics also inducing phobia associated unconditioned/conditioned place avoidance. Retrograde tracing from PeF revealed robust inputs from serotonergic neurons in the lateral wings of the dorsal (lwDRN) and median raphe nucleus (MRN) and glutamatergic neurons in the parabrachial nucleus (PBN). Optogenetic excitation of lwDRN/MRN terminals in the PeF inhibited CO2 (a suffocation stimuli) induced panic and induced unconditioned and conditioned place preference. Chemogenetic excitation of PBN glutamate projections to PeF induced panic.
Conclusions: The data here support the hypothesis that exciting orexin/glutamate neurons in the PeF induces panic and also phobic associated responses and serotonergic and glutamate projections to the PeF respectively represent panic /phobia off inputs.
Supported By: Supported by K01 AG 044466 to PLJ, and R01 MH 065702 and MH 052619 to AS.
Keywords: Panic Disorder, Anxiety Disorder, Phobia, Orexin, Serotonergic System

74. Mechanisms of Agoraphobia: Contribution of Orexin and mGluR2 Signaling in the Amygdala

Andrei Molosh[1], Erik Dustrude[1], Jodi Lukkes[1], William Truitt[1], Seema Bhatnagar[2], Luc ver Donck[3], Justine Kent[4], Marc Ceusters[3], Pascal Bonaventure[4], Philip Johnson[1], and Anantha Shekhar[1]

[1]IU School of Medicine, [2]University of Pennsylvania, [3]Janssen Research and Development, [4]Johnson & Johnson

Background: Panic disorder (PD) is characterized by recurrent panic attacks (PAs) and can lead to phobias. Contributing mechanisms at molecular and circuitry levels are poorly understood, but phobia development can be correlated to deregulation of fear responses. Perifornical hypothalamic (PeF) neurons that are positive for orexin neuropeptides exhibit terminal fields in the amygdala, a critical region for learning and expression of fear behavior. We have characterized cellular, molecular, and behavioral consequences of orexinergic and glutamatergic signaling in the amygdala within phobia-related models of fear learning.
Methods: Utilizing brain slice electrophysiology and selective pharmacological interventions we characterized the cellular effects of orexin in the central amygdala (CeA). Using optogenetic methodologies, we also investigated the role of PeF-amygdala glutamate projections in fear conditioning. To modulate these respective neurotransmitters in a preclinical fear conditioning model, we utilized OX1R and OX2R antagonists and a metabotropic glutamate receptor 2 (mGlur2) positive allosteric modulator (PAM). Finally, we preformed post-hoc analysis of PD patients from a mGlur2 PAM clinical trial.
Results: We observed that OX application depolarizes CeA neurons and also potentiates presynaptic glutamate release via OX1R. Systemic or intra-amygdala injection of OX1R antagonist reduced expression of conditioned fear. Importantly, optogenetic stimulation of PeF glutamatergic inputs to the amygdala enhanced conditioned fear, and pretreatment with mGlur2 PAM enhances extinction of fear memories. Finally, all patients with PD showed complete remission of panic symptoms after being treated with mGlur2 PAM.
Conclusions: Treatment with mGluR2 PAM or/and OX1R selective antagonists could be effective treatment for panic and fear-related symptoms.
Supported By: NIMH R01 MH065702; NIMH R01 MH052619; NCATS UL1 TR001108; K01 AG044466; Other
Keywords: Anxiety, Orexin, Glutamate, Phobia, Amygdala

75. Evaluation of Selective Orexin Receptor Antagonists in Preclinical Models of Panic Attack Provocation

Pascal Bonaventure[1], Anantha Shekhar[2], Brock Shireman[3], Lauren Frederici[2], Andrei Molosh[2], and Philip Johnson[2]

[1]Johnson and Johnson Pharmaceutical Research and Development LLC, [2]Indiana University School of Medicine, [3]Janssen

Background: Orexin neurons originating in the perifornical and lateral hypothalamic area are highly reactive to anxiogenic stimuli and have strong projections to anxiety and panic-associated circuitry. Recent studies support a role for the orexin system in coordinating an integrative stress response. Although the two cognate orexin receptors are colocalized in many brain regions, the orexin 2 receptor (OX2R) most robustly maps to the histaminergic wake-promoting region, while the orexin 1 receptor (OX1R) distribution is more exclusive and denser in anxiety and panic circuitry regions, such as the locus coeruleus. Overall, this suggests that OX1Rs play a critical role in mobilizing anxiety and panic responses. Here, we tested selective OX1R and OX2R antagonists in preclinical models, using panicogenic stimuli that induce panic attack in the majority of people with panic disorder.
Methods: Dual OXR antagonist (DORA-12), selective OX1R antagonists (Compound-56 and JNJ-54717793) and selective OX2R antagonist (JNJ-1037049) were tested in an acute hypercapnia-panic provocation model and/or a model involving chronic inhibition of GABA synthesis in the perifornical hypothalamic area followed by intravenous sodium lactate infusion.
Results: All compounds except the selective OX2R antagonist attenuated CO2 -induced anxiety-like behaviors. The selective OX1R antagonists but not the selective OX2R antagonist nor the dual OXR antagonist attenuated CO2 -induced cardiovascular responses ($n = 7$-12, alpha level was set at 0.05).
Conclusions: These data indicate that selective OX1R antagonism may represent a novel approach of treating anxiety disorders, with no apparent sedative effects.
Supported By: Janssen
Keywords: Orexin, Panic disorder, Animal Model, Orexin Receptor

76. Role of Orexins in Mediating Sex Differences and Resilience to Repeated Stress

Seema Bhatnager[1]

[1]Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine

Background: Women are twice as likely as men to suffer from stress-related psychiatric disorders. However, the biological basis of these sex differences is poorly understood. Orexins are altered in important disorders such as anxiety and depression. In a series of experiments, we studied the contribution of orexins to sex differences in outcomes relevant to stress-related psychiatric diseases.
Methods: The role of orexins in mediating habituation to repeated restraint stress (30min/day for 5 consecutive days) and subsequent cognitive flexibility were examined in adult male and female rats. The functional role of orexins was examined using DREADDs to inhibit orexin activation throughout repeated restraint. We examined dendritic morphology and spine densities in putative orexin neurons using Golgi staining.
Results: Females exhibited impaired habituation with subsequent deficits in cognitive flexibility compared to males. Increased orexin expression and activation was observed in females. Inhibition of orexins in females promoted habituation and reduced cognitive impairments. Repeated stress reduced dendritic complexity of putative orexinergic neurons in males but not in females and control females had significantly more dendritic spines than control males.

Conclusions: The results demonstrate sex differences in morphology, expression and the functions of orexinergic neurons. Orexins mediate the impairments in habituation to repeated stress and in subsequent cognitive flexibility exhibited by females. Finally, the morphological characteristics of orexin neurons may be less adapted to repeated stress in females. These findings provide evidence for a broad role for orexins in mediating sex differences in functions relevant to stress-related psychiatric diseases.

SYMPOSIUM
The Structure of the OCD Brain: Effects of Medication, Chronicity and Disease-Specificity

3:00 p.m. - 5:00 p.m.
Chair: Odile van den Heuvel
Co-Chair: Carles Soriano-Mas

77. Effects of Psychopharmacological Treatment for OCD on Brain Morphometry Across the Lifespan

Iliyan Ivanov[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Quantitative MRI frequently finds abnormal regional brain morphologic endpoints, e.g., cortical thickness (CT), surface area (SA), subcortical volumes, in psychiatric disorders, but these endpoints may be influenced by psychotropic treatment. Preclinical work suggests that medication-induced changes in dendritic density underlie morphometric effects; these changes are common for different classes of psychotropics but vary with patient age. Here we assessed age-by-drug interactions involving morphometric endpoints in obsessive-compulsive disorder (OCD), a common, lifelong, pharmacologically treated psychiatric disturbance.
Methods: Bilaterally, for 34 cortical and 8 subcortical regions we analyzed MRI-derived CT, SA, and/or volume data from 33 ENIGMA-OCD centers. Cross-sectional data were analyzed from 2176 OCD patients (1040 medicated/1136 unmedicated) and 2003 healthy controls, aged 6-65 years, using the general linear model.
Results: Medicated OCD, unmedicated OCD, and control groups all showed decreasing brain-wide CT, SA, and volume with increasing age ($p<0.0005$) in most regions. Effects of medication ($p<0.001$-0.0005) and age-by-medication interactions ($p<0.05$-0.0005) manifested in numerous brain regions. Thereby, child and adolescent medicated subjects had higher CT than unmedicated subjects. Adult medicated OCD subjects, however, had lower CT than unmedicated OCD and controls. Results remained significant when sex, intracranial volume, ENIGMA-center, and OCD severity were accounted for. SA and volume effects were similar, but less pronounced. Effects were strongest for SRIs, but also existed for tricyclics, anti-psychotics, and benzodiazepines.
Conclusions: This is the first report of age-dependent effects of psychopharmacologics on brain morphometrics. OCD and its medicinal treatment may alter the normal course of morphometric development, perhaps in relation to dendritic density.
Supported By: NIMH BD2K U54 EB020403-02
Keywords: Obsessive-Compulsive Disorder, Aging, Brain Imaging, fMRI

78. Machine Learning Classification of Obsessive-Compulsive Disorder Using Structural Neuroimaging Data: ENIGMA Working Group

Willem Bruin[1], Jonathan Shock[2], Rajat Thomas[1], Nynke Groenewold[2], Premika Boedhoe[3], Paul M. Thompson[4], Odile van den Heuvel[3], Dan J. Stein[2], and Guido van Wingen[5]

[1]Academic Medical Centre, University of Amsterdam, [2]University of Cape Town, [3]VU University Medical Center, [4]Keck School of Medicine, University of Southern California, [5]Amsterdam UMC

Background: Recent meta-analyses of structural neuroimaging data within ENIGMA consortia have reported significant but small group differences in brain structure between patients with obsessive-compulsive disorder (OCD) and healthy controls. We aimed to determine whether patients could be distinguished from controls at the individual level using multivariate pattern analysis, and to investigate whether clinical variables would influence classification performance.
Methods: Structural T1 images from 2,304 OCD patients and 2,066 healthy controls were obtained from 34 sites across the world. FreeSurfer was used to determine cortical thickness, cortical surface area and subcortical volumes. All 158 FreeSurfer variables were used as features for classification, with age and sex as covariates. Eight common machine learning algorithms were used, as well as different cross-validation (CV) procedures to determine the generalizability of the results. Additional classifications were performed using stratification for medication status, disease severity, chronicity, and age of onset.
Results: Within-site classification performance with 10-fold CV varied greatly between sites, with area under the receiver-operator curve (AUC; range (SD)) 0.21(0.15)-0.89(0.08). Between-site classification performance was low with 10-fold CV stratified for site (0.57(0.02)-0.60(0.02)), and at chance level with leave-one-site-out CV (0.51(0.08)-0.54(0.08)). Classification performance improved considerably when accounting for medication status and age of onset.
Conclusions: Between-site classification performance is poor and appears to result from heterogeneity between sites. These findings suggest that patients are difficult to distinguish from healthy controls using structural MRI data when combining multi-site data and not accounting for clinical diversity. In contrast, medication use has profound effects on brain structure and enables good single subject classification.
Supported By: NWO/ZonMw Vidi 917.15.318
Keywords: Obsessive Compulsive Disorder (OCD), Structural MRI, Machine Learning

79. Association Between Illness Duration and Psychotropic Medication in Obsessive-Compulsive Disorder and Altered Brain Structural Covariance Networks: A Multi-Center Analysis

Je-Yeon Yun[1], Premika S.W. Boedhoe[2], Neda Jahanshad[3], Paul M. Thompson[3], Dan J. Stein[4], Odile van den Heuvel[2], and Jun Soo Kwon[5], ENIGMA-OCD Consortium

[1]Seoul National University Hospital, [2]VU University Medical Center, Amsterdam, [3]Keck School of Medicine, University of Southern California, [4]University of Cape Town, [5]Seoul National University College of Medicine

Background: Brain's structural covariance network refers to the organized patterns of co-varying brain morphology that are thought to reflect trajectories of brain development and maturation. In particular, obsessive-compulsive disorder (OCD) is often diagnosed early in life, but the effect of illness duration and psychotropic medication on the brain structural covariance networks remains unknown. This study examined individualized brain structural covariance networks using graph theory. We compared individuals diagnosed with OCD to healthy controls (HC) and evaluated trends in relation to their duration of illness and medication status.

Methods: T1-weighted brain magnetic resonance images acquired from 1,616 OCD patients and 1,463 HC across 37 datasets participating in the ENIGMA-OCD Working Group were analyzed; among these, twelve datasets were included for meta-analysis according to the medication status. Global network characteristics that measure the degree of network segregation (clustering coefficient and modularity), integration (global efficiency), and their balance (small-worldness) in addition to the degrees of inter-individual overlap for hub profiles (dice similarity coefficient) were calculated from individualized cortical-subcortical structural covariance networks.

Results: Global network characteristics showed lower network segregation and small-worldness as well as decreased dice similarity coefficient in OCD compared to HC; medication status did not reveal significant influence on these global characteristics in OCD.

Conclusions: Our findings of altered structural covariance patterns in relation to the longer illness duration for OCD may reflect increased connectedness of brain regions related to self-referential information processing, and isolation of brain areas relevant for insight, behavioral control, and visuospatial reasoning.

Supported By: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B03028464). ENIGMA is also supported, in part, by an NIH grant (U54 EB020403), and by public and private funding agencies worldwide.

Keywords: Obsessive Compulsive Disorder (OCD), Structural Covariance, Graph Theory, Duration of Illness, Medications

80. Subcortical Brain Volume, Regional Cortical Thickness and Surface Area Alterations Across ADHD, ASD, and OCD

Premika Boedhoe[1], Daan van Rooij[2], Martine Hoogman[2], Lianne Schmaal[3], ENIGMA ADHD Working Group, ENIGMA ASD Working Group, ENIGMA OCD Working Group, Paul M. Thompson[4], Dan J. Stein[5], Jan Buitelaar[2], Barbara Franke[2], and Odile van den Heuvel[6]

[1]Janssen, [2]Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, [3]Orygen, The National Centre of Excellence in Youth Mental Health, [4]Keck School of Medicine, University of Southern California, [5]University of Cape Town, [6]VU University Medical Center, Amsterdam

Background: Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) are common childhood-onset neurodevelopmental disorders. No structural imaging study to date has compared these disorders. The ENIGMA consortium is ideally positioned to investigate structural brain abnormalities across these disorders on a large scale.

Methods: Structural T1-weighted MRI scans of controls (n=5.827) and individuals with ADHD (n=2.271), ASD (n=1.777), and OCD (n=2.323) from 151 samples worldwide were analyzed with FreeSurfer using standardized processing protocols. We examined subcortical volume, regional cortical thickness and surface area differences within a mega-analytical framework, pooling extracted measures from each site. Analyses were performed separately for pediatric, adolescent, and adult subgroups using linear mixed-effects models controlling for age, sex, and site (and ICV for subcortical and surface area measures). FDR was used for multiple testing correction.

Results: Pediatric OCD patients had larger hippocampal volumes compared to ADHD patients. Pediatric and adolescent ADHD patients also showed smaller ICV than controls, OCD and ASD patients. No subcortical differences were observed across disorders in adulthood. On the cortical level, adult ASD patients showed thicker cortices in frontal areas compared to controls, OCD and ADHD patients, while no differences were observed in surface area between the disorders across the lifespan. Overall, subcortical and cortical effects were subtle (Cohen's d -0.22-0.30).

Conclusions: These findings suggest that subcortical differences between ADHD ASD and OCD seem most distinct in childhood while differences seem to diminish in adolescence and adulthood. Cortical differences across the disorders seem to be most pronounced in adulthood.

Supported By: NIH: BD2k (Big Data), U54 EB020403-02 (PI: Thompson)

Neuroscience Campus Amsterdam (NCA), IPB-grant (PI's: Schmaal / van den Heuvel)

Keywords: Structural Brain Imaging, OCD, ADHD, ASD, Neurodevelopmental Disorders

SYMPOSIUM
Neuropathophysiology Associated With Delusions and Hallucinations
3:00 p.m. - 5:00 p.m.
Chair: Dean Salisbury

81. Theta Phase Synchrony is Sensitive to Corollary Discharge Deficits and Delusion Severity in Schizophrenia

Judith Ford[1], Brian Roach[2], Rachel Loewy[1], Barbara Stuart[1], and Daniel Mathalon[3]

[1]University of California, San Francisco, [2]Northern California Institute for Research and Education & University of California, San Francisco, [3]University of California, San Francisco & San Francisco VA Health Care System

Background: Across the animal kingdom, responses in auditory cortex are dampened during vocalizing compared to passive listening, reflecting the action of the corollary discharge mechanism. In humans, it is seen as suppression of the EEG-based N100 event-related potential, with less N100-suppression seen in people with schizophrenia (SZ) and those at clinical high risk (CHR) for psychosis. Because N100 is an admixture of theta (4-7Hz) power and phase synchrony, we asked which is responsible for N100 effects and if they outperform N100's sensitivity to corollary discharge, psychosis, and symptoms.
Methods: Theta phase and power values were extracted from EEG data acquired from CHR youth (n=71), early illness SZ (ESZ; n=84), and healthy controls (HC; n=103) as they said "ah" (Talk) and then listened to the sounds played back (Listen). A principal components analysis extracted theta inter-trial coherence (ITC; phase consistency) and event related spectral power, peaking in the N100 latency range.
Results: Theta ITC-suppression (Cohen's d=1.46) was greater than N100-suppression (Cohen's d=.63) in HC. Both were both reduced in ESZ, but only N100-suppression was reduced in CHR. When deprived of the variance shared with theta-ITC suppression, N100-suppression was no longer sensitive to group differences (HC vs. ESZ or HC vs. CHR). Deficits in theta ITC-suppression were correlated with delusions (p=.007) in ESZ. Suppression of theta power was not affected by Group.
Conclusions: Theta ITC-suppression may provide a simpler assay of the corollary discharge mechanism than N100-suppression and be a more direct reflection of psychotic symptoms.
Supported By: Department of Veterans Affairs (VA Merit I01CX000497, Senior Research Career Scientist award) and National Institute of Mental Health (R01MH076989, K02MH067967, T32MH089920, R01MH058262)
Keywords: Schizophrenia, Electrophysiology, Delusions

82. Functional Connectivity of Voice Hearing: From Psychosis to the Trauma Spectrum

Ann Shinn[1], Melissa Hwang[1], Jonathan Wolff[1], Lauren Lebois[1], Sherry Winternitz[1], Kerry Ressler[1], Dost Ongur[1], and Milissa Kaufman[1]

[1]McLean Hospital/Harvard Medical School

Background: Voice hearing (VH), or hearing voices in the absence of external stimuli, is a transdiagnostic experience that can occur in trauma spectrum disorders as well as in psychotic disorders.
Methods: We studied 28 women with posttraumatic stress disorder (PTSD) and VH, as measured by the auditory hallucination item (B16) in the Structured Clinical Interview for DSM-IV-TR (SCID), versus 24 women with PTSD and no VH (NVH). Individuals with schizophrenia or other psychotic disorders were excluded. We acquired high-resolution structural scans and resting state blood oxygenation level dependent (BOLD) images (124 volumes, TR/TE 3000ms/30ms) on a 3T Siemens Tim Trio scanner. We used CONNv18a, which includes rigorous denoising tools, for functional connectivity analysis. We compared VH to NVH, adjusting for motion and other symptoms. We performed ROI-to-ROI analysis across the 48 cortical and 21 subcortical regions of the Harvard-Oxford atlas and 26 cerebellar regions from the Automated Anatomical Labeling (AAL) atlas, using a significance threshold of $p<0.05$, FDR-corrected.
Results: VH patients showed hypoconnectivity within multiple region pairs, including left supplementary motor area-bilateral planum polare (left PP p-FDR=0.029; right PP p-FDR=0.029), left amygdala-right caudate (p-FDR=0.048); and left orbitofrontal cortex-right parietal regions (supramarginal gyrus p-FDR=0.038; superior parietal lobule p-FDR=0.040), among others, relative to NVH patients. VH patients also showed hyperconnectivity between region pairs, including left Heschl's gyrus and regions of the cerebellar vermis (VER 7 p-FDR=0.011; VER 6 p-FDR=0.013), among others.
Conclusions: Models of VH in psychosis (e.g., inner speech, memory-based, and top-down models) may serve as useful frameworks for also understanding VH in trauma spectrum.
Supported By: NIMH K23
Keywords: Auditory Hallucinations, Resting State Functional Connectivity, Psychosis, Posttraumatic Stress Disorder

83. Age-Associated Deviation in Amygdala Functional Connectivity is Related to Hallucinations in Psychosis Spectrum Youth

Maria Jalbrzikowski[1], Vishnu Murty[2], Brenden Tervo-Clemmens[1], William Foran[1], and Beatriz Luna[1]

[1]University of Pittsburgh, [2]Temple University

Background: We created normative growth charts of amygdala functional connectivity in typically developing youth and

assessed age-associated deviations of these trajectories in psychosis spectrum youth and explored how these disruptions are related to clinical symptomatology.
Methods: Resting state functional neuroimaging data from four samples (3 cross- sectional, 1 longitudinal) was collected on 1062 participants (typically developing controls=622, psychosis spectrum=194, other psychopathology=246, ages 10-25 years). We assessed deviations in youth with psychosis spectrum and other psychopathology in age-related changes in resting state fMRI (rsfMRI) amygdala to whole brain connectivity from a normative range derived from control youth. We explored relationship between age-associated deviations in amygdala connectivity and positive symptoms in the patient group.
Results: Normative trajectories demonstrated significant age-related decreases in centromedial amygdala connectivity with the rest of the brain. In contrast, psychosis spectrum youth failed to exhibit any significant age-associated changes between the centromedial amygdala and prefrontal cortices, striatum, occipital cortex, and thalamus (all $q<.1$). Exploratory analyses revealed that greater age-related deviation in centromedial amygdala-thalamus connectivity was associated with increased severity of positive symptoms ($r=0.19$, $p=0.01$, $q=0.05$) in psychosis spectrum youth. Centromedial amygdala-thalamus age-associated deviation was associated with hallucinations ($r=0.23$, $p=0.003$) but not unusual thought content ($r=0.08$, $p=0.32$).
Conclusions: Using neurodevelopmental growth charts to identify a lack of normative development of amygdala connectivity in psychosis spectrum youth may help us better understand the neural basis of affective impairments in psychosis, informing prediction models and interventions.
Supported By: K01 MH112774 P50 MH103204 R01 MH080243
Keywords: Amygdala, Adolescence, Hallucinations, Schizophrenia, Resting State fMRI

84. White Matter Connectivity Abnormalities in a Cortical-Subcortical Auditory Hallucination-Related Circuit in First Episode Psychosis

Dean Salisbury[1], Yiming Wang[2], Frank Yeh[2], and Brian Coffman[1]

[1]University of Pittsburgh School of Medicine, [2]University of Pittsburgh

Background: A left-hemisphere circuit including Broca's and Wernicke's areas and the putamen are related to auditory hallucinations (AH), as is over-activity in primary auditory cortex. Structural pathology in early psychosis in the white matter tracts connecting these hubs is unknown.
Methods: White matter connectivity among these areas using diffusion spectrum imaging (DSI) in 40 first-episode psychosis (FEP) and 32 matched healthy comparison subjects (HC) was measured using generalized fractional anisotropy (gFA).
Results: FEP and HC did not differ in gFA across the auditory transcallosal (ATC) fibers or left and right arcuate fasciculus (AF) fibers. However, AH+ ($n=23$) had reduced gFA within the ATC compared to AH- ($n=17$, $p=.009$), and within the left hemisphere AF ($p=.040$), but not differ right. For left Broca's to putamen fibers, all FEP showed reduced gFA ($p=.038$), but not in the right hemisphere ($p=.37$). AH+ showed reduced left Broca's to putamen gFA compared to AH- ($p=.046$) and in left hemisphere Wernicke's to putamen gFA ($p=.049$). Finally, the FEP group overall showed trend-level reductions in gFA between right Wernicke's and putamen ($p=.076$), with AH+ reduced in relation to AH- ($p=.026$).
Conclusions: FEP hallucinators were reduced in the left hemisphere cortical-subcortical language circuit and inter-hemispheric auditory connectivity. Wernicke's connectivity appeared to be abnormal bilaterally in hallucinators. gFA reductions likely manifest in slowed conduction times. Thus, at the first psychotic episode, AH is associated with impaired left-language system and inter-hemispheric auditory communication, likely reflecting mistiming of information flow between language-related cortical centers.
Supported By: NIH R01 MH108568, NIH P50 MH103204.
Keywords: First Episode Psychosis, Auditory Hallucinations, Diffusion Spectrum Imaging, Left Language Areas

SYMPOSIUM
Modeling Deviations from Normal Age-Related Variation in Brain Structure in the Population to Understand Individual Differences in Mental Illness

3:00 p.m. - 5:00 p.m.
Chair: Lianne Schmaal
Co-Chair: Christopher Ching

85. Cortical Thickness and Subcortical Volume Trajectories Across the Lifespan: Data From 14,600 Healthy Individuals Aged 6-90 Years

Sophia Frangou[1], Amirhossein Modabbernia[1], Gaelle Doucet[1], Dominik Moser[1], and Danai Dima[2], ENIGMA Lifespan Working Group

[1]Icahn School of Medicine at Mount Sinai, [2]City University London

Background: Age is a critical determinant of brain morphometry. We formed the Lifespan Working group of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium to perform a large-scale analysis of cortical thickness data across more than 79 samples and 14,600 healthy individuals aged 6-90 years.
Methods: We used fractional polynomial (FP) regression to characterize age-related trajectories in brain morphometry. Normalized growth centiles were constructed using the parametric Lambda, Mu, and Sigma (LMS) method. Inter-individual variability was analyzed using meta-analysis and one-way analysis of variance.
Results: The volume of subcortical regions followed an inverted U-shaped trajectory while cortical thickness in almost

all regions decreased during the first two to three decades of life and showed an attenuated or plateaued slope afterwards. Exceptions were the entorhinal, anterior cingulate and temporopolar cortices that followed attenuated age-related U-shaped trajectories. Age and its FP combinations explained up to 48% variance in morphometry. Sample, strength of the MRI scanner magnetic field and FreeSurfer version jointly accounted for a median of 17% of the variance.
Conclusions: Our results could shed light on the uncertainties about age-related developmental trajectories of cortical thickness. The estimated centile values will provide scientists and clinicians with more efficient tools to detect brain morphological deviations and their association with behavioral, cognitive and clinical outcomes
Supported By: R01MH116147
Keywords: Brain Development and Aging, Volumetric Neuroimaging, ENIGMA Consortium, Healthy Subjects, Lifespan

86. Understanding the Heterogeneous Phenotype of Psychiatric Disorders Using Normative Models

Andre Marquand[1], **Thomas Wolfers**[2], Mariam Zabihi[1], Seyed Mostafa Kia[1], Richard Dinga[3], and Christian Beckmann[1]

[1]Radboud University, [2]RadboudUMC, [3]University of Amsterdam

Background: Psychiatric disorders are all extremely heterogeneous which is a major barrier to understanding mechanisms and developing treatments. The predominant case-control approach to studying psychiatric disorders ignores such heterogeneity and despite decades of effort, data driven methods to parse the heterogeneity of psychiatric disorders have not progressed beyond simple proof of concept studies. We have recently introduced normative modelling - or 'brain growth charting' techniques to fractionate psychiatric cohorts at the level of individual participants. Here we demonstrate the value of this method by applying it understand the heterogeneous neurobiology of a wide range of psychiatric disorders.
Methods: Multiple large normative models of brain development were estimated from large healthy cohorts (total N > 2500) on the basis of quantitative biomarkers derived from structural MRI (e.g. brain volume, cortical thickness, surface area). Multiple psychiatric cohorts were then tested against these normative models, providing statistical inferences at the level of individual patients in addition to classical case-control differences.
Results: For all disorders, striking, widespread and highly individualized patterns of atypicality were observed. In some cases, these patterns overlapped with case control differences, but in other cases different and complimentary patterns were observed. In all cases the overlap between the patterns of atypicality for individual subjects was low.
Conclusions: We show that the traditional case-control approach - that effectively focusses on the 'average patient' conceals considerable inter-individual variability. We show normative modelling is an excellent technique to understand the heterogenous neurobiology of psychiatric disorders and provides a workable route towards precision medicine in psychiatry.
Supported By: NWO, EU, Wellcome Trust, MRC
Keywords: Heterogeneity, Normative Model, Case Control Studies

87. Deviations From Normative Age-Brain Associations in Over 3,000 Individuals With Major Depressive Disorder

Lianne Schmaal[1], Laura Han[2], Johanna Bayer[1], Andre Marquand[3], Richard Dinga[2], James Cole[4], Tim Hahn[5], Brenda Penninx[2], Dick Veltman[2], and Paul Thompson[6], ENIGMA MDD Consortium

[1]Orygen, The National Centre of Excellence for Youth Mental Health, [2]VU University Medical Center, [3]Donders Institute for Brain, Cognition and Behaviour, Radboud University, [4]King's College London, [5]Goethe-University Frankfurt, [6]University of Southern California

Background: Major depressive disorder (MDD) is a complex heterogeneous disorder. Identifying brain alterations as individual deviations from normative patterns of brain-age associations, instead of patient group mean differences, can provide important insights into heterogeneous patterns of brain abnormalities observed in MDD.
Methods: We estimated normative models of (1) age predicting individual structural brain measures, and (2) structural brain measures predicting age (Brain Age model) using machine learning in healthy individuals (N=2,515) from the ENIGMA MDD consortium. We applied model parameters to independent samples of healthy individuals (N=2,513) and MDD patients (N=3,433) to obtain predicted values of brain structure (model 1) and age (model 2). Z-scores quantifying differences between predictive and true values were calculated, representing individual deviations from the normative range.
Results: The estimated normative models showed good model fit in the training sample; e.g. a correlation of R=0.86 between actual and predicted age for the Brain Age Model, and good generalization to independent healthy and MDD samples. We identified heterogeneous patterns of brain deviations in MDD patients (model 1). Patients with more extreme deviations showed different clinical characteristics compared to patients residing within the normative range. Additionally, patients were estimated on average ~1 year older than controls (model 2), but we also observed large between-person variation in brain age gaps. Further analyses showed associations between brain age gap and clinical symptoms.
Conclusions: Our work shows substantial heterogeneity in deviations from normal age-related variation in brain structure in individuals with MDD. The impact of and solutions for confounding effects of scan site will also be discussed.
Supported By: NIH U54 EB040203, NIH RO1 MH116147-01
Keywords: Depression, Heterogeneity, Brain Structure, Normative Model

88. Advanced Brain Age and its Clinical Correlates in Bipolar Disorder: A Global, Multi-Site Analysis of Data From the ENIGMA Bipolar Disorders Working Group

Lisa Eyler[1], Garrett Timmons[1], Bernhard Baune[2], Geraldo Busatto[3], Xavier Caseras[4], Udo Dannlowski[5], Dominik Grotegerd[5], Tim Hahn[6], Tomas Hajek[7], Josselin Houenou[8], Fleur Howells[9], Mikael Landén[10], Ulrik Malt[11], Philip Mitchell[12], Benson Mwangi[13], Edith Pomarol-Clotet[14], Pedro Rosa[4], Theodore D. Satterthwaite[15], Kang Sim[16], Jair Soares[13], Marcio Soeiro-de-Souza[4], Sophia Thomopoulos[17], Eduard Vieta[18], Marcus Zanetti[4], Laura Han[19], Lianne Schmaal[20], Christopher R.K. Ching[21], Paul M. Thompson[21], and Ole A. Andreassen[22], for the ENIGMA Bipolar Disorder Working Group

[1]UCSD, [2]University of Adelaide, [3]University of São Paulo, [4]Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, [5]University of Münster, [6]Goethe-University Frankfurt, [7]Dalhousie University, [8]CEA Saclay, INSERM U955 Unit, Team 14 "Translational Psychiatry", IMRB, APHP, CHU Mondor, Créteil, [9]University of Cape Town, Neuroscience Institute, [10]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the Gothenburg University, [11]Institute of Clinical Medicine, University of Oslo, Oslo University Hospital, [12]School of Psychiatry, University of New South Wales, Black Dog Institute, Prince of Wales Hospital, [13]McGovern Medical School, University of Texas Health Science Center at Houston, [14]FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, CIBERSAM, [15]University of Pennsylvania, Perelman School of Medicine, [16]West Region and Research Division/Institute of Mental Health, [17]Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging & Informatics, University of Southern California, [18]University of Barcelona, Hospital Clinic, [19]VU University Medical Center, [20]Orygen, The National Centre of Excellence in Youth Mental Health, [21]Imaging Genetics Center, Keck School of Medicine of University of Southern California, [22]Norwegian Centre for Mental Disorders Research (NORMENT), KG Jebsen Centre for Psychosis Research, Oslo University Hospital

Background: Subcortical volumes and cortical thickness are reduced in bipolar disorder (BD), including in regions that show age-related decline. We studied whether brain age was advanced in 23 samples of BD participants compared to non-mentally-ill comparison (NC) participants from the ENIGMA Bipolar Disorder Working Group and examined relationships with clinical features.

Methods: Models of normative variation in brain features based on age using machine learning were developed from Freesurfer-derived cortical and subcortical size measures on over 2400 NC men and women from the ENIGMA Major Depressive Disorder Working Group. These models were applied to estimate brain-based age of 704 NC men, 887 NC women, 517 BD men and 828 BD women ranging in age from 8 to 79 years. The difference between predicted age and actual age was calculated (brain age gap).

Results: Age was predicted accurately in these independent NC samples (mean absolute error [MAE] men=6.8 years; [MAE] women=6.5 years). Mean brain age gap among BD men was 1.4 years greater than that among NC men; the gap among BD women was .77 years greater than among NC women. These differences were significant after accounting for significant age and site effects (men:$F[1,1217]=21.9, p<0.001$; women:$F[1,1217]=23.0, p<0.001$). Brain age gap was smaller among men and women who were euthymic and among women taking lithium, but larger among women taking antiepileptics ($p's < 0.05$).

Conclusions: Brain-based age was significantly, but only slightly, advanced among BD men and women in a large, global sample; heterogeneity of brain age gap was related to clinical features which suggests potential avenues for slowing neuroprogression.

Supported By: NIH Big Data to Knowledge (BD2K) award (U54 EB020403 to Paul Thompson); NIMH 083968, Desert-Pacific Mental Illness Research, Education, and Clinical Center; National Science Foundation (Science Gateways Community Institutes; XSEDE); French National Agency for Research (ANR MNP 2008 to the 'VIP' project) and by the Fondation pour la Recherche Médicale (2014 Bio-informarcis grant); National Research Foundation, South Africa; University Research Committee, University of Cape Town; South-Eastern Norway Regional Health Authority (2015 – 2015078), Oslo University Hospital, a research grant from Mrs. Throne-Holst, and the Ebbe Frøland foundation; Swedish Research Council, the Swedish Brain foundation, and the Swedish Federal Government under the LUA/ALF agreement (ALF 20170019, ALFGBG-716801); FAPESP-Brazil (2013/03905-4), CNPq-Brazil (#478466/2009 & 480370/2009), and the Brain & Behavior Research Foundation (2010 NARSAD Independent Investigator Award granted to Geraldo F. Busatto); German Research Foundation (DFG, grant FOR2107 DA1151/5-1 and DA1151/5-2) to UD; SFB-TRR58, Projects C09 and Z02 to UD) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to UD); ISCIII; Catalonian Government (2017-SGR-1271 to the Research Unit of FIDMAG); Plan Nacional de I+D+i and Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación and the European Regional Development Fund (FEDER): Miguel Servet research contracts (CPII13/00018 to R.S. and CPII16/00018 to E.P.-C) and Research Projects (PI14/01148 to E.P.-C., PI14/01151 to R.S. and PI15/00277 to E.C-R.); NIH R01 MH 085667, the Dunn Foundation and Pat Rutherford, Jr. Chair in Psychiatry at UTHealth to Jair C. Soares; Singapore Bioimaging Consortium (RP C-009/2006); Canadian Institutes of Health Research grant #341717, Brain and Behavior Research Foundation (Independent Investigator Award #23412)

Keywords: Bipolar Disorder, Brain Magnetic Resonance Imaging (MRI), Aging, FreeSurfer, Mood Stabilizers

FRIDAY, MAY 17, 2019

PLENARY
Negative Emotion and Threat: Developmental Frameworks, Molecular Techniques, and Multimodal Assays
8:45 a.m. - 11:00 a.m.
Chair: Scott Langenecker

89. Development of Emotion Regulation Neurobiology and the Fundamental Role of Early Experiences

Nim Tottenham

Columbia University

Early experiences play a central role in shaping the structure and function of the human brain. This is important because the neurobiology that underlies emotion regulation behaviors is very slow to develop in humans, rendering this neurobiology highly malleable to postnatal influences. This talk will present neuroimaging and behavioral evidence of neurobiological trends in emotion regulation circuitry across childhood and adolescence and highlight the prominent role of caregiving experiences (both positive and adverse) on neurobehavioral development. Special attention will be given to early adverse caregiving and neurobehavioral phenotypes that follow. These outcomes will be discussed in the context of developmental timing and sensitive periods as they inform mental health.
Keywords: Brain Development, Childhood Adversity, Adverse Childhood Experiences, Adolescents, Early Life Stress

90. Mixing Apples With Oranges, or Why Cortisol and Inflammation Come up Even When You are not Looking for Them

Carmine Pariante

Institute of Psychiatry, Psychology and Neuroscience, King's College London

We have recently proposed that one solution to the tension between hypothesis-driven and hypothesis-free approach is to mix apples and oranges: integrating cross-species and cross-tissues 'omics' data to find mechanisms that recur across different experimental and clinical models. Surprisingly, or perhaps reassuringly, when you do this, rather than finding never-heard-of mechanisms, you end up again with the usual suspects: cortisol and inflammation. In recent studies, we have integrated the transcriptome from the hippocampus of adult rats exposed to prenatal stress with the transcriptome from the blood of adult humans exposed to early life trauma. Using a stringent bioinformatic analysis, we have identified three genes: the Forkhead box protein O1 (FoxO1), Alpha-2-Macroglobulin (A2M), and Transforming Growth Factor Beta 1 (TGF-β 1). All three genes have SNPS that show significant Gene x Environment interactions with early life stressors in predicting depressive symptoms. Moreover, and of relevance here, all three genes are functionally linked to cortisol and inflammation, both through network analysis and by direct experimental manipulation. For example, in our own in vitro experiments in human hippocampal neuronal precursors, FoxO1 is upregulated by cortisol and mediates cortisol-induced reduction of hippocampal precursors proliferation, while TGF-β 1 is downregulated by cortisol. A2M has traditionally been viewed as an inflammatory fluid proteinase scavenger, and high levels of A2M have been associated with systemic inflammation. Thus, these two biological systems remain at the core of mental illness pathogenesis, even when you are not looking for them!
Keywords: Early Life Stress, Depression, Transcriptomics, Hypothalamic Pituitary Adrenal (HPA) Axis, Inflammation

91. Clinical Translation of Brain Connectomics

Susan Whitfield-Gabrieli

MIT

Psychiatric neuroimaging has provided insights into brain differences of psychiatric disorders; however, this knowledge has not fundamentally altered patient diagnosis or treatment. The future quality of health care in psychiatry will benefit from a timely translation of basic research findings into more effective and efficient patient care. I will describe ways in which the intrinsic functional and structural architecture of the human brain, as elucidated by resting state networks (RSNs) and tractography respectively, can provide neuro-markers supporting 1) early identification of individuals at risk for mental health difficulties, so that preventive treatment can reduce or even avert future difficulties, 2) neuroprediction, aimed at personalized or precision medicine targeted for selection of an optimal treatment program, and 3) cutting-edge, noninvasive, behavioral interventions such as mindfulness based real-time fMRI neurofeedback, used to augment current available treatments and limit the progression of psychiatric disorders.
Keywords: Brain Connectivity, Translational Neuroscience, Biomarker

92. Making Connections: Network Approaches to Understanding Mood and Cognition

Olusola Ajilore

University of Illinois at Chicago

Understanding the brain from a network perspective has revolutionized the way we conceptualize psychiatric disorders. This presentation will present data on using multimodal neuroimaging techniques to understand how brain network alternations link mood and cognition in the context of internalizing psychopathology, how these network abnormalities respond to treatment, and how novel treatments may be designed to target network dysfunction. Finally, we will expand the notion of the "network" to include novel ways to assess mood and cognition using passive sensing with smartphones.
Keywords: Connectomics, Mood, Anxiety, Cognition, mHealth

SYMPOSIUM
Sleep, Reward Circuitry, and Psychopathology in Youth: Novel Mechanistic Insights From Neuroimaging and Intervention Studies

12:30 p.m. - 2:30 p.m.
Chair: Erika Forbes
Co-Chair: Adriane Soehner

93. Tired and Impulsive: Preliminary Evidence of the Vulnerability of Youth With ADHD to the Neural Consequences of Insufficient Sleep

Jared Saletin[1], Gabriela de Queiroz Campos[2], Jessica Haddad[1], Mary Carskadon[1], and Daniel Dickstein[1]

[1]Alpert Medical School of Brown University, [2]Brown University

Background: Attention-deficit-hyperactivity-disorder (ADHD) is a common disorder of childhood and associated with sleep dysregulation. How ADHD and sleep interact in moderating brain function is unknown. Here we present preliminary evidence highlighting the neural vulnerability of those with ADHD to sleep-loss.
Methods: We first conducted an ALE meta-analysis of 134 fMRI articles, investigating whether ADHD and sleep-loss share common neural effects. We then quantified sleep in ADHD using 12 weeks of actigraphy in 13 children (8F; 12.6±0.7y). We finally examined how ADHD symptoms moderate the effects of acute sleep-loss on brain function (go/no-go inhibition task; resting-state) in 12 children (6F; 11.5±1.1y). We assessed ADHD severity in all children using the Conners-3.
Results: Our meta-analysis revealed ADHD and sleep-loss share reductions in activation within inhibitory-control networks: dorsal anterior cingulate (dACC) and middle/inferior frontal (M/IFG) cortices ($p<.005$; $k=20$mm). In our experimental work, hyperactivity-symptoms were associated with irregular sleep patterns ($b=-0.0025$; $p=.032$). Moreover, following acute sleep restriction, relative to rested wakefulness, those with higher hyperactivity experienced greater reductions in inhibition-related dACC and M/IFG activations ($p<.005$; $k=20$mm), together with greater reductions in resting default-mode connectivity ($r=-.50$; $p=.049$ [one-tailed]).
Conclusions: These results support a new appreciation for sleep in ADHD. First, ADHD and sleep-loss share common reductions in inhibition-related brain activation. Second, ADHD-symptoms index greater dysregulation of sleep. Finally, more severe symptoms were associated with greater neural impairments as a consequence of sleep-loss. In sum, ADHD is associated with vulnerability to the neural consequences of short sleep. Mitigating insufficient sleep may improve clinical status among youth with ADHD.
Supported By: K01MH109854 (to JMS); Rhode Island Foundation Medical Research Grant (to JMS).
Keywords: ADHD, Sleep Deprivation, Child and Adolescent Psychiatry, Brain Imaging, fMRI, Impulsivity

94. Experimentally-Imposed Circadian Misalignment Alters Neural Response to Monetary Reward in Healthy Adolescents

Brant Hasler[1], Duncan Clark[1], Adriane Soehner[2], Bedda Rosario[2], Wambui Ngari[1], and Erika Forbes[2]

[1]University of Pittsburgh School of Medicine, [2]University of Pittsburgh

Background: Adolescents exhibit progressively later timing of sleep and circadian rhythms that is mismatched with the early schedules imposed by high school, resulting in circadian misalignment. Observational evidence links circadian misalignment to mood disturbance and substance abuse, as well as an altered neural response to reward, but precludes determination of causality. In the present study, we tested, for the first time, whether experimentally-imposed circadian misalignment alters the neural response to monetary reward.
Methods: Healthy adolescents ($n=22$, ages 13-17) completed two in-lab sleep schedules followed by a card-guessing monetary reward fMRI task: 'Aligned' conditions based on typical summer sleep-wake times (midnight-9:30am: fMRI at 11 am) and 'Misaligned' conditions set to four hours earlier (8pm-5:30am: fMRI at 7 am), in counterbalanced order. fMRI analyses focused on Win outcome > baseline and Loss outcome > baseline contrasts (whole brain voxel-wise $p<0.005$, cluster-level FDR-corrected $p<0.05$); Dim Light Melatonin Onset (endogenous circadian phase marker) was included as a covariate.
Results: During Aligned versus Misaligned scans, adolescents exhibited higher Win-related activation in the precuneus ($k=307$, $t=5.23$, $p<0.001$) and a cluster encompassing the ventral anterior cingulate and caudate ($k=208$, $t=4.72$, $p<0.001$). No clusters exhibited higher Win-related activation during the Misaligned scan, but a cluster encompassing the right rolandic operculum ($k=208$, $t=5.32$, $p<0.001$) exhibited higher Loss-related activation during the Misaligned scan.
Conclusions: These findings provide the first experimental evidence that circadian misalignment causes altered neural response to monetary reward in healthy adolescents. Misalignment-induced changes in reward processing may lead to enhanced sensation-seeking activities, including substance use.
Supported By: K01 DA032557
Keywords: Circadian Rhythms, Sleep, Reward, Adolescence

95. Identifying Sensitive Periods for the Impact of Insufficient Sleep on Reward-Related Brain Function and Future Depression Among At-Risk Youth

Adriane Soehner[1], Michele Bertocci[1], Anna Manelis[1], Genna Bebko[1], Cecile Ladouceur[1], Simona Graur[1], Kelly Monk[1], Lisa Bonar[1], Mary Beth Hickey[1], David Axelson[2], Benjamin Goldstein[3], Tina Goldstein[1], Boris Birmaher[1], and Mary Phillips[1]

[1]University of Pittsburgh, [2]Nationwide Children's Hospital and Ohio State University, [3]University of Toronto

Background: Insufficient sleep is a well-replicated risk factor for depression in youth, yet the functional neural mechanisms

and sensitive developmental periods underlying this risk relationship remain poorly understood. In a youth sample enriched for depression risk via parental history of mood, anxiety, and behavior disorders, we identified a pubertal window in which insufficient sleep may affect future depression via neural reward processing pathways.
Methods: Fifty-one at-risk youth (9-17 years-old; 13.9±2.3yr; 37 female) without bipolar disorder completed a monetary reward fMRI paradigm. Regression tested the extent to which self-rated pubertal status moderated associations between self-report past-week sleep duration and BOLD response to win-control in the whole brain (voxel-wise $p<0.001$, FWE cluster-level correction $p<0.05$). Analyses adjusted for age, sex, and parental history of bipolar disorder. Sleep-related BOLD activation was tested as a predictor of scan-day and 2-year follow-up depression severity.
Results: Pubertal status moderated associations between sleep duration and win-related activation in a superior parietal cluster encompassing bilateral anterior precuneus and somatosensory cortices ($k=207$; $t44=4.09$, $p<.0001$; FWE-corrected $p<0.05$). Johnson-Neyman testing indicated that shorter sleep duration was associated with greater precuneus/somatosensory activation only among early/pre/mid pubertal youth ($p<0.05$). In pre/early/mid pubertal youth ($N=19$), sleep-related precuneus/somatosensory activation to wins predicted greater depression severity on scan-day ($B=0.50$, $p<0.05$) and at a 2-year follow-up ($B=2.66$, $p<0.05$).
Conclusions: We provide the first preliminary evidence for early pubertal development as a sensitive window in which insufficient sleep may increase risk of future depression via reward-related parietal activation. Findings could inform optimal timing for the implementation of sleep-based depression prevention strategies.
Supported By: NIMH R01MH060952; NIMH K01MH111953
Keywords: Sleep Duration, Reward Processing, Depression, At-Risk Youth, Longitudinal

96. Transdiagnostic Sleep and Circadian Intervention for Youth With Eveningness: Evaluating Biological Moderators of Treatment Effects

Michael Dolsen[1] and Allison Harvey[1]

[1]University of California Berkeley

Background: Substantial sleep and wake changes occur during adolescence, which are linked to increased physical and mental health risk. This study examined whether a transdiagnostic sleep intervention can improve sleep, eveningness (later sleep timing), and health among "at-risk" youth. Moderators of treatment response were also tested.
Methods: Adolescents with an eveningness chronotype were randomized to either the Transdiagnostic Sleep and Circadian Intervention for Youth (TranS-C; $n=89$) or Psychoeducation (PE; $n=87$). Biological moderators included hormones (testosterone, dehydroepiandrosterone [DHEA], and estradiol) and inflammatory markers (interleukin [IL]-6 and C-reactive protein [CRP]).
Results: Compared to PE, TranS-C was associated with a greater reduction in eveningness ($p=0.01$) and an earlier endogenous circadian phase ($p=0.04$). TranS-C relative to PE was not associated with greater pre-post change on primary sleep or health outcomes (p's>0.05). Regarding treatment moderators, female adolescents in TranS-C with higher estradiol exhibited reduced eveningness compared to PE ($p<0.01$). For male adolescents with higher DHEA, TranS-C was associated with reduced emotional risk compared to PE ($p=0.02$). There was a reduction in pre-post emotional risk for participants with higher CRP and improved pre-post total sleep time ($p=0.04$). Reduced pre-post emotional risk was also observed for participants with higher IL-6 and earlier pre-post bedtimes ($p=0.04$).
Conclusions: Relative to PE, TranS-C resulted in improved sleep and circadian functioning. There was evidence that higher levels of hormones and inflammatory markers may be related to improved treatment response. The present study represents an initial step towards identifying biological moderators of treatment effects in adolescents with an eveningness chronotype.
Supported By: NICHD R01HD071065
Keywords: Sleep, Circadian Rhythms, Treatment, Adolescence, Inflammation

SYMPOSIUM
Closing the Loop to Expose Neural Dynamics and Pathology: From Theory to Real-Time Experimental Methodologies

12:30 p.m. - 2:30 p.m.
Chair: Argyris Stringaris
Co-Chair: Hanna Keren

97. fMRI Neurofeedback With Simultaneous EEG Recordings: Insights About Brain Neural Dynamics and Implication for Novel Depression and PTSD Interventions

Jerzy Bodurka[1]

[1]Laureate Institute for Brain Research

Background: Intervention to influence emotional deficits in Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD).
Methods: Real-time fMRI neurofeedback (rtfMRI-nf) with simultaneous EEG to upregulate left amygdala (LA, experimental group EG) BOLD activity during happy memory recall. In the control, nf was from a region not involved in emotions. The association between frontal EEG asymmetry (FEA, right vs left) in the alpha band and BOLD was studied. The linear increase in the LA upregulation level across four nf runs introduces trends in fMRI connectivity and in EEG coherence, characterized with connectivity and coherence slope (FCS, ECS). The effect of nf on BOLD functional connectivities of the amygdala and other brain regions was investigated.
Results: Only in the EG did LA rtfMRI-nf training associate with pre-post significantly decreased depression in MDD (HDRS,$n=14$,$p<0.05$) and decreased PTSD symptoms in veterans (CAPS,$n=16$,$p<0.001$). In both MDD and PTSD, only in

the EG, we found correlations between LA BOLD activity and FEA, enhanced LA FCS with left fronto-temporal regions, and ECS-enhancements during nf-training positively associated with HDRS ($p<0.02$) and CAPS ($p<0.002$). Increased connectivity with the precuneus associated with depression symptom reduction (MADRS, $p<0.05$), and in PTSD, an increase in precuneus connectivity with left lateral superior frontal regions associated with CAPS reduction ($p<0.005$).

Conclusions: LA-nf training reduces MDD, PTSD symptoms, normalizes emotion processing, enhances left fronto-temporal EEG coherence and normalizes FEA. Therapeutic effect nf training is not limited to the amygdala and normalized other regions' functional connectivities.

Supported By: Research Supported by: Laureate Institute for Brain Research, and The William K. Warren Foundation

US DOD Award: W81XWH-12-1-0607; NIMH/NIH Awards 1R01MH098099;

Keywords: Real-Time fMRI Neurofeedback, Concurrent EEG/fMRI, Amygdala, Depression, PTSD

98. Closing the Loop to Expose Neural Dynamics and Pathology: From Theory to Real-Time Experimental Methodologies

Stephen M. LaConte[1], Brooks King-Casas[2], and Pearl Chiu[2]

[1]Virginia Tech, [2]Virginia Tech Carilion Research Institute

Background: The default mode network's (DMN) interference with task positive networks has been associated with cognitive deficiencies and a broad range of neuropsychiatric disorders, including major depression [1]. At the same time, the evidence for cognitive behavioral therapy (CBT) is both strong and similarly broad as an effective treatment for many of the same psychiatric problems in which the DMN has been reported aberrant [2]. Using realtime fMRI (rtfMRI) to enable neurofeedback of DMN, we examined whether individuals with major depression would demonstrate impaired ability to modulate their DMN compared with healthy individuals.

Methods: 29 MDD and 9 control participants. DMN feedback used support vector regression (SVR) realtime fMRI (rtfMRI) [3], modified to decode resting state network activity [4].

During feedback scans, the SVR decoded the incoming motion corrected fMRI data to estimate the level of DMN activity. This value was presented to the subjects using an analog meter display.

Results: We have generated SVR maps for control participants, which are consistent with previously published maps of the DMN [1,7]. Results indicate the differential ability of each participant group to modulate DMN, with controls performing better than MDD participants who received CBT who in turn performed better than MDD participants who did not receive CBT.

Conclusions: This study suggests that DMN modulation correlates with disease state (controls perform better than MDD participants) and may overlap mechanistically with therapeutic change in cognitive behavioral therapy (MDD participants who received CBT performed better than MDDs who did not).

Keywords: Real-Time fMRI Neurofeedback, MDD, Default Mode Network

99. Alpha-Synchronized Stimulation of the Left Dorsolateral Prefrontal Cortex in Depression Using Real-Time EEG-Triggered TMS

Brigitte Zrenner[1], Pedro Caldana Gordon[1], Paolo Belardinelli[1], Eric J. McDermott[1], Surjo R. Soekadar[2], Andreas J. Fallgatter[2], **Christoph Zrenner**[1], Ulf Ziemann[1], and Florian Müller-Dahlhaus[3]

[1]University Neurology Hospital Tübingen, [2]University Psychiatry Hospital Tübingen, [3]University Psychiatry Hospital Mainz

Background: High-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) was found to be beneficial in the treatment of depression, but response rates are low and effect sizes small. Recently it was shown that synchronizing TMS pulses with ongoing endogenous brain oscillations reduces variability and increases efficacy of TMS-induced plasticity when targeting the motor cortex, but it remained unclear whether such a paradigm is feasible, safe and has neuromodulatory effects when targeting the DLPFC of patients diagnosed with major depressive disorder (MDD).

Methods: In seventeen patients with antidepressant-resistant MDD we conducted a randomized controlled single-session crossover trial of alpha-synchronized rTMS of left DLPFC. Stimulation conditions in separate sessions were: (1) alpha−synchronized rTMS, in which the stimulation was repeatedly triggered at the trough of endogenous alpha oscillations, (2) intermittent theta-burst stimulation (iTBS), and (3) a random alpha phase control condition (Replay).

Results: Triggering TMS at the trough of instantaneous alpha oscillations by real-time analysis of the electrode F5 EEG signal was feasible in all subjects. Alpha-synchronized rTMS, but not iTBS or Replay, reduced resting-state alpha activity in left DLPFC and increased TMS-induced beta oscillations over frontocentral channels. Further, alpha-synchronized rTMS and iTBS differentially modulated working memory performance. No serious adverse events were reported.

Conclusions: Findings demonstrate that alpha-synchronized rTMS of left DLPFC is both feasible and safe in MDD and suggest that it has different neurophysiological and behavioral effects as non-alpha-synchronized rTMS paradigms. Future studies need to investigate the therapeutic potential of alpha-synchronized rTMS in MDD.

Supported By: This study was funded by the AKF (Angewandte Klinische Forschung) program of the Medical Faculty Tübingen (to F. M.-D. and B.Z.). S.R.S. received special support from the Brain & Behavior Research Foundation as 2017 NARSAD Young Investigator Grant recipient and P&S Fund Investigator, as well as the European Research Council (ERC) under the project NGBMI (759370).

Keywords: rTMS, Combined TMS-EEG Study, Closed Loop Stimulation, Major Depression, Theta and Alpha Oscillations

100. Mood Machine Interfaces: A Closed-Loop Circuit for Regulating Mood

Hanna Keren[1] and Argyris Stringaris[1]

[1]National Institute of Mental Health, National Institutes of Health

Background: Depression is the leading cause of disability worldwide, characterized mainly by periods of low mood. Rewards are thought to impact on mood course, yet the dynamics of this relationship remain unclear. Here we describe a novel reward based closed-loop system designed to manipulate mood.
Methods: We present the results of the closed-loop experimental set up that uses Reward-Prediction-Errors (RPEs) as the system input in order to manipulate mood. The RPE values are adaptively modified through a proportional-integral (PI) control algorithm derived from non-linear system identification.
Results: We validate this experiment on 45 subjects and show that this strategy can artificially generate mood transitions, both decreasing and increasing the mood state ($p<0.001$ for a test between the generated mood levels). Moreover, we show that it is possible to derive computational parameters of mood reactivity, such as stability, speed and rigidity which show a relationship to depression scores (significant negative correlation between depression scores and control reactivity, $p<0.01$).
Conclusions: Overall, we show that we can apply knowledge from computational modelling to develop an algorithm that influences clinically relevant variables. We discuss how this methodology may enable us to understand mood manipulation and potentially form the basis of targeted treatment strategies for low mood.
Supported By: NIMH intramural program
Keywords: Mood, Reward, Prediction Errors, Control, Real-Time

SYMPOSIUM
Biological Aging and Neuropsychiatric Disorders of Later Life

12:30 p.m. - 2:30 p.m.
Chair: Patrick Brown

101. Declining Skeletal Muscle Mitochondrial Function is Associated With Increased Risk of Depression in Later Life

Patrick Brown[1], Nicholas Brennan[2], Adam Ciarleglio[3], Chen Chen[3], Carolina Montes Garcia[4], Stephanie Gomez[4], Steven Roose[1], Bret R. Rutherford[5], Eleanor Simonsick[2], Richard Spencer[2], and Luigi Ferrucci[2]

[1]College of Physicians and Surgeons, Columbia University/New York State Psychiatry, [2]National Institute on Aging, [3]Columbia University, [4]New York State Psychiatric Institute, [5]NYSPI and Columbia University

Background: Late life depression (LLD) is a chronic and heterogeneous disorder. Recent studies have implicated non-normative age-related processes in its pathogenesis. This investigation examined both cross-sectional and longitudinal associations between skeletal muscle mitochondrial function and LLD.
Methods: Data from 603 men and women from the Baltimore Longitudinal Study on Aging (BLSA) were analyzed, of whom 167 provided data from a follow-up visit. Muscle bioenergetics was measured by post-exercise recovery rate of phosphocreatine using phosphorus magnetic resonance spectroscopy. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale.
Results: There was no cross-sectional association between baseline depression status and either kPCr ($p = .615$) or ATPmax, ($p = .503$). Covariate-adjusted longitudinal linear and Firth logistic regression models however showed that greater decreases in skeletal muscle mitochondrial function from baseline to follow-up were associated with greater increases in CES-D (ATPmax: $= -0.472$, $t = -1.984$, $p = .049$) and higher odds of clinically significant depressive symptoms (CES-D>16) at follow-up (ATPmax,: $= -0.984$, $z = -2.427$, $p = .015$; kPCr: $= -1.008$, $z = -2.638$, $p = .008$).
Conclusions: Preliminary findings suggest that declining skeletal muscle mitochondrial function in older adults is associated with both increased and clinically significant depressive symptoms at follow-up, thereby identifying mitochondrial dysfunction as a potential key pathophysiological mechanism in adults with LLD.
Keywords: Geriatric Depression, Mitochondria Function, Biological Aging

102. Inflammation Effects on Striatal Dopamine: Implications for Late Life Depression

Jennifer Felger[1], Ebrahim Haroon[1], Andrew Miller[1], and Zhihao Li[2]

[1]Emory University, [2]Shenzen University

Background: A growing body of work indicates that peripheral inflammation and cytokines decrease availability and release of striatal dopamine. We present evidence from humans and non-human primates (NHPs) regarding the impact of peripheral inflammation on striatal dopamine, reward and motor circuitry, motivation and motor behaviors that may contribute to symptoms of depression, particularly later in life.
Methods: In NHPs, gene expression (RNA seq) and immune cell activation was assessed in relation to dopamine content in ventral and dorsal striatum of post-mortem tissue from a model of chronic cytokine-induced depressive behavior ($n=7$ interferon [IFN]-α; $n=4$ control). Forty-eight medically-stable, unmedicated outpatients (age$\sim$38) with major depressive disorder (MDD) underwent resting-state fMRI to assess consequences of high inflammation (cytokines and C-reactive protein [CRP]) on global brain functional connectivity (GBFC) and targeted FC.
Results: Dopamine was decreased in the nucleus accumbens and putamen ($p<0.05$) in association with activated

inflammatory pathways, glutamate receptor signaling, and immune cell (Iba-1+MHC-II+) accumulation in perivascular, meningeal and parenchyma spaces in IFN-α-exposed NHPs. Increased plasma CRP and cytokines in MDD were associated with decreased FC in dopaminergic corticostriatal reward and motor circuits in both targeted and GBFC analyses ($p<0.05$), which correlated with anhedonia and motor slowing ($r=-0.5$-0.8). GBFC revealed vmPFC as a hub for network-level effects of inflammation on FC involving a number of other brain regions.

Conclusions: Peripheral cytokines induce inflammation and decrease dopamine in striatum, which may have functional consequences on corticostriatal circuitry and behavior. Increasing levels of inflammation during aging may contribute to these processes. Treatment implications for late-life depression is discussed.

Supported By: R21 MH106904, R01 MH109637, Dana Foundation, BBRF

Keywords: Dopamine, Adolescent Depression, Inflammation, Motivation, Psychomotor Activity

103. Dopaminergic Decline, Psychomotor Slowing, and Late Life Depression

Bret Rutherford[1], Mark Slifstein[2], Anissa Abi-Dargham[2], Melanie Wall[1], Patrick Brown[3], Yaakov Stern[4], and Steven Roose[3]

[1]Columbia University & New York State Psychiatric Institute, [2]Stony Brook University, [3]College of Physicians and Surgeons, Columbia University/New York State Psychiatric Institute, [4]College of Physicians and Surgeons, Columbia University

Background: Decreased processing and gait speed are common in late life depression (LLD), explain much of the disability associated with LLD, and predict antidepressant non-response. Since progressive age-related reductions in dopamine levels may contribute to slowing, our goal was to evaluate dopamine augmentation as a novel therapeutic strategy for LLD.

Methods: Adults aged >60 years with a DSM 5 depressive disorder, significant depressive symptoms, and decreased gait speed (< 1m/s) received 3 weeks of treatment with levodopa (L-DOPA) monotherapy at 150mg, 300mg, and 450mg doses. [11C]-raclopride positron emission tomography (PET) and multimodal magnetic resonance imaging (MRI) were conducted pre- and post-L-DOPA.

Results: N=37 subjects having mean age 75.3 ± 7.5 and HRSD 15.5 ± 6.0 participated in the clinical studies. L-DOPA resulted in increased processing speed (Digit Symbol Substitution Test; 150mg: +1.7 and d=0.2, 300mg: +3.9 and d=0.5 , 450mg: +4.2 and d=0.5) and gait speed (150mg: +0.05 and d=0.01, 300mg: +0.11 and d=0.3 , 450mg: +0.13 and d=0.4). Subjects experienced 4.6 ± 6.4 HRSD points of improvement over the 3-week study ($p<0.01$). PET scanning (N=10) revealed reduced [11C]-raclopride binding potential (ΔBPND) in the striatum overall ($t = 5.41$, df 8, $p = 0.001$) as well as the caudate ($t = 2.66$, df 8, $p = 0.029$) and putamen ($t = 5.44$, df 8, $p = 0.001$) individually.

Conclusions: In these slowed LLD patients, L-DOPA monotherapy was associated with moderate effect size improvements in processing speed, gait speed, and depressive symptoms in addition to increased dopamine release in the striatum.

Supported By: NIMH R61/R33

Keywords: Depression, Dopamine, Processing Speed, Gait

SYMPOSIUM
Inflammation Markers, Symptoms and Treatment in Schizophrenia and Related Psychoses

12:30 p.m. - 2:30 p.m.
Chair: Thomas Weickert

104. Association Between Serum C-Reactive Protein, Positive and Negative Symptoms of Psychosis in a General Population-Based Birth Cohort

Golam Khandaker[1], Jan Stochl[2], Stan Zammit[3], Glyn Lewis[4], Robert Dantzer[5], and Peter Jones[2]

[1]University of Cambridge School of Clinical Medicine, [2]University of Cambridge, [3]University of Bristol, [4]University College London, [5]University of Texas MD Anderson Cancer Center

Background: Association of inflammation with symptoms that are commonly shared between psychiatric disorders may help to explain the apparent trans-diagnostic effect of inflammation, which is associated with depression, schizophrenia and other disorders. Schizophrenia include diverse symptoms, but the relationship between inflammatory markers and specific psychotic symptoms has not been examined.

Methods: In the general population-based ALSPAC birth cohort, serum CRP levels were assessed around age 16 years. Ten positive and ten negative symptoms of psychosis were assessed using self-report questionnaires around age 17 years. Based on 2421 participants, we examined association of CRP with: (1) positive and negative symptom dimension scores obtained from factor analysis; (2) individual symptoms using regression analysis. Regression models were adjusted for sex, body mass, concurrent depressive symptoms, substance use, and other potential confounders.

Results: Most prevalent positive symptoms were paranoid ideation (4.8%), visual (4.3%) and auditory (3.5%) hallucinations. Negative symptoms were more strongly correlated with concurrent depressive symptoms ($r=0.51$; $P<0.001$) than positive symptoms ($r=0.19$; $P<0.001$). At group level, the association of CRP with positive and negative symptom dimension scores was similar. At symptom level, after adjusting for potential confounders including depressive symptoms, CRP was associated particularly with auditory hallucinations (adjusted OR=2.22; 95% CI, 1.04-4.76) and anhedonia (adjusted OR=1.13; 95% CI, 1.02-1.26).

Conclusions: The association of inflammation with depression and schizophrenia may arise from auditory hallucinations and anhedonia, which are associated with inflammation specifically and are shared between these disorders. A better understanding of inflammation-related phenotypes could

inform clinical trials of anti-inflammatory drugs for these disorders.
Supported By: Wellcome Trust (201486/Z/16/Z)
Keywords: Immunopsychiatry, Inflammation, Psychotic Symptoms, Epidemiology

105. Schizophrenia is Associated With an Aberrant Immune Response to Epstein Barr Virus

Faith Dickerson[1], Lorraine Jones-Brando[2], Glen Ford[3], Giulio Genovese[4], Cassie Stallings[1], Andrea Origoni[1], Colm O'Dushlaine[4], Emily Katsafanas[1], Kevin Sweeney[1], Sunil Khushalani[1], and Robert Yolken[2]

[1]Sheppard Pratt, [2]Johns Hopkins School of Medicine, [3]VanPelt Biosciences, [4]Stanley Center for Psychiatric Research

Background: Epstein Barr Virus (EBV) is a highly prevalent human herpesvirus capable of infecting the CNS and establishing persistent infection.
Methods: We employed solid phase immunoassay techniques to measure IgG class antibodies to Epstein Barr Virus virions and defined proteins in 432 individuals with schizophrenia and 311 individuals without a psychiatric disorder. Western blot testing was performed to document reactivity to specific EBV proteins. Polygenic risk for schizophrenia was calculated from genome sequencing arrays. Levels of antibodies between the groups were compared by multivariate analyses incorporating clinical, genetic, and demographic measures.
Results: Individuals with schizophrenia had marked elevations in the levels of antibodies to EBV virions as compared to controls (effect size =.356; 95% CI .168, .543; p<.0002). Analyses indicated increased levels of reactivity to EBV Viral Capsid Antibody (VCA) (effect size =.197; 95% CI .025, .370; p=.025) but not to EBV nuclear antigen-1 (EBNA-1) or to other herpesviruses. Western blot analysis confirmed increased reactivity to VCA proteins in the schizophrenia group and a lack of increased levels of antibodies to EBNA-1. Genetic analyses indicated an additive effect of increased levels of antibodies to EBV virions and genetic susceptibility to schizophrenia, with individuals with elevated levels of both markers having a 8.86-fold odds (95% CI 2.59, 30.37; p<.001) of a schizophrenia diagnosis.
Conclusions: Individuals with schizophrenia have increased levels of antibodies to some but not all EBV proteins indicating an aberrant response to Epstein Barr Virus infection which may contribute to the immunopathology of schizophrenia and related disorders.
Supported By: Stanley Medical Research Institute
Keywords: Epstein Barr Virus, Infection, Herpes Virus

106. Complement and Microglia Mediate Glutamatergic Neurodegeneration in Persistent Toxoplasma Infection of the Brain

Jianchun Xiao[1], Ye Li[2], Raphael Viscidi[2], Mikhail Pletnikov[2], and Robert Yolken[2]

[1]Johns Hopkins University School of Medicine, [2]Johns Hopkins University

Background: Toxoplasma gondii, a common neurotropic parasite, is increasing being linked to neuropsychiatric disorders including schizophrenia, Alzheimer's disease, and Parkinson's disease. However, the pathogenic mechanisms underlying these correlations are not clear. Toxoplasma can reside in the brain for extensive periods in the form of tissue cysts. Such persistence requires a continuous immune response to prevent the parasite reactivation. This inflammation can cause synaptic and neuronal loss, leading to disruption of brain connectivity and behavioral deficits.
Methods: We employed a mouse model of chronic Toxoplasma infection to examine neurodegenerative–associated pathological changes. Brain regions were analyzed for ongoing neurodegeneration using FluoroJadeB (FJB) and for neuroinflammation using Iba1, GFAP and multiple complement components.
Results: We documented the presence of ongoing neurodegeneration in the prefrontal cortex region of infected mice bearing a high parasite burden. The brain areas that are most affected were the anterior cingulate and somatomotor cortex. Glutamatergic neurons are the primary neuron displaying neurodegeneration. Complement proteins such as C1q and C3 bind to the degenerating neurons. Additionally, expression of multiple complement components, including C1q, C1r, C3, and C4, are profoundly upregulated, at both the RNA and protein levels. Some of the degenerating neurons are surrounded and infiltrated by activated microglia, possibly recruited by CX3CL1 overexpression.
Conclusions: These studies suggest that chronic Toxoplasma infection leads to cortical glutamatergic neurodegeneration that is mediated by activated microglia and complement. Our study provides a mechanic explanation for the involvement of chronic Toxoplasma infection in neuropsychiatric disorders and points the way towards novel methods of disease prevention and treatment.
Supported By: SMRI
Keywords: Toxoplasma, Neurodegeneration, Neuroinflammation, Complement

107. Reduction in Peripheral C-Reactive Protein Levels With Canakinumab Administration is Related to Reduced Positive Symptom Severity in Patients With Schizophrenia and Inflammation

Thomas Weickert[1], Isabella Jacomb[2], Rhoshel Lenroot[1], Julia Lappin[1], Danielle Weinberg[2], William Brooks[2], David Brown[3], Daniel Pellen[2], Jochen Kindler[2], Adith Mohan[1], Denis Wakefield[1], Andrew Lloyd[1], Clive Stanton[4], Maryanne O'Donnell[4], Dennis Liu[5], Cherrie Galletly[6], and Cynthia Shannon Weickert[2]

[1]University of New South Wales, [2]Neuroscience Research Australia, [3]Westmead Hospital, [4]Prince of Wales Hospital, [5]Northern Adelaide Local Health Network, [6]University of Adelaide

Background: Cytokine interleukin 1-beta (IL-1β) levels are significantly increased in schizophrenia and first episode psychosis. Canakinumab is an approved human anti-IL-1β monoclonal antibody that interferes with the bioactivity of

IL-1β. The extent to which canakinumab can reduce peripheral inflammation markers, e.g., high sensitivity C-reactive protein (hsCRP), and psychotic symptom severity in schizophrenia is unknown.
Methods: We conducted a randomized, placebo-controlled, double-blind, parallel groups trial of canakinumab in schizophrenia. Twenty-seven chronically ill patients with schizophrenia who had elevated peripheral inflammation markers (IL-1β, IL-6, hsCRP and/or neutrophil to lymphocyte ratio) at baseline were randomized to a one-time subcutaneous injection of adjunctive canakinumab (150 mg) or placebo (normal saline). Peripheral hsCRP was measured at baseline and 1, 4- and 8-weeks post injection. Positive and Negative Syndrome Scale scores were assessed at baseline and 4- and 8-weeks post injection.
Results: Separate t-tests comparing canakinumab and placebo to baseline showed significant peripheral hsCRP reductions at all time points (all p's<0.02) in the canakinumab group only and significant positive symptom severity score reductions at week 8 (p=0.05) in the canakinumab group and at week 4 (p=0.02) in the placebo group. There was a trend for low peripheral hsCRP to be strongly correlated with low positive symptom severity scores (r=0.57, p=0.07) only at week 8 in the canakinumab group.
Conclusions: Canakinumab significantly reduces peripheral hsCRP levels which may be related to positive symptom severity reduction in schizophrenia. Peripheral hsCRP reduction is potentially beneficial to general health in schizophrenia. Future studies should consider increased doses to confirm adjunctive canakinumab benefits in schizophrenia.
Supported By: Stanley Medical Research Institute; NARSAD Independent Investigator Award
Keywords: Schizophrenia, Schizoaffective Disorder, Inflammation, C-Reactive Protein, Positive Symptoms, IL-1beta

SYMPOSIUM
Structural and Substructural Investigation of the Brain in Posttraumatic Stress Disorder by the ENIGMA Worldwide Consortium
12:30 p.m. - 2:30 p.m.
Chair: Rajendra Morey

108. Hippocampal Subfield Volumes Relate to Unique Phenotypes of PTSD: International Analysis by the PGC-ENIGMA PTSD Working Group

Lauren Salminen[1], Mark W. Logue[2], Emily C. Clarke[3], Emily L. Dennis[4], Juan E. Iglesias[5], Jasmeet Hayes[6], Soraya Seedat[7], Steven E. Bruce[8], Christopher D. Whelan[4], Neda Jahanshad[1], Paul M. Thompson[1], and Rajendra A. Morey[9], PGC-ENIGMA PTSD Working Group

[1]Keck School of Medicine University of Southern California, [2]National Center for PTSD at VA Boston Healthcare System & Boston University School of Medicine, [3]Duke University, [4]USC, [5]University College London, [6]VA Boston Healthcare System; Boston University School of Medicine, [7]Stellenbosch University, [8]University of Missouri St. Louis, [9]Duke University Medical Center & Durham VA Medical Center

Background: Subregions of the hippocampus are cytoarchitecturally and functionally distinct and may be differentially impacted by trauma exposure and PTSD. Here we used a harmonized neuroimaging protocol based on FreeSurfer 6.0 to identify a common hippocampal subfield marker of PTSD across more than 30 cohorts worldwide (PTSD, n=1,211; Control, n=1,782; Mage=38.5(13.6) years).
Methods: Mixed models were conducted to identify substructural signatures of PTSD in 11 hippocampal subregions after adjusting for cohort, sex, age, age squared, and intracranial volume. Subsequent analyses examined childhood trauma, depression, and alcohol use disorder as multivariate predictors of subfield volumes.
Results: We observed smaller volumes in the hippocampal tail (β= -0.09) and amygdala transition area (β= -0.07; p's <0.05) of individuals with current PTSD compared to controls with varying levels of trauma exposure. The PTSD group also demonstrated smaller volumes in the CA1 and presubiculum (β's= -0.06; p's<0.05) after covarying for civilian versus military status, and smaller volumes in the CA4 (β= -0.08) and parasubiculum (β= -0.1; p's<0.05) after excluding 162 individuals with lifetime PTSD but no current diagnosis. Examination of individual clinical variables revealed a negative effect of depression on volumes of the dentate gyrus (β= -0.11), molecular layer (β= -0.09; p's<0.01), and CA1-CA4 (β= -0.12 to -0.14, p's<0.001), but no significant effect of PTSD. Conversely, we observed larger CA3 volumes (β= 0.13, p<0.05) in the PTSD group after adjusting for an aggregate marker of high versus low clinical risk.
Conclusions: Collectively these results suggest that variability in PTSD phenotypes may be related to underlying differences in hippocampal substructure.
Supported By: NIH U54 EB020403-04S1; NIH R01 MH111671-01A1; Duke Health Scholars Award; VA Mid-Atlantic MIRECC; Cohen Veterans Bioscience
Keywords: PTSD - Posttraumatic Stress Disorder, Hippocampal Subfields, Trauma Exposure, Big Data Analysis, Brain Imaging

109. Mega-Analysis of Cortical Morphometric Differences Between PTSD Patients and Non-PTSD Controls

Xin Wang[1], Hong Xie[1], Tian Chen[1], Brian O'Leary[1], Andrew Cotton[1], Donald White[1], Rajendra Morey[2], and Israel Liberzon[3], ENIGMA Post-Traumatic Stress Disorder Working Group

[1]University of Toledo, [2]Duke University, [3]University of Michigan

Background: Multiple studies have reported morphometric abnormalities in PTSD, but small sample size of individual studies has limited statistical power to detect smaller scale changes. Whole cortex mega-analyses combining regional analyses and higher discrimination vertex analyses in large numbers of subjects provide an opportunity to overcome small sample limitations.
Methods: The PGC-PTSD Group has accumulated cortical morphometric data from 3500 subjects at both regional and surficial vertex (1 mm2) levels from 31 PTSD laboratories.

PTSD effects were examined separately in 46 adult studies (ages 18 − 69) and 5 child studies (ages 6 − 18), controlling for study, age, gender, intracranial volume, and scanner differences. Regions which showed significant interactions with age and/or gender after false discovery rate correction (FDR, <0.05) were further probed for interaction effects using the Johnson-Neyman method.
Results: The regional analyses of adult studies revealed primarily cortical thinning (and volume reduction) in frontal, temporal, and occipital cortices of PTSD patients vs. controls (P values ranging from 0.0000089 to 0.011). Analyses of interaction effects suggested possible age and gender effects in some regions. Vertex analyses suggest more focal cortical thinning (FDR corrected $P < 0.05$) in several areas consistent with findings from regional analyses.
Conclusions: Findings suggest that PTSD may associate with morphometric changes in a number of cortical regions, and that some changes can be age or gender specific. We will explore PTSD effects in different ages and the effects of confound conditions to further characterize PTSD-related cortical morphometric changes.
Keywords: PTSD - Posttraumatic Stress Disorder, Cortical Thickness, Cortical Volume, Mega Analysis

110. Amygdala Subregions Volumes are Associated With PTSD

Emily Clarke[1], Rajendra Morey[2], Rachel Phillips[2], Courtney Haswell[2], and Kevin LaBar[2]

[1]Duke University, [2]Duke University Medical Center & Durham VA Medical Center

Background: The amygdala is a subcortical structure involved in emotion processing and associative fear learning. Functional magnetic resonance imaging (MRI) studies have shown that individuals with PTSD have an exaggerated amygdala response to emotional stimuli when compared with control subjects. While animal studies have demonstrated changes in amygdala morphology with chronic stress, particularly in basolateral and centromedial amygdala complexes, this level of investigation has been largely absent in human studies.
Methods: This study assessed US military veterans (N=346) with lifetime PTSD (N=141) and trauma-exposed non-PTSD controls (N=206), who served since 9/11 (2001). High resolution T1-weighted anatomical scans optimized for tissue contrast were acquired on a 3T GE scanner. Automated segmentation of amygdala subregions was completed using FreeSurfer 6.0 on nine subregions including basal, lateral, accessory basal, anterior amygdaloid, central, medial, cortical, corticoamygdaloid transition area, and paralaminar.
Results: We found that lifetime PTSD was associated with smaller volumes of the left accessory basal (p=0.043, d=0.01), right lateral (p=0.019, d=0.06), and right paralaminar (p=0.018, d=0.17) nuclei as well as larger volumes of the left and right medial (p= 0.003, 0.035; d=-0.29,-0.20) and cortical (p=0.010, 0.015; d=-0.18,-0.19) and right accessory basal (p=0.002, d=-0.12) and central (p=0.025, d=-0.19) nuclei after Bonferroni correction. In addition, alcohol use significantly affected the volumes of several subregions.
Conclusions: Our results are consistent with animal models of chronic stress, as the basolateral complex, associated with fear learning, was smaller in the PTSD group whereas the centromedial complex, associated with fear expression, was larger in the PTSD group.
Supported By: NIH; VA MIRECC
Keywords: Amygdala, PTSD, Veterans, Central Nucleus of the Amygdala, Basolateral Amygdala

111. Lower White Matter Integrity in PTSD: Results From the PGC-Enigma PTSD Working Group

Emily Dennis[1], Negar Fani[2], Seth Disner[3], Lauren Salminen[4], Paul M. Thompson[4], Peter Kochunov[5], Neda Jahanshad[4], and Rajendra Morey[6], ENIGMA Post-Traumatic Stress Disorder Working Group[4]

[1]Brigham & Women's Hospital, Harvard Medical School, [2]Emory University, [3]Minneapolis VA Health Care System, [4]Imaging Genetics Center, USC Keck SOM, [5]Maryland Psychiatric Research Center, University of Maryland School of Medicine, [6]Duke University Medical Center & Durham VA Medical Center

Background: Results from diffusion MRI (dMRI) studies of PTSD (post-traumatic stress disorder) have been inconsistent, with some reporting higher fractional anisotropy (FA) while others report lower FA in patients compared to controls.
Methods: We present results from the PGC-ENIGMA PTSD Working Group examining dMRI across sites. Participants were included from 23 different studies, for a total of 1341 patients and 1699 controls (1207 trauma-exposed). Sites processed dMRI brain scans with the ENIGMA-DTI protocol (http://enigma.usc.edu). FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated and were averaged within the entire skeleton, 5 midline, and 18 bilaterally averaged white matter (WM) regions of interest (ROIs) from the JHU atlas. Case/control effect sizes were calculated within each site, and statistical results were pooled across sites to meta-analyze group differences. The significance threshold was set at $p < 0.05/20 = 0.0025$.
Results: We found borderline lower FA ($0.05>p>0.0025$) in the PTSD group in the tapetum (Cohen's D=-0.11, p=0.0061). We found similar results in a model including un-exposed controls as well. There were only a few sites that included both trauma-exposed and un-exposed participants, but among those cohorts, trauma exposure was associated with significantly lower FA in the splenium of the corpus callosum (D=-0.31, p=0.00011) and borderline differences in the tapetum (D=-0.19, p=0.043).
Conclusions: We found lower FA in PTSD in the tapetum, which connects the left and right temporal lobes and disruption may be associated with memory dysfunction. Future analyses will examine PTSD severity, as well as potential comorbidities such as depression.
Supported By: NIH; DoD; USAMRMC; VA
Keywords: PTSD - Posttraumatic Stress Disorder, Diffusion Tensor Imaging (DTI), Meta-Analysis

SYMPOSIUM
The Suitability of Neuroscientific Measures for Assessment of Individual Differences: Strategies for Improvement
12:30 p.m. - 2:30 p.m.
Chair: Annmarie MacNamara

112. Individual Differences Neuroscience: From Within- To Between-Subjects Differences in Psychopathology

Greg Hajcak[1], Roman Kotov[2], Alexandria Meyer[1], Katherine Luking[2], and Brady Nelson[2]

[1]Florida State University, [2]Stony Brook University

Background: Human neuroscience research has produced few significant advances in diagnosing, predicting, treating, and preventing mental illness. I'll argue that one major reason for poor progress in clinical neuroscience is a failure to adequately consider the distinction between within- and between-subjects comparisons. Explaining differences between people requires measures with good psychometric properties. Robust, group-level differences from within-subject contrasts does not imply adequate internal consistency for understanding individual differences.
Methods: I will present a range of neuroimaging data (i.e., both fMRI and EEG) from multiple tasks (i.e., emotional face matching, simple reward). I'll focus on internal consistency, and further issues related to difference scores in large sample of adolescents (N=177). Finally, I will examine sensitivity, specificity, and positive and negative predictive value of neural measures, when used alone and in conjunction with self-report measures.
Results: In our data, certain within-subjects effects (e.g., amygdala activation to faces versus shapes) were completely unreliable as contrast-based scores ($r \sim .05$). Other measures (e.g., increased striatal activation to reward versus loss) were both robust and internally reliable ($r \sim .30$). We demonstrate how neural measures can be used to improve classification when combined in series with self-report measures.
Conclusions: Neuroscience studies need to distinguish between robust within-subjects effects and reliable between-subjects variability. These psychometric issues may explain some poor progress in human neuroscience research. I'll propose basic approaches for choosing and optimizing tasks and resultant fMRI/ERP measures, and how they might be combined in the real world to improve classification of psychopathology.
Supported By: NIMH; R01 MH097767
Keywords: Neuroimaging, Psychometrics, Classification

113. Lessons From Test Construction: The Establishment of Norms and Item Analysis for Cognitive Affective ERPs

Annmarie MacNamara[1], Daniel Foti[2], Michael Imburgio[1], David Clark[3], and Anna Weinberg[4]

[1]Texas A&M University, [2]Purdue University, [3]Michigan State University, [4]McGill University

Background: Cognitive affective neuroscience tasks are not typically subjected to the rigors of test construction. For example, although the error-related negativity (ERN) has been shown to predict risk for psychopathology, it is unknown what values might constitute a "normal" or "abnormal" ERN (there are no established norms). In addition, task stimuli for assessing individual differences in neural measures of affective reactivity (e.g., positive and negative pictures) are rarely selected to maximize these differences (item analysis is not performed).
Methods: We present examples of norming and item analysis as two ways to improve neuroscientific measures for the examination of individual differences. First, we examined the distributions of event-related potential (ERP), the ERN, in an unselected sample of adults ($N = 800$). Second, we used item-response theory (IRT) modeling techniques to identify emotional pictures that best differentiated individuals ($N = 80$) in terms of affective processing, as measured by ERP, the late positive potential (LPP).
Results: First, the 25th, 50th, and 75th percentile scores for the ΔERN (error - correct) were -2.37μV, -5.41μV, and -8.65μV, respectively. Second, item-response models fit the data well and were reliable ($\alpha s > .80$; discrimination $> .80$). Pictures that were the most informative about individual levels of latent trait theta (affective reactivity) were not necessarily the most likely to elicit the largest LPPs.
Conclusions: It may be worthwhile to establish norms for a variety of neuroscientific measures. In parallel, it may be fruitful to work to improve task design; item response theory may provide a useful means of selecting stimuli.
Supported By: A. MacNamara is supported by National Institute of Mental Health grant, K23MH105553
Keywords: Event Related Potentials, Individual Differences, Emotion, Error Monitoring, Assessment

114. Test-Retest Reliability of Task-Evoked Bold fMRI: Implications for Individual Differences Neuroscience

Annchen Knodt[1], Maxwell Elliott[1], and Ahmad Hariri[1]

[1]Duke University

Background: The utility of neuroimaging phenotypes for the study of individual differences depends on how reliably they can be measured over time. Task-evoked activity measured with BOLD fMRI is increasingly used for mapping variability in behavior and risk for mental illness. However, the test-retest reliability of these measures may not be sufficient for individual differences research.
Methods: Here, we calculate the test-retest reliability of regional activation for 7 fMRI tasks from the Human Connectome Project (HCP) where 45 participants were scanned twice, with a mean test-retest interval of approximately 140 days. Test-retest reliability of task-evoked activation within a priori regions of interest (ROIs) was quantified using the intra-class correlation coefficient (ICC).
Results: Robust (i.e., $p < 0.05$, FWE corrected) task-evoked signal was observed for all tasks within target ROIs at each time point. However, the test-retest reliability was generally poor regardless of the specific task-based contrast examined.

The test-retest reliability further did not systematically vary as a function of target region, with a range of ICC values observed for both cortical and subcortical ROIs.
Conclusions: Collectively, these analyses suggest that, at best, caution is warranted when advancing task-evoked regional activation as a neuroimaging phenotype in individual differences research.
Supported By: The Human Connectome Project is funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research, and by the McDonnell Center for Systems Neuroscience at Washington University.
Keywords: Test-Retest Reliability, Human Connectome Project, Task fMRI, Individual Differences

115. Developing Treatment Targets for Substance Use Disorders With Machine Learning Classifiers

Vaughn Steele[1]

[1]NIH/NIDA

Background: Machine learning classifiers are used to identify patterns, which are not readily observable, in complex datasets holding promise toward individualized medicine. When applied to datasets generated from event-related potentials (ERP) and structural or functional magnetic resonance imaging (s/fMRI), precision can be improved in diagnosis, treatment assignment, and predicting individuals at greatest future risk. However, robust classification requires extracting reliable signals from ERP or s/fMRI data. Given the cost in time and resources of collecting such data, researchers must plan their experiments to ensure that stable estimates of the measured cognitive processes are efficiently and effectively acquired.
Methods: Methods will be discussed for extracting reliable ERP and fMRI measures, using an example of error-related measures to demonstrate factors such as the minimum number of error trials and participants necessary for analysis. I will describe how to combine machine learning classifiers with reliable neural signals, using examples involving the prediction of antisocial traits and behaviors and outcomes of substance abuse treatment.
Results: Machine learning classifier of fMRI (N = 139) data collected during a response inhibition (Go/NoGo) task prior to a 12-week cognitive behavioral substance abuse treatment program predicted who would (82.24%) and would not (78.13%) complete the program (permutation analyses: p = .026).
Conclusions: Based on machine learning derived treatment targets and dysregulated circuits to monitor throughout treatment, I developed a transcranial magnetic stimulation intervention for cocaine use disorder. With such methods, advanced models could be developed aiding individualized medicine to benefit the diagnosis and treatment of a wide-range of neuropsychiatric populations.
Supported By: The Intramural Research Program of the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH), Baltimore, MD, USA

Center on Compulsive Behavior, NIH, Bethesda, MD, USA
Keywords: Substance Abuse, Machine Learning, Prediction, ERP, BOLD fMRI

SYMPOSIUM
Psychotropic Drug Development in the 21st Century; The NIMH Experimental Medicine Program
12:30 p.m. - 2:30 p.m.
Chair: Jeffrey Lieberman

116. Results of the NIMH FAST-MAS Phase IIa Proof of Mechanism Study of the Effects of the Selective κ Opioid Antagonist JNJ-67953964 on fMRI Ventral Striatal Activity in Anhedonic Patients

Andrew Krystal[1], Diego Pizzagalli[2], Moria Smoski[3], Sanjay Mathew[4], John Nurnberger[5], Sarah Lisanby[6], Dan Iosifescu[7], James Murrough[8], Richard Weiner[9], Joseph Calabrese[10], Gerard Sanacora[11], Richard Keefe[12], Allen Song[3], Wayne Goodman[4], Steven Szabo[12], Alexis Whitten[2], Keming Gao[13], and William Potter[6]

[1]UCSF, [2]Harvard Medical School/McLean Hospital, [3]Duke University School of Medicine, [4]Baylor College of Medicine, [5]Indiana University, [6]National Institute of Mental Health, [7]NYU School of Medicine, [8]Icahn School of Medicine at Mount Sinai, [9]Duke University, [10]Case Western Reserve University School of Medicine, [11]Yale University, [12]Duke University Medical Center, [13]Case Western Reserve University School of Medicine

Background: Compelling preclinical research indicates the promise of κ opioid receptor (KOR) antagonism for treating anhedonia. However, we lack human data with selective KOR antagonists. This NIMH Fast-Fail Trials in Mood/Anxiety Spectrum Disorders (FAST-MAS) study attempted to establish proof of mechanism (POM) for KOR antagonism by testing if selectively and robustly engaging this target with JNJ-67953964 modulates ventral striatal reward circuitry.
Methods: Adults with mood (N=70) or anxiety (N=19) disorders with anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] score≥20), were randomized to 8-weeks of double-blind treatment with JNJ-67953964 10 mg (N=45) or placebo (N=44). Primary outcome was nucleus accumbens activation in anticipation of rewards assessed with an fMRI monetary incentive delay task.
Results: Compared with placebo, JNJ-67953964 significantly enhanced nucleus accumbens activation during reward (p=0.0095) (primary outcome) and loss anticipation (p<0.001) and improved the SHAPS (secondary clinical measure) (p=0.035). There was no effect for reward learning across blocks in the probabilistic reward task (secondary behavioral measure) but reward learning was, in general, significantly improved with JNJ-67953964 vs placebo (p=0.05). Highlighting the reward-specificity of the findings, there were no significant HAM-D/HAM-A treatment effects. JNJ-67953964 was not associated with any side-effects that would limit its use.
Conclusions: This study establishes POM for KOR antagonism, thereby increasing the probability of finding effects on

clinical anhedonia endpoints in appropriately powered trials. It also: specifically predicts anti-anhedonic effects of JNJ-67953964; establishes early phase methods for developing anhedonia therapies; and serves as a model for implementing "Fast-Fail" drug development methodology, incorporating rigorous POM testing before proceeding to trials with clinical endpoints.

Supported By: NIMH Contract HHS-N271-2012-000006-I
Keywords: Kappa Opioid Receptor Antagonist, Fast-Fail, Nucleus Accumbens, Proof of Mechanism

117. Biomarker Assessment of Dose Dependent Target Engagement of mGluR-2,3 Partial Agonist for Schizophrenia Treatment

Jeffrey Lieberman[1], Donald Goff[2], Stephen Marder[3], Adrienne Lahti[4], Daniel Javitt[5], Joshua Kantrowitz[5], Ragy Girgis[6], Jack Grinband[6], Larry Kegeles[6], Melanie Wall[6], and Tse-We Chou[6]

[1]College of Physicians & Surgeons, Columbia University, [2]NYU Langone Medical Center, [3]UCLA & VA Greater Los Angeles, [4]University of Alabama at Birmingham, [5]Columbia University/Nathan Kline Institute for Psychiatric Research, [6]Columbia University

Background: There is a desperate need for novel drugs for treatment of schizophrenia. Glutamate is a prioritized target for drug development. Attempts to develop mGlu-R partial agonists were unsuccessful. Upon reviewing the data, we concluded that doses to achieve adequate target engagement were tested. This study tested the ability to an mGluR-2,3 partial agonist to inhibit the effects of a pharmacologic model of schizophrenia as reflected by fMRI.
Methods: To evaluate the effects of the mGluR2/3 partial agonist LY2140023 (Pomaglumetad Methionil, "POMA") at selected doses on ketamine-stimulated glutamate release in prefrontal cortex, as measured by pharmacoBOLD fMRI. Ketamine-induced glutamate release is hypothesized to simulate the synaptic dysregulation in schizophrenia. This study will determine which POMA dose is sufficient to engage the primary target (mGlu2/3 receptors). Both treatment arms will be compared only to placebo.

Study population: 100 healthy volunteers (100 randomized, for 81 completers)

Design: 3-arm randomized (1:1:1) double blind administration of 1) low dose (40 mg BID) POMA, 2) high dose (160 mg BID) POMA, or 3) placebo

Outcome measures: Ketamine-induced prefrontal glutamate activity as measured by PharmacoBOLD (primary).
Results: The results indicated that POMA reduced ketamine stimulated bold in a dose dependent fashion, but cardio-respiratory effects also contributed to the bold signal.
Conclusions: The results supported the hypothesis that POMA will suppress ketamine induced increases in fMRI bold activity compared to placebo indicating its glutamate target engagement.
Supported By: NIMH Contract
Keywords: Schizophrenia, Drug Development, Biomarkers, Drug Discovery

118. The Challenges of Testing D1 Agonists in Schizophrenia

Anissa Abi-Dargham[1], Jared Van Snellenberg[1], Ragy Girgis[2], Mark Slifstein[1], Jonathan Javitch[3], and Jeffrey Lieberman[3]

[1]Stony Brook University, [2]Columbia University, [3]College of Physicians & Surgeons, Columbia University

Background: Multiple lines of research have converged to suggest a prominent role for the D1 receptor in the treatment of cognitive deficits in schizophrenia. D1 is a prominent mediator of dopamine's effects in the prefrontal cortex, and there is robust evidence for suboptimal stimulation of D1 receptors in dorso-lateral prefrontal cortex in schizophrenia, suggesting that D1 agonists may be beneficial.
Methods: In this presentation we will show our prior work imaging D1 occupancy by DAR100A in non-human primates (NHP) and administration of this drug subacutely to patients with schizophrenia at doses based on the knowledge gained from the work in NHP. This work lead to subsequent discussions within the context of the NIMH Experimental Medicine Studies Trials Program and the choice of a newer D1 agonist with a more favorable pharmacokinetic profile, and occupancy levels determined in humans and in NHP.
Results: This presentation will review the results of the discussion of experimental designs most appropriate to test the D1 mechanism in schizophrenia. Issues of power, task selection, mode of administration, subject's selection will be reviewed and contrasted with the available data from studies in humans and NHP. Because of the importance of this mechanism and the cost of these studies, the careful evaluation of all these points is an important question for the field to consider and discuss openly.
Conclusions: This study will be a POC designed rationally to provide a definitive testing of D1 agonists effects acutely on WM circuitry and performance in schizophrenia.
Supported By: NIMH
Keywords: D1, Target Engagement, Working Memory, Cognition

119. Translating Neuroscience Into Drug Development: Evolving NIMH Strategy

William Potter[1]

[1]National Institute of Health/NIMH

Background: Major pharmaceutical companies have pulled back from investment in new drugs for psychiatric indications and it is falling to NIMH to explore ways of filling this gap.
Methods: Analysis of molecular targets for drug action vs those that have been adequately tested in humans was based on a set of criteria of what constitutes adequate testing. These include target engagement, functional brain effects and exploration of behaviors that go beyond traditional assessments in DSM defined disorders.
Results: Among >100 targets proposed over decades less than 10 have been adequately ruled in or out as

psychotherapeutic. PET receptor occupancy and functional read outs of drug activity provide methods for studying some inadequately evaluated targets. These include the kappa opioid, metabotropic glutamate and dopamine 1 targets discussed in this panel. How these were selected as well outlining a new strategic approach for assessing non-validated mechanisms will be presented.
Conclusions: Given the disappointing results from approaches taken since the 1980's to establish the therapeutic role in psychiatric disorders of the many mechanisms that go beyond those provided by currently marketed drugs a new strategy is needed. At a minimum, a concerted effort to rule in or out mechanisms for which methods are available to adequately test the hypothesis will prevent futile efforts and make more resources available for other possibilities. The described approach may also provide a means of "rescuing" agents that have failed to date because of a failure to identify the proper dose range for clinical studies.
Supported By: NIMH
Keywords: Translational Research, Molecular Biomarkers, Target Engagement, Drug Development

SYMPOSIUM
Neuroplastic and Antidepressant Actions of General Anesthetics
12:30 p.m. - 2:30 p.m.
Chair: Hanna Antila
Co-Chair: Brian Mickey

120. Modulation of Infant Brain Activity by General Anesthetics

Laura Cornelissen[1]

[1]Boston Children's Hospital

Background: General anesthetics generate spatially defined brain oscillations in the EEG that relate fundamentally to neural-circuit architecture. Long-term morphological and functional alterations are current issues of interest in pediatric anesthesiology. In this lecture, I will provide an overview of the neurobiological effects of general anesthetics, with an emphasis on our recent results suggesting that these drugs have age-related changes in EEG characteristics that mirror different stages of early human brain development and may impact outcomes.
Methods: Multichannel EEG recordings were performed in 91 children aged 0-3 years undergoing elective surgery. We mapped spatial power and coherence over the frontal, parietal, temporal and occipital cortices during anesthesia. Frequency of profound EEG suppression was additionally assessed.
Results: During sevoflurane exposure: (i) theta (4-8Hz) and alpha (8-12Hz) oscillations emerge by ~4 months; (ii) alpha oscillation power increased from 4-10 months; (iii) frontal alpha-oscillations emerged at ~6 months; (iv) frontal slow oscillations were coherent from birth until 6 months; (v) frontal alpha oscillations become coherent at ~10 months and persist into older ages. Profoundly suppressed brain activity was observed in 51% subjects, with a median duration of 10s (95% CI:8-12). Younger infants exhibited a higher number of suppression events, and the incidence decreased with postnatal age.
Conclusions: Key developmental milestones in the maturation of the thalamo-cortical circuitry likely generate changes in EEG patterns. Characterization of anesthesia-induced EEG oscillations in children demonstrates the importance of developing age-dependent strategies to monitor the brain states of children receiving powerful modulators of neural activity. These data can guide future studies investigating neurodevelopmental pathologies involving altered excitatory-inhibition balance such as depression or Rett syndrome.
Supported By: International Anesthesia Research Society
Keywords: Anesthesia, Pediatric, Developmental Trajectories, Electroencephalography (EEG), Brain Connectivity

121. Propofol for Treatment-Resistant Depression: Clinical and Neural Effects

Brian Mickey[1], Andrew Prescot[2], Robert Welsh[2], Perry Renshaw[2], and Scott Tadler[2]

[1]University of Utah School of Medicine, [2]University of Utah

Background: Propofol is a widely used general anesthetic that engages gamma-aminobutyric acid (GABA) receptors and N-methyl-D-aspartate (NMDA) glutamate receptors. We hypothesized that propofol has antidepressant properties and that it may trigger neuroplasticity by altering excitatory-inhibitory balance in the prefrontal cortex.
Methods: We studied 30 subjects (age 18-45, 50% female) with moderate-to-severe medication-resistant depression. Ten participants each received a series of 10 propofol infusions at a frequency of 3 times per week. Propofol was dosed to strongly suppress electroencephalographic (EEG) activity for 15 minutes. Twenty matched subjects received a series of 10 electroconvulsive therapy treatments. Depression was measured with the Hamilton Depression Rating Scale (HDRS-24) and the Quick Inventory of Depressive Symptomatology (QIDS-SR). We quantified levels of GABA, glutamate, and glutamine in the medial prefrontal cortex serially in four propofol subjects using proton magnetic resonance spectroscopy (MRS).
Results: HDRS-24 scores decreased by a mean of 20 points, corresponding to a mean 58% improvement from baseline (Hedges effect size = 1.3, $p=0.009$). QIDS-SR scores improved similarly in the propofol and electroconvulsive therapy groups ($p>0.20$). The degree of intraoperative EEG suppression predicted clinical response to propofol ($p=0.008$). Prefrontal GABA and glutamate levels correlated with each other ($p=0.003$). The ratio of glutamate to GABA decreased among propofol responders and increased or remained stable among non-responders ($p=0.005$).
Conclusions: Propofol may trigger antidepressant effects similar to electroconvulsive therapy but with fewer side effects. Controlled studies are warranted to further evaluate propofol's antidepressant efficacy and mechanisms of action. EEG and MRS measures of excitatory-inhibitory balance represent promising biomarkers for future research.
Supported By: Other
Keywords: NMDA Receptor, GABA, Glutamate, Treatment Resistant Depression, Inhibition/ Excitation Balance

122. Antidepressant Mechanisms of Isoflurane and Nitrous Oxide

Samuel Kohtala[1], Wiebke Theilmann[1], Marko Rosenholm[1], Nobuaki Matsui[2], Ipek Yalcin[3], Henna-Kaisa Wigren[1], and **Tomi Rantamäki**[1]

[1]University of Helsinki, [2]Tokushima University, [3]CNRS, Strasbourg

Background: Isoflurane and nitrous oxide (N2O) have been shown to bring rapid antidepressant effects in patients but the underlying mechanisms remain unclear. We present our recent findings regarding how isoflurane and N2O, at different dosing regimens, acutely regulate EEG and key molecular determinants associated with the rapid antidepressant effects of ketamine.
Methods: Effects of drugs on brain activity were investigated in C57BL/6 mice or Wistar rats using EEG, while western blot and qPCR were used to investigate molecular markers in prefrontal cortex samples. Learned helplessness was used to assess antidepressant-like behavior. Sample size (N) of 3-5 was used for EEG, 5-7 for biochemical and 7-9 for behavioral experiments.
Results: Isoflurane dose-dependently (1% - 2.0%) increased phosphorylation of TrkB and GSK3β. Immediate-early genes (IEGs) (e.g. arc) were, however, reduced during anesthesia ($p<0.005$) while a rebound increase occurred during anesthesia recovery in a subset of animals. Medetomidine, a drug that produces prominent sedation accompanied with slow EEG oscillations, also increased p-TrkB ($p<0.05$) and p-GSK3β ($p<0.005$) without changes in IEGs. These changes, however, did not result in antidepressant-like behavioral changes in learned helplessness. Arc mRNA and p-MAPK were up-regulated during N2O exposure (both $p<0.05$). Levels of p-TrkB ($p<0.05$) and p-GSK3β ($p<0.005$) became regulated only upon N2O discontinuation, during a brain state dominated by slow EEG activity and immobility.
Conclusions: Our results suggest that cortical excitability and the subsequent regulation of TrkB-GSK3β signaling during homeostatic slow oscillations are essential for rapid antidepressant responses. Whether deep anesthesia evokes hyperexcitation and subsequent rebound TrkB-GSK3β signaling during the recovery phase remains to be investigated.
Supported By: This study has been supported by the Academy of Finland (grants 276333, 284569, 305195, 312664) and the Business Finland.
Keywords: Ketamine, Major Depressive Disorder (MDD), Nitrous Oxide, Electroencephalography (EEG), NTRK2

123. Inhaled Nitrous Oxide as a Rapid Acting Antidepressant

Charles Conway[1]

[1]Washington University School of Medicine

Background: N-methyl-D-aspartate receptor antagonists (e.g., ketamine) have rapid antidepressant effects in treatment-resistant depression (TRD). Ongoing studies demonstrate that nitrous oxide, an inhalational general anesthetic and N-methyl-D-aspartate receptor antagonist, may be a rapidly acting TRD treatment.
Methods: In a placebo-controlled crossover pilot trial, 20 TRD patients were randomly assigned to 1-hour inhalation of 50% nitrous oxide/50% oxygen or 50% nitrogen/50% oxygen (placebo); primary endpoint was 21-item Hamilton Depression Rating Scale (HDRS-21) change at 24 hours. Additionally, ongoing studies are assessing multiple aspects of the clinical/neurophysiological effects of nitrous oxide in TRD including: dose optimization (25%, 50% versus placebo), use in bipolar TRD, and brain imaging studies to study effects on brain connectivity.
Results: In the pilot study, nitrous oxide demonstrated clinically significant antidepressant effects over placebo in TRD: depressive symptoms improved at 2 and 24 hours post-nitrous oxide compared with placebo (mean HDRS-21 difference 2 hours, −4.8 points, $p = .002$; 24 hours, −5.5 points, $p < .001$; difference, $p < .001$). Four TRD patients responded and three remitted (HDRS-21 ≤ 7 points) with nitrous oxide, vis-à-vis one responder and no remitters with placebo (OR response 4.0, OR remission, 3.0). No serious adverse events occurred. Preliminary analysis suggests that in non-depressed controls, nitrous oxide may increase resting state connectivity in regions associated with depression (e.g., default mode network).
Conclusions: Nitrous oxide, a known NMDA antagonist, may be an effective antidepressant in TRD. Studies of dose optimization, as well as imaging studies of the effects of nitrous oxide on the brain, are ongoing.
Supported By: NARSAD, NIMH R21, Stanley Medical Research Institute, Taylor Foundation
Keywords: Treatment Resistant Depression, Depression, NMDA Antagonists, Inhalation, Rapid Antidepressant

SYMPOSIUM
Early Findings From the Multi-Center Social Processes Initiative in Neurobiology of the Schizophrenia(s)

12:30 p.m. - 2:30 p.m.
Chair: Aristotle Voineskos

124. Separable and Replicable Neural Strategies During Social Brain Function in People With and Without Severe Mental Illness

Colin Hawco[1], Robert Buchanan[2], Navona Calarco[1], Benoit Mulsant[1], Joseph Viviano[1], Erin Dickie[1], Miklos Argyelan[3], James Gold[2], Marco Iacoboni[4], Pamela DeRosse[3], George Foussias[1], Anil Malhotra[3], and Aristotle Voineskos[1]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]Maryland Psychiatric Research Center, University of Maryland School of Medicine, [3]The Zucker Hillside Hospital, [4]David Geffen School of Medicine at UCLA

Background: Case-control study design and disease heterogeneity may be major limiting factors impeding biomarker

discovery in brain disorders, including serious mental illnesses. In order to identify biologically/behaviorally driven as opposed to diagnostically driven sub-groups, we used hierarchical clustering to identify participants with similar patterns of brain activity during a facial Imitate/observe fMRI task.
Methods: In a 3-site study, participants (N=179; schizophrenia spectrum disorder (109) and healthy controls (70)) were scanned during the performance of the task. Hierarchical clustering was performed to identify data-driven groups, who shared similar patterns of neural circuit activation. The number of groups was determined using cluster stability analysis, defined as local minimums for instability across a range from 2 to 10 clusters. The new data-driven groups were compared on social and neurocognitive test performance.
Results: Three clusters were found with distinct patterns of neural activity. Participants showed greater similarity to their cluster than to their diagnostic category or site. The largest cluster represented 'typical activators', with activity in the canonical 'simulation' circuit. The other clusters represented a 'diffuse/inefficient' activating group, and an 'efficient/deactivating' group. The efficient/deactivating group had the highest social cognitive and neurocognitive test scores ($F(2, 170)=5.32$, $p=0.006$; post-hoc t tests $p<0.05$). The same three cluster patterns were identified in a replication sample.
Conclusions: Our findings demonstrate replicable different patterns of neural activity among individuals during a socio-emotional task independent of DSM-diagnosis or scan site. Our findings may provide objective neuroimaging biomarkers for subgroups of individuals in target engagement research aimed at enhancing cognitive performance independent of diagnostic category.
Supported By: This work was supported by the National Institute of Mental Health (Grant Nos. 1/3 R01MH102324−01; 2/3 R01MH102313−01; and 3/3 R01MH102318−01).
Keywords: Schizophrenia, Social Cognition, fMRI, Cluster Analysis, Biotypes

125. Social Cognitive Network Connectivity is Associated With Social Cognitive Performance Across Individuals With Schizophrenia Spectrum Disorders and Healthy Controls

Lindsay Oliver[1], Colin Hawco[1], Anil Malhotra[2], Robert Buchanan[3], and Aristotle Voineskos[1]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]Zucker Hillside Hospital, [3]Maryland Psychiatric Research Center, University of Maryland School of Medicine

Background: Schizophrenia spectrum disorders (SSDs) often feature social cognitive deficits, linked to functional outcome, though their neural basis remains unclear. Our objective was to determine how functional connectivity of social cognitive networks relates to social cognitive performance and functional outcome across individuals with SSDs and healthy controls. We hypothesized that increased connectivity in the mentalizing network and decreased connectivity in the mirroring network during a complex social cognitive task would be associated with better social cognitive performance.
Methods: Across three sites, 178 people with SSDs and 118 healthy controls completed the Empathic Accuracy task during functional magnetic resonance imaging. Participants also completed measures of social cognition and functional outcome outside the scanner. Background connectivity analysis was used during the Empathic Accuracy task to extract functional connectivity in social cognitive networks.
Results: The Empathic Accuracy task engaged both regions of the mentalizing and mirroring networks. Background connectivity analysis revealed greater connectivity in the mirroring network in participants with lower social cognitive performance in comparison to higher social cognitive performers ($p < .05$). Mirroring network connectivity was also negatively associated with social cognitive performance outside the scanner ($p < .001$) and social functioning scores ($p < .001$) across individuals with SSDs and healthy controls.
Conclusions: Our results may suggest that reduced compensatory connectivity within the mirroring network, or more efficient use of the mentalizing network, is associated with better social cognitive performance and social functioning across people with SSDs and healthy individuals, aligning with a network efficiency model.
Supported By: 1/3R01MH102324-01, 2/3R01MH102313-01, 3/3R01MH102318-01
Keywords: Schizophrenia, Social Cognition, Functional Connectivity, Functional Outcome

126. Connectomes of Structural Similarity and Social Cognitive Function in Schizophrenia Spectrum Disorders

Anil Malhotra[1], Philipp Homan[2], Robert Buchanan[3], and Aristotle Voineskos[4]

[1]The Zucker Hillside Hospital, [2]The Feinstein Institute for Medical Research, Zucker School of Medicine at Northwell Hofstra, [3]Maryland Psychiatric Research Center, University of Maryland School of Medicine, [4]Centre for Addiction and Mental Health, University of Toronto

Background: Neurocognitive and social cognitive deficits are important factors in the poor functional outcome of patients with schizophrenia spectrum disorders (SSDs). These deficits may be related to the network organization of the human connectome, as the SSDs have long been considered disorders of dysconnectivity in the human brain. In this study, we tested the relationship between individual network architecture versus neurocognitive and social cognitive performance.
Methods: We used cortical network mapping based on the similarity of inter-regional morphometric parameters measured by multimodal MRI (diffusion weighted imaging and structural MRI) to compute similarity networks in each of 180 patients with schizophrenia spectrum disorder and 122 healthy controls. Using graph theory, we derived metrics describing network organization and efficiency as well as variation in network nodes and entered them in a partial least squares regression to predict variation in general and social cognition.

Results: We found that deficits in social cognition were predicted by increased network segregation. In addition, the relationship between nodal degree (the number of edges connecting a node to the rest of the network) and verbal intelligence was significantly weaker in SSDs compared to healthy controls. Finally, patients with SSDs showed increased clustering and decreased network integration compared to controls.
Conclusions: Individual modeling of brain network characteristics provides the means to elucidate the association between cognition and brain organization across diagnostic groups. Specifically, these results suggest that distinct features of aberrant cortical network architecture contribute to deficits in social as well as general cognition across the schizophrenia spectrum.
Supported By: R01 MH102313
Keywords: Schizophrenia, Neuroimaging, Cognition, Connectome

127. Examining Subcortical-Cortical Connectivity in Schizophrenia Using Personalized Intrinsic Network Topography

Erin Dickie[1], Saba Shahab[1], Dayton Miranda[1], Joseph D. Viviano[2], Miklos Argyelan[3], Anil Malhotra[3], and Aristotle Voineskos[1]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]Centre for Addiction and Mental Health, [3]The Zucker Hillside Hospital

Background: Spatial patterns of brain functional connectivity can vary substantially at the individual level. Individualized as opposed to group mapping of functional connectivity may allow for more meaningful biological markers of psychiatric disorders. The implications of such individualized differences in schizophrenia spectrum disorders (SSDs) has not been explored.
Methods: We employed MRI data from n = 198 patients with SSD and n= 284 healthy controls (HC) from four cohorts: CAMH, ZHH, COBRE (Christensen et al 2014), and UCLA CNP (Poldrack et al 2016). Using Personalized Intrinsic Network Topography (PINT; Dickie et al., 2018), we identified 80 ROIs on the cortical surface from 6 intrinsic networks using the resting state connectivity in each participant. Functional timeseries were extracted from these personalized cortical ROIs and correlated with timeseries from striatum and cerebellar subregions defined by Choi et al. (2012) and Buckner et al (2011).
Results: After PINT, the correlation between all cortical networks tested and the expected subregions of the striatum and cerebellum was increased in both patients and controls (lowest $t(418)=4.28$, $p=0.00002$). We observed robust patterns of cortical-subcortical hypo-connectivity and hyper-connectivity in the SSD compared to HC both before (127 hypo, 182 hyper) and after (136 hypo, 236 hyper) PINT (FDR corrected $p<0.05$, controlling for age, sex, scanner and in-scanner motion).
Conclusions: Our results indicate that individual approaches may better characterize cortico-subcortical connectivity. Subcortical-cortical connectivity showed robust SSD differences. Personalized brain mapping approaches may support individually targeted therapy using interventions such as repetitive Transcranial Magnetic Stimulation.
Supported By: R01MH102324
Keywords: Resting State Functional Connectivity MRI (fcMRI), Schizophrenia, Cortico-Striatal-Thalamic-Cortical Circuit, Cortico-Cerebellar Circuits, Intrinsic Connectivity Networks

SYMPOSIUM
Master-Regulator Genes, Neuroplasticity, and Psychopathology
3:00 p.m. - 5:00 p.m.
Chair: Joan Kaufman

128. Neuroplasticity and Psychopathology: Master Regulators With a Focus on Doublecortin (DCX) and Fear Processing

Marissa Maheu[1], Sumeet Sharma[1], and **Kerry Ressler**[1]

[1]McLean Hospital

Background: An important approach to understanding multifaceted risk for disease is through understanding "master regulators" of plasticity. Wnt, and Otx2 may constitute master regulators of different forms of plasticity which have are implicated in learning and stress-related disorders. Here we also focus on Doublecortin (DCX), which mediates multiple aspects of neural development, including neuronal migration and dendritic outgrowth. However, its role in amygdala-dependent learning and adult plasticity are unexplored.
Methods: Adult mice underwent classical fear conditioning, in which a tone (conditioned stimulus; CS) was paired with an aversive foot shock (unconditioned stimulus; US). Fear learning was subsequently measured with freezing in response to the CS or to non-conditioned tones. DCX RNA and protein expression were measured in basolateral amygdala (BLA).
Results: 24 hrs after fear acquisition ($p = 0.0066$) and fear expression testing ($p =0.012$), BLA DCX expression had been modulated such that mice that froze more in response to the CS displayed higher DCX levels than did their low-freezing counterparts. High DCX mice were also more likely to associate unpredictable foot shock with unpaired auditory cues ($p = 0.003$), and to generalize fear to unconditioned tones that were similar in frequency to the CS ($p < 0.0001$).
Conclusions: DCX is dynamically regulated in response to fear learning and correlates with individual differences in fear acquisition, expression, and generalization. Taken together, these data implicate DCX as a potential molecular marker of fear learning. Advances in understanding master regulators provides novel ways to understand neural plasticity from development to psychopathology in adulthood.
Supported By: NIH, NARSAD, Canadian research fund
Keywords: PTSD - Posttraumatic Stress Disorder, Neurodevelopment, Plasticity, Amygdala, Mental Health

129. OTX2 Regulation of Critical Period Brain Development

Takao Hensch[1]

[1]Boston's Children's Hospital/Harvard University

Background: Accumulation of non-cell autonomous Otx2 homeoprotein in postnatal cortex has been implicated in both the onset and closure of critical period plasticity. A major Otx2 source is the choroid plexus, while proper localization is mediated by perineuronal net (PNN) components. Specifically, a glycosaminoglycan recognition motif drives the maturation of pivotal parvalbumin-positive (PV+) interneurons across cortical regions. Disrupted PV+ network function and deficits in PNN integrity are implicated in a variety of psychiatric illnesses, suggesting both a potential global role for Otx2 function and innovative therapeutic strategies for establishing mental health.
Methods: Otx2 localization, PV+ circuit maturation and cortical function were assessed under three conditions: 1) mice carrying an AA point mutation in the sugar-binding motif, 2) acute Otx2 disruption in the adult choroid plexus, and 3) Mecp2-deficient mice with/without Otx2 disruption in the developing choroid plexus.
Results: In Otx2-AA mice, not only visual, but also auditory plasticity was delayed, including tonotopic map expansion in A1 and the anxiolytic acquisition of acoustic preferences in mPFC. Genetic disruption of adult choroid-expressed Otx2 impacts these distant PV+ circuits, reopening binocular plasticity to restore vision in amblyopic mice. In Mecp2-deficient animals, PV+ circuit hypermaturation was moderated by genetic or virally-mediated Otx2 knockdown in the choroid plexus, prolonging lifespan and preventing behavioral regression typical of RTT syndrome.
Conclusions: Widespread Otx2 actions control the maturational trajectory across cortical modalities. The ability to regulate adult cortical plasticity through the choroid plexus underscores its importance in brain physiology and offers novel therapeutic approaches to recover a broad range of neurodevelopmental disorders.
Supported By: NIMH 2P50MH094271
Keywords: GABA, Choroid Plexus, Parvalbumin Interneurons, Perineuronal Nets, MECP2

130. OTX2 Mediates Transcriptional Impact of Early Life Stress in Mouse Ventral Tegmental Area

Catherine Pena[1], Allyson Friedman[2], Carole Morel[3], Aarthi Ramakrishnan[3], Rachael Neve[4], Li Shen[3], Ming-Hu Han[3], and Eric Nestler[3]

[1]Princeton University, [2]Hunter College, [3]Icahn School of Medicine at Mount Sinai, [4]Massachusetts General Hospital

Background: Early life stress (ELS) increases the lifetime risk of depression. Using a mouse model of ELS, we recently identified OTX2 as a putative upstream regulator of transcriptional alterations in the ventral tegmental area (VTA), a key brain reward region implicated in depression (Peña et al., Science, 2017). Otx2 knockdown in a postnatal sensitive window mimicked the long-lasting behavioral effects of ELS in male mice. We sought to understand whether transient Otx2 knockdown in the sensitive window also mimicked the enduring transcriptional and physiological consequences of ELS.
Methods: RNA-sequencing was performed in whole VTA from adult mice after ELS or transient juvenile Otx2-knockdown and compared to control (standard-reared, LacZ-knockdown) with standard bioinformatic analysis pipelines (n=6 samples/group). In a separate cohort of mice, Otx2 or LacZ was knocked down in opposite hemispheres of adult VTA and dopamine neuron firing was measured by cell-attached recordings in slice preparation. Dopamine neuron firing was likewise measured in standard-reared or ELS adult male mice.
Results: Juvenile knockdown of Otx2 mimics the enduring transcriptional alterations induced by ELS in the VTA, compared to control. Transcriptional similarities are evident using both traditional thresholded ($p<0.05$ and fold-change$>30\%$) and threshold-free analyses. Both ELS and Otx2 knockdown increase VTA dopamine neuron firing rate compared to their respective controls. At a functional level, VTA Otx2 may mediate the changes in dopamine neuron physiology (n=4-7, $p<0.05$).
Conclusions: Early life stress alters VTA transcriptional development and physiological function through Otx2, providing novel insights into the mechanisms of enhanced depression vulnerability.
Supported By: K99MH115096; P50 MH096890; R21MH112081; Hope for Depression Research Foundation
Keywords: Early Life Stress, Depression, Ventral Tegmental Area, OTX2, RNA-seq

131. OTX2, Child Abuse, and Psychosis

Janitza Montalvo-Ortiz[1], James J. Hudziak[2], Nicholas Wymbs[3], Catherine Orr[4], Matthew D. Albaugh[2], Robert Althoff[4], Kerry O'Loughlin[4], Hannah Holbrook[4], Hugh Garavan[4], Stewart Mostofsky[5], Joel Gelernter[6], and Joan Kaufman[7]

[1]Yale School of Medicine/VA CT Healthcare Center, [2]University of Vermont, College of Medicine, [3]Kennedy Krieger Institute, [4]University of Vermont, [5]Center for Neurodevelopment and Imaging Research at Kennedy Krieger Institute, [6]Yale School of Medicine/VA CT Healthcare Center/NC-PTSD, [7]Kennedy Krieger Institute/Johns Hopkins Medical Institute

Background: Using unbiased transcriptomics the transient down-regulation of the Orthodenticle homeobox 2 (Otx2) gene was putatively associated with the development of depressive-like behaviors in a mouse model of early life stress. Given that genes associated with schizophrenia have recently been shown to have OTX2-binding sites, and child abuse is a potent predictor of psychotic symptoms and schizophrenia diagnoses, we examined the association of peripheral indices OTX2 in relation to measures of psychotic symptoms in a cohort of children participating in a study of risk and resilience in maltreated children.

Methods: The sample included 135 children (Ages: 8-15 years old; X=11.4, SD=1.9). DNA specimens were derived from saliva samples and processed using the Illumina 450K beadchip. Psychotic symptoms were assessed using the CBCL Thought Problem scale. A subset of the children (N=46) with DNA specimens also had neuroimaging data, with rsfMRI data processed using SPM12 and custom MATLAB scripts.
Results: After controlling for demographic factors, cell heterogeneity, and three principal components, maltreatment history ($p < .001$) and methylation in OTX2 ($p < .035$) significantly predicted psychotic symptoms in the children. Increased OTX2 methylation was also found to be associated with increased functional connectivity between the right vmPFC and bilateral regions of the medial frontal cortex and the cingulate (FEW correction, $p<.05$).
Conclusions: These preliminary data suggest the potential applicability of this mouse model of early life stress in delineating the mechanisms by which adverse early experience confers risk for a broad range of stress-related psychopathologies, including the onset of psychotic symptoms and psychotic disorders.
Supported By: This work was supported by the Zanvyl and Isabelle Krieger Fund (JK), the NIH R01MH098073 (JK, JH), R01 MD011746-01 (JK); the National Center for Posttraumatic Stress Disorder – Veterans Affairs Connecticut (JG, JK); the VA Cooperative Study #575B, Genomics of Posttraumatic Stress Disorder in Veterans (JG, JK); the Biological Sciences Training Program through 5T32 MH14276; and NARSAD (JLMO).
Keywords: Childhood Psychosis, Child Abuse, Epigenetics, DNA Methylation, Neuroimaging

SYMPOSIUM
Harnessing Biomarkers to Identify and Prevent Treatment Resistant Depression
3:00 p.m. - 5:00 p.m.
Chair: James Murrough

132. Structural and Connectomic Brain Features of Treatment Resistant Depression and Antidepressant Response to Ketamine

James Murrough[1], Nicholas Van Dam[2], Mora Grehl[1], Aaron Tan[1], and Laurel Morris[1]

[1]Icahn School of Medicine at Mount Sinai, [2]University of Melbourne

Background: Treatment-resistant depression (TRD), characterizing patients with major depressive disorder (MDD) who do not benefit from conventional antidepressant treatments, is a major public health problem. Ketamine has been reported to be beneficial for patients with TRD, however few studies have investigated brain structural and connectomic patterns specific to TRD and antidepressant response to ketamine.
Methods: Subjects (N=102) underwent structural and resting state functional neuroimaging with MRI at 3T and depression severity was measured using the Montgomery-Asberg Depression Rating Scale (MADRS). We examined the relationship between whole-brain gray matter voxel-based morphometry (VBM) and level of treatment-resistance defined using the Maudsley Staging Model (MSM) in unmedicated patients with MDD (N=61) and healthy controls (N=41). A subset of patients (N=27) received a single IV infusion of ketamine (0.5mg/kg) and outcome was measured 24 hours post-treatment. Resting-state functional connectivity (RSFC) was computed using seeds determined from the TRD VBM analyses to determine functional circuit predictors of antidepressant response. All analyses were whole-brain corrected, $p<0.05$.
Results: MDD was associated with decreased gray matter volume (GMV) in the left dorsolateral prefrontal cortex ($p<0.0005$), adjusting for TRD status, age and sex. TRD (MSM score >2) was uniquely associated with decreased GMV in the right retrosplenial cortex and precuneus ($p<0.0001$). Response to ketamine was associated with decreased connectivity between retroplenial cortex and the ventromedial prefrontal cortex (vmPFC, $p<0.005$).
Conclusions: We found that TRD was associated with reduced GMV within posterior midline cortical structures, important components of the default mode network. Reduced connectivity within this circuit positively predicted antidepressant response to ketamine.
Supported By: K23 NIMH (Murrough)
Keywords: Depression, Multimodal Neuroimaging, Treatment Resistant Depression, Ketamine, Voxel Based Morphometry

133. Baseline Functional Connectivity and Cerebral Perfusion Markers of Response to Sertraline Vs. Placebo: A Data-Driven Multi-Modal Neuroimaging Study

Madhukar Trivedi[1], Cherise Chin Fatt[1], Crystal Cooper[1], Manish Jha[2], Gregory Fonzo[3], Charles South[1], Bruce Grannerman[1], Thomas Carmody[1], Tracy Greer[1], Benji Kurian[1], Maurizio Fava[4], Patrick McGrath[5], Phil Adams[5], Melvin McInnis[6], Ramin Parsey[7], Myrna Weissman[5], Mary Phillips[8], and Amit Etkin[9]

[1]U.T. Southwestern Medical Center, [2]Icahn School of Medicine at Mount Sinai, [3]Stanford University, [4]Massachusetts General Hospital, [5]Columbia University, [6]University of Michigan School of Medicine, [7]Stony Brook University, [8]University of Pittsburgh School of Medicine, [9]Stanford University School of Medicine; Veterans Affairs Palo Alto Healthcare System

Background: Despite increasing numbers of neuroimaging studies of major depressive disorder (MDD), brain-based biomarkers of antidepressant response are not yet identified. We applied data-driven approaches to identify patterns of resting-state functional connectivity and cerebral perfusion that differentially predict response to sertraline vs. placebo.
Methods: Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study participants completed structural, resting state fMRI, and arterial spin labeling (i.e., cerebral perfusion) scans at baseline. Participants were randomized to either sertraline or placebo for 8-weeks. Atlas-based parcellations were used to compute resting-state functional connectivity (rsfc) (n=279). A whole brain voxel-wise approach was used for cerebral perfusion

analysis (n=231). Linear mixed model intent-to-treat analyses were used to identify rsfc patterns (FDR correction for rsfc pairs n=7260) and brain regions (voxel-wise FDR) that predicted differential treatment outcome. Statistical significance was set at FDR $p<0.05$.
Results: Higher connectivity within sensory and higher-order cortical networks (e.g., dorsal attention, default mode, somatomotor, and executive control networks) predicted better outcomes specifically for sertraline, as did greater between-network connectivity of salience and dorsal attention networks. Both placebo and sertraline outcome were predicted (in opposite directions) by between-network hippocampal connectivity. Greater perfusion in the putamen and anterior insula, inferior temporal gyrus, fusiform, parahippocampus, inferior parietal lobule, and orbital frontal gyrus predicted better outcome with sertraline as compared to placebo. A composite moderator of perfusion markers had an effect size of 0.56 to differentially predict sertraline vs. placebo response.
Conclusions: Assessment of pre-treatment connectivity and perfusion patterns may enable prediction of favorable response to antidepressant medication.
Supported By: U01MH092221 and U01MH092250
Keywords: Functional Connectivity, Structural Brain Imaging, Arterial Spin Labeling, Depression, Personalized Medicine

134. Towards a Mechanistic Understanding of Brain Stimulation

Corey Keller[1], Danny Huang[1], Ashesh Mehta[2], Laszlo Entz[3], and Boglarka Hajnal[3]

[1]Stanford University, [2]North Shore LIJ-Hofstra Medical Center, [3]National Institute of Clinical Neuroscience, Budapest

Background: Brain stimulation treatments are increasingly used to treat medication-resistant psychiatric disorders. Repetitive TMS (rTMS) is FDA-approved for depression and OCD, and clinical trials for PTSD and substance use are underway. Despite this, how repetitive stimulation induces human brain plasticity is unknown and necessary to develop next-generation personalized treatments.
Methods: We combine direct electrical stimulation with direct subdural brain recordings to overcome limitations of non-invasive brain stimulation studies. To understand the effect of a single stimulation session, we applied 15 minutes of 10Hz prefrontal intracranial electrical stimulation (5s on, 10s off, 3000 pulses), patterned to mimic rTMS, to 15 patients with medically-refractory epilepsy. We measured both pre/post and intra-stimulation excitability changes using intracranial cortical evoked potentials.
Results: Cortical regions (1) anatomically close to the stimulated site and (2) exhibiting strong evoked potentials underwent changes in excitability following stimulation. We demonstrate high accuracy (72−95%) and discriminability (81−99%) in predicting regions exhibiting changes using individual subjects' pre-stimulation connectivity profile. We observed a four-phase neural response during repetitive stimulation, consisting of acute neural changes during and directly after each stimulation train and a buildup across stimulation trains. Each phase strongly related to baseline connectivity profiles (pintratrain = 0.0035, t=3.7, N=15; pintertrain = 0.0012, t=6.86). The neural response to just one minute of stimulation reliably predicted long-term brain changes (70-82% accuracy).
Conclusions: Together this work sheds light on the mechanism underlying plasticity induction in humans. Furthermore, utilization of pre-stimulation network attributes and intra-stimulation cortical dynamics can be utilized to optimize brain stimulation treatments.
Supported By: F31NS080357-01 and T32-GM007288
Keywords: TMS, ECoG, Epilepsy, Plasticity, Evoked Potentials

135. Differential Early and Late Antidepressant Effects of Subcallosal Cingulate DBS

Helen Mayberg[1], Ki Seung Choi[1], Justin Rajendra[2], Callie McGrath[3], and Paul Holtzheimer[4]

[1]Icahn School of Medicine at Mount Sinai, [2]NIH, [3]Emory, [4]Dartmouth

Background: Behavioral effects of subcallosal cingulate deep brain stimulation (SCC DBS) for treatment resistant depression (TRD) occur in two stages: a rapid shift in interoceptive and exteroceptive awareness with first exposure to high frequency stimulation, and a slower progressive improvement in depression symptoms over weeks to months with ongoing chronic treatment. Intermittent monitoring of cerebral blood flow (CBF) allows characterization of this chronology.
Methods: Resting state CBF using positron emission tomography (PET) was measured in 17 TRD patients during DBS treatment: pre-surgical baseline, 1-month post-op prior to DBS, 1-mo and 6-mo of chronic DBS. Whole brain analyses examined the differential trajectory of regional CBF changes (2x2 ANOVA; time/6-mo response).
Results: A significant main effect of time ($p<.005$) and a response by time interaction ($p<.005$) was identified. Regardless of 6-mo response status, all patients showed CBF decreases in the SCC, ventral medial frontal (BA10) and right anterior insula 1 mo after intraoperative testing that was maintained with chronic DBS. Distal cortical changes were seen only with chronic stimulation: increases in dorsolateral prefrontal (46) and premotor (BA 6) cortices in both groups at 1 month, but this remained stable only in responders. Late changes in the posterior cingulate were seen uniquely in responders at 6 months.
Conclusions: The trajectory of CBF changes with DBS is not linear, consistent with the chronology of behavioral effects. An initial limbic 'reset' followed by a slower process of cortical adaptation are posited as contributing mechanisms of action.
Supported By: Dana Foundation, Stanley Medical Research Foundation, Hope for Depression Research Foundation. NIH UH3NS103550, 1R01MH102238, 1R01MH106173. Research devices donated by Abbott Labs, Medtronic. FDA IDE G060028, G130107; Clinicaltrials.gov NCT00367003, NCT01984710
Keywords: Treatment Resistant Depression, Deep Brain Stimulation, Subcallosal Cingulate, Positron Emission Tomography, Imaging

SYMPOSIUM
Stress and Developmental Risk for Psychopathology: From Epigenetics to Brain Circuits

3:00 p.m. - 5:00 p.m.
Chair: Aysenil Belger
Co-Chair: Vljay Mittal

136. Bullying Victimization in Typically Developing and Clinical High Risk (CHR) Adolescents: A Multimodal Imaging Study

Teresa Vargas[1], Katherine Damme[1], and Vijay Mittal[1]

[1]Northwestern University

Background: Bullying has been shown to increase the risk of developing a psychotic disorder. To date, no studies have examined brain behavior relationships within the context of bullying victimization in clinical high-risk (CHR) youth, a group characterized by both gray and white matter abnormalities. The present study employed multimodal neuroimaging to examine possible neural mechanisms associated with bullying victimization.
Methods: 51 CHR and 53 healthy volunteers underwent clinical interviews, parent reports and MRI scans. Regions of Interest (ROIs) were picked based on sensitivity to environmental stress, including hippocampal, amygdala, and orbitofrontal cortex (OFC) structural ROIs, and uncinate fasciculus white matter integrity.
Results: CHR individuals were more exposed to bullying victimization than healthy volunteers, and bullying was associated with depressive symptoms across the whole sample. CHR individuals exhibited smaller volumes in OFC, but not in other ROIs. Increased bullying exposure was associated with lower medial OFC volumes in CHR and HV groups independently.
Conclusions: Bullying victimization may affect or be affected by volumetric OFC differences in both healthy and CHR individuals. However, given CHR showed greater exposure to bullying as well as underlying vulnerability (e.g. lower volumes), results also point to etiological clues and novel intervention targets.
Supported By: Northwestern University Society Biology and Health Cluster fellowship (T.V.), grants R01MH112545, R21/R33MH103231 and R21MH110374 (V.M).
Keywords: Bullying Victimization, Clinical High Risk For Psychosis, Medial Orbitofrontal Cortex

137. Stress Reveals Unique Impact of Anxiety, Cognitive Disorganization, and Psychosis Symptoms on Working Memory Circuitry and Performance

Andrea Pelletier-Baldelli[1], Alana Campbell[1], Joshua Bizzell[1], and Aysenil Belger[1]

[1]University of North Carolina at Chapel Hill

Background: Impaired working memory and disorganized cognition (e.g. thought disorganization, distractibility) are risk factors for transitioning to psychosis and are also evident in individuals with anxiety and/or ADHD. The onset of stressful events may alter these cognitive and clinical presentations.
Methods: The present study examined the impact of stress on working memory circuitry and task performance, along with relationships with attenuated psychotic symptoms, cognitive disorganization, and anxiety in a transdiagnostic sample ($n = 54$, ages 9-16, $M = 12.81$, $SD = 2.02$). Circuitry was represented by combined ERP P3 signal and fMRI activation during a working memory task (1-back) before and after a stressor (TSST or MIST) using the fusion ICA toolbox.
Results: n-back accuracy improved post-stress (68%) compared to pre-stress (61%) ($t = -3.55$, $p = 0.001$). Cognitive disorganization was associated with a greater change in task accuracy ($\beta = 0.34$ $p = 0.01$). No significant relationships were found involving the fused ERP/fMRI components and psychosis symptoms or cognitive disorganization; anxiety related to the component stress changes at a trend-level ($\beta = -0.31$, $p = 0.08$). When controlling for the impact of cognitive disorganization, anxiety was significantly related to the neural circuitry stress-related changes ($\beta = -0.30$, $p = 0.04$).
Conclusions: Findings indicate the strongest relationship between stress-related changes in circuitry involved anxiety, regardless of diagnostic grouping or severity of cognitive disorganization. However, in regard to behavior, individuals with higher cognitive disorganization benefited from the stressor and showed the most improved post-stress task performance.
Supported By: R01MH103790-01A1
Keywords: Adolescent Stress, Developmental Psychopathology, Multimodal Fusion, Transdiagnostic

138. Stress-Induced Prefrontocortical Dopamine Response is Altered in Subjects at Clinical High Risk for Psychosis Using Cannabis

Romina Mizrahi[1], Christin Schifani[2], Pablo Rusjan[1], and Sylvain Houle[1]

[1]CAMHPET Centre, [2]CAMH

Background: Stress and cannabis use are risk factors for the development and relapse to psychosis. We have previously reported that subjects at clinical high risk for psychosis (CHR) exhibit a higher striatal dopamine response to acute stress compared to healthy volunteers (HV) and that chronic cannabis use blunts this response. However, it is unknown if this abnormal dopamine response to stress and cannabis extends to the prefrontal cortex (PFC). Here, we investigated the effect of acute psychosocial stress on dorsolateral PFC (dlPFC) and medial PFC (mPFC) dopamine release in CHR with and without chronic cannabis use using [11C]FLB457 positron emission tomography (PET) and a validated stress challenge.
Methods: Thirty-three participants completed two [11C]FLB457 PET scans (14 CHR without cannabis use, 8 CHR chronic cannabis users (CHR-CU) and 11 HV); one while

performing a Sensory Motor Control Task (control) and another while performing the Montreal Imaging Stress Task (stress). Dopamine release was defined as percent change in D2 receptor binding potential between control and stress scans using a novel correction for injected mass of [11C] FLB457.
Results: Stress-induced dopamine release (ΔBPND) was significantly different between groups in mPFC ($F(2,30)=5.40$, $p=0.010$) with CHR-CU exhibiting lower ΔBPND compared to CHR ($p=0.008$). Similarly, salivary cortisol response (ΔAUCI) was significantly lower in CHR-CU as compared to CHR ($F(2,29)=5.08$, $p=0.013$; posthoc $p=0.018$). There were no differences among groups in dlPFC ($p>0.05$).
Conclusions: Given the global trend to legalize cannabis, this study is important as it highlights the effects of chronic cannabis use on cortical dopamine function in high-risk youth.
Supported By: CIHR
Keywords: Adolescent Stress, Cannabis, Dopamine, Cortex, PET

139. Methlyome-Wide Changes Associated With Childhood Trauma and its Long-Term Outcomes

William Copeland[1], Karolina Aberg[2], Robin Chan[2], Min Zhao[2], Lin Ying Xie[2], E. Jane Costello[3], and Edwin van den Oord[2]

[1]University of Vermont, [2]Center for Biomarker Research and Precision Medicine, School of Pharmacy, Virginia Commonwealth University, [3]Duke University Medical Center

Background: It is not well understood how childhood traumatic experiences are biologically embedded. This study uses a prospective longitudinal study that began in childhood, continued into adulthood, and collected bloodspots at each timepoint to test whether childhood trauma was linked to DNA methylation status.
Methods: DNA was extracted from 1,233 bloodspots from subjects (median age 15.23) in the Great Smoky Mountains Study before trauma exposure, after trauma exposure and a decade later in adulthood. A sequencing-based approach was used that provided almost complete coverage of all 28 million CpGs in the genome. We analyzed whole blood methylation as well as cell type specific analyses within constituent populations of granulocytes, T cells, B cell and monocytes.
Results: Childhood trauma was associated with 200+ methylation sites across cell types (top MWAS p vales $< 1.0 \times 10\text{-}9$). Pathways identified overlapped with genes associated with depression, inflammation, cannabis, and schizophrenia in GWAS. Machine learning algorithms combined with 10-fold cross validation were used to obtain an unbiased estimate of the combines effect of all associated sites in whole blood and summarize results into a single methylation risk score (MRS). Results suggest that the MRS shared over 10% of the variation in cumulative trauma exposure. The MRS made a unique contribution to the prediction of health outcomes later in life that could not be captured by clinical data or the number of adverse events.
Conclusions: Childhood trauma has a significant impact on the methylome, particularly T-cells and granulocytes, and these changes are associated with adult health outcomes.
Supported By: R01 NIMH
Keywords: DNA Methylation, Childhood Trauma, Depression, Childhood Maltreatment

SYMPOSIUM
From Inflammation to Circuits - Cells, Synapses and Signaling Pathways in Depression
3:00 p.m. - 5:00 p.m.
Chair: Ebrahim Haroon
Co-Chair: Robert McCullumsmith

140. Inflammatory Cytokines and Stem Cell Progeny in Major Depression

Maura Boldrini[1], Yan Liu[2], Alexandria Tartt[3], Camille Fulmore[3], Gorazd Rosoklija[4], Andrew Dwork[4], Mark Underwood[4], Victoria Arango[4], and J. John Mann[2]

[1]College of Physicians & Surgeons, Columbia University, [2]New York State Psychiatric Institute, [3]Columbia University/NYSPI, [4]Columbia University

Background: Inflammation and microglia activation may contribute to the neuroplasticity deficits we observed in subjects with major depression (MDD), including smaller anterior dentate gyrus (DG). MDD increases pro-inflammatory cytokines interleukin (IL)-1 and IL-6 in the peripheral blood and cerebral spinal fluid, and a depressive-like phenotype is induced by increasing inflammation. Interleukins have anti-neurogenic and pro-gliogenic effect in the hippocampus.
Methods: In the whole DG of matched untreated subjects with ($n=36$), selective serotonin reuptake inhibitor (SSRI)-treated MDD ($n=12$), and non-psychiatric non-suicide controls ($n=36$), we performed immunocytochemistry and stereology to quantify neural progenitor cells (NPC), neuroblasts and mature granule neurons (GNs), as well as DG volume, using our established methods. We assayed by Luminex 51-Plex (Affymetrix, Inc.) 51 cytokines and chemokines, and performed Western Blots to quantify interleukin-6, IL-1beta, IL-1R, and TNF-α.
Results: MDD had smaller anterior ($p=.005$), mid ($p=.000010$) and posterior ($p=.013$) DG volume than controls, as well as fewer NPCs ($p=.001$), neuroblasts ($p=.027$) and GNs ($p=.032$) in anterior DG. SSRI-treated MDD did not differ from non-psychiatric non-suicide controls in any of these measures. Among 51 cytokines and chemokines tested, we found greater levels of inflammatory cytokine TNFα ($p=.019$) in MDD brain tissue compared with controls. We are further testing levels of pro- and anti-inflammatory cytokines and correlating them with a number of NPCs, neuroblasts, and GNs in MDD-Suicide and controls.
Conclusions: If alteration of TNFα, IL-1β or IL-6 signaling is confirmed, together with a relationship with neurogenesis deficits in MDD, future treatments targeting neuroinflammation may restore MDD symptomatology and DG cell viability MDD.

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Keywords: Neuroinflammation, Hippocampus, Neurogenesis, Depression, Hippocampal Volume

141. From Inflammation to Anhedonia - Role of Glutamate, Regional Homogeneity and Network Dysfunction

Ebrahim Haroon[1], Xiangchuan Chen[1], Agnes H. Kim[1], Bobbi Woolwine[1], Trusharth Patel[1], Zhihao Li[2], Jennifer Felger[1], and Andrew Miller[1]

[1]Emory University, [2]Shenzen University

Background: Inflammation may selectively target glutamate activity in subcortical regions. Increased glutamate activity at intra-synaptic sites promotes neural plasticity and resilience while precipitating toxicity at extrasynaptic sites. We examined if these intra/extrasynaptic imbalances induced by inflammation could be discerned using patterns of spontaneous brain-oxygen-level-dependent (BOLD)-oscillations during resting-state functional MRI (rsfMRI).
Methods: Basal ganglia glutamate (Glu, using magnetic resonance spectroscopy); spontaneous BOLD-oscillations and network integrity (using graph-theory-based connectivity analysis) along with assessments of behavior and inflammation (as reflected by c-reactive protein − CRP) were measured in depressed subjects (n=42). Hierarchical clustering was used to divide patients into High (n=22) and Low CRP-Glu groups (n=20) with and without combined elevations of CRP and Glu. Models controlling for age, sex, body mass index and race were used following correction for multiple comparisons to compute significant differences (FDRp). Effect sizes and power estimates for primary effects were Cohen's d=0.73-1.2 and Beta=0.81-0.94, respectively.
Results: Decreased concordance in BOLD-oscillatory activity between neighboring voxels (Regional Homogeneity or 'ReHo') within the MRS volume-of-interest (FDRp=0.01) and within a brain-wide ReHo-covariance network located to 41-regions-of-interest (ROI) previously implicated in depression was associated with High CRP-Glu subgroup. This 41-ROI network was decomposed into four Subnetworks, and ReHo decreases within Subnetwork4 encompassing reward processing regions predicted anhedonia (b=-0.47, p<0.001). Subnetwork4-ReHo predicted its network integrity (b=0.51, FDRp=0.004) and High CRP-Glu*ReHo*network integrity predicted anhedonia severity (b=-0.45, FDRp=0.007). Path-analysis confirmed above findings (p=0.01).
Conclusions: Measures of local BOLD activity such as ReHo may emerge as a measure of target-engagement in the brain to test the efficacy of glutamate and inflammation-modulating agents.
Supported By: R01MH H107033, K23MH091254, R01MH112076, R01MH087604
Keywords: Psychoneuroimmunology, Glutamate, BOLD Oscillations, Intrinsic Connectivity Networks, Mood Disorders

142. Synaptic Density Alterations are Associated With Depression Severity and Network Alterations

Sophie Holmes[1], Dustin Scheinost[1], Sjoerd Finnema[2], Mika Naganawa[1], Margaret Davis[2], Nicole DellaGioia[1], Nabeel Nabulsi[1], David Matuskey[1], Gustavo Angarita[2], Robert Pietrzak[3], Ronald Duman[1], Gerard Sanacora[1], John Krystal[1], Richard Carson[1], and **Irina Esterlis**[2]

[1]Yale University School of Medicine, [2]Yale University, [3]VA National Center for PTSD

Background: Synaptic loss produced as a consequence of chronic stress contributes to the emergence of depressive-like behavior in animals. Reduced synaptic density and deficits in cortical functional connectivity are also hypothesized to contribute to symptoms associated with major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). We can now quantify synaptic density in vivo by measuring synaptic vesicle glycoprotein 2A (SV2A) with the radioligand [11C] UCB-J and positron emission tomography (PET).
Methods: Twenty-six individuals with a clinical diagnosis [MDD only (n=11); PTSD with and without comorbid MDD (n=15)] and 21 matched comparison controls (HC) participated in MRI and PET scanning. [11C]UCB-J was administered as a bolus and individuals were scanned for 1hr. Distribution volume, VT (corrects for metabolism of the radiotracer), was the outcome measure.
Results: Severity of depression was inversely correlated with SV2A density in the dlPFC (r=-0.633, p=0.001), ACC (r=-0.634, p=0.001) and hippocampus (r=-0.487, p=0.012). Individuals with higher levels of depression (n=12) in both groups exhibited lower SV2A availability compared to healthy and mildly-depressed participants (n=14; F3,28=5.34, p=0.005). By combining PET with MRI functional connectivity, we also show an association between SV2A density and aberrant network function transdiagnostically (r=-.60, p=0.002). Lastly, deficits in synaptic density and functional connectivity were related to worse cognitive performance (verbal memory r=0.41, p=0.034; working memory r=-0.65, p=0.030).
Conclusions: This study provides the first in vivo evidence linking deficits in synaptic density to network alterations, symptoms of depression and cognitive function. Our findings provide further incentive to develop synaptogenic medications to alleviate the debilitating symptoms of depression.
Supported By: Nancy Taylor Foundation, VA NCPTSD, NARSAD
Keywords: PET Imaging, Depression, PTSD, Synaptic Density, Cognition

143. Kinome Analysis Identifies Glutamate-Related Kinase Network Dysregulation in Depression

Sinead O'Donovan[1], Eduard Bentea[1], and Robert McCullumsmith[1]

[1]University of Toledo

Background: Kinases contribute to the neuropathology of depression by modulating intracellular signaling cascades that regulate the functioning of neurotransmitter and bioenergetic

systems such as glutamate, inflammation and dopamine. We examined if kinase activity could be used to investigate molecular deficits underlying depression.
Methods: Postmortem dorsolateral prefrontal cortex specimens from pools of depressed (n= 10 male; n=10 female) and control (n=10 male; n=10 female) subjects were used to characterize serine/threonine sub-kinome using PamChip arrays to evaluate kinase activity. Bioinformatic analysis was used both to identify kinase hits within a random sampling model and examine associated alterations in protein networks. Kinases with z-score >2 following random sampling analysis were considered to be significantly over-represented in depressed compared to control populations. Peptide sequences were identified as differentially phosphorylated at +/- 1.15-fold-change level.
Results: Three kinase subfamilies - PKCd, PASK, and MLK- were over-represented in female MDD vs. female CTL, while two different kinase subfamilies - AMPK and PIM - were over-represented in male MDD vs. male CTL. A single kinase subfamily (TP53RK) was common to both comparisons. Functional protein association network analysis (STRINGv10.5) identified protein interactions between PKCd and MAPK and Src kinase in females and AMPK and mTOR-RPTOR in males.
Conclusions: Sex-specific changes in kinase/protein signaling networks previously implicated in depression including PKCd-MAPK (proinflammatory) and -Src kinase (dopamine/glutamate) systems in females and AMPK-mTOR (glutamate) networks in males were noted. Kinome array analysis can thus help subtype intracellular protein network disruptions in depression.
Supported By: NIMH R01 MH107487
Keywords: Depression, Kinome, Postmortem

SYMPOSIUM
Malleability of Motivated Behavior: Neural, Cognitive, and Psychological Targets
3:00 p.m. - 5:00 p.m.
Chair: Sophia Vinogradov

144. Cognitive Neurostimulation: Volitional Regulation of Ventral Tegmental Area

Rachel Adcock[1], Kathryn Dickerson[2], Jeff MacInnes[3], and R. Alison Adcock[1]

[1]Duke University, [2]Duke University Medical Center, [3]University of Washington

Background: Activation of the ventral tegmental area (VTA) is centrally implicated in motivation and learning. We hypothesized that, if given real-time fMRI (rt-fMRI) neurofeedback, healthy individuals could learn to sustain activation of the VTA without external rewards or cues.
Methods: Seventy-three healthy adults were randomly assigned to four groups: 1) VTA Feedback, 2) Attentional Control, 3) NAcc Feedback, or 4) False-Feedback (FF). All groups completed a Pre-Test, three Training runs, and Post-Test. Training differed across groups. A thermometer feedback device reflected either: 1) mean BOLD signal within the VTA; 2) a repeating pattern unrelated to brain activity; 3) mean BOLD signal from the NAcc; or 4) noise feedback they believed was veridical. Participants were instructed to Activate (increase motivation using personally-relevant imagery), Count, or Rest.
Results: Pre-Test: no group differences in VTA activation ($p>0.05$). Training: VTA-Feedback group sustained VTA activation vs. the Control group ($p<0.05$). Post-Test: VTA-Feedback group sustained VTA activation greater than the Pre-Test, baseline, and both control groups ($ps<0.05$). VTA Feedback increased functional connectivity among mesolimbic regions ($p<0.05$). No group significantly activated the NAcc above baseline during training ($p>0.1$) or Post-Test ($p>0.1$), nor showed significant connectivity changes ($p>0.1$).
Conclusions: These results demonstrate two novel findings: learning and generalization after VTA neurofeedback training, and the ability to sustain VTA activation without external rewards. These findings suggest that VTA rtfMRI cognitive neurostimulation could be used to help regulate motivation and sustain neuromodulatory states conducive to learning.
Supported By: R01 MH9743; Alfred P. Sloan Foundation, the Esther A. & Joseph Klingenstein Fund, and the Dana Foundation
Keywords: Reward Learning, Dopaminergic Circuitry, Motivation, Real-Time fMRI Neurofeedback

145. Social Cognitive Training Enhances Neural Activation Patterns Associated With Reward Processing in Schizophrenia

Karuna Subramaniam[1], Bruno Biagianti[1], Christine Hooker[2], Melissa Fisher[3], Srikantan Nagarjan[1], and Sophia Vinogradov[4]

[1]UCSF, [2]Rush University Medical Center, [3]University of Minnesota Medical Center, [4]University of Minnesota Medical School

Background: Amotivation in schizophrenia is a central predictor of poor functioning and is thought to occur due to deficits in anticipating future rewards, suggesting that impairments in anticipating pleasure can contribute to functional disability in schizophrenia. In healthy controls (HC), reward motivation is associated with anticipatory activity in frontal-striatal networks. By contrast, schizophrenia participants (SZ) show hypoactivation within these frontal-striatal networks during this motivated anticipatory brain state. Here, we investigated whether intensive computerized social cognitive training in schizophrenia could increase activity within frontal-striatal circuits to improve motivation during the anticipatory phase of stimuli that predicted upcoming reward.
Methods: In our double-blind randomized clinical controlled trial, SZ were randomly assigned to either targeted social cognitive training (SCT, N=17) or targeted cognitive training (TCT) without the social training component (N=17). We used a standard Monetary Incentive Delay task (MID) during fMRI, to assay the neural activation patterns associated with immediate anticipation and outcome of monetary reward (gain) in each group, at baseline and after training intervention.
Results: After 16 weeks of SCT, participants showed significant prefrontal activity increases, which were associated with improvements in their ability to earn rewarding outcomes.

These neuroplastic changes were not observed in the control group who completed TCT, indicating that these brain-behavioral improvements were specific to SCT.
Conclusions: These data results indicate that behavioral and neural impairments related to motivated behavior in schizophrenia are malleable to social cognitive training. Such findings contribute to our understanding of how such impairments arise and how they may be successfully treated.
Supported By: NARSAD1698; K01MH105615-5
Keywords: Prefrontal Cortex, Social Cognitive Training, Motivation, Reward, Brain Plasticity

146. The Malleability of Social Motivation in Recent-Onset Schizophrenia

Tim Campellone[1] and Danielle Schlosser[2]

[1]Pear Therapeutics, [2]Verily Life Science

Background: Motivation impairment is a core feature of schizophrenia that presents early in the course of illness. Recent models have unpacked motivation impairment into distinct, but inter-related components. In this study, we examined components of social motivation in people with recent-onset schizophrenia and determined whether a mobile intervention could improve performance on a social motivation task.
Methods: Sixty-four people with recent-onset schizophrenia completed a task where they had repeated social interactions with either positive or negative outcomes. During each interaction, participants rated their anticipated pleasure, decided how much to trust a social partner, and whether to expend effort to increase the likelihood of future interactions. A subset ($n = 38$) completed this task again after 12 weeks of participating in PRIME, a user-centered mobile application targeting goal-accomplishment and social engagement.
Results: Compared to controls, people with recent-onset schizophrenia anticipated less pleasure ($B = -0.06$, $p < 0.05$, $d = -0.44$), placed less trust ($B = -0.12$, $p < 0.01$, $d = -0.53$), and expended less effort to increase the likelihood of future interactions with positive outcomes ($B = -0.08$, $p < 0.05$, $d = -0.48$). After 12 weeks, participants who received PRIME had greater increases in anticipated pleasure ($F(1,56) = 4.75$, $p = 0.03$) and effort expended to increase the likelihood of future interactions ($F(1,56) = 4.66$, $p = 0.04$) compared to a waitlist condition ($n = 21$).
Conclusions: Our findings show that people with recent-onset schizophrenia have impairments in measurable components of social motivation. However, these impairments are significantly improved after 12 weeks of a mobile application that targets goal-accomplishment and social engagement.
Supported By: NIMH: R34, K23, T32
Keywords: Schizophrenia, Social Interaction Task, Motivation, Digital Health

147. Social Cognitive Training Improves Measures of Reward Processing in Schizophrenia

Sophia Vinogradov[1], Melissa Fisher[2], and Mor Nahum[3]

[1]University of Minnesota Medical School, [2]University of Minnesota, [3]Hebrew University of Jerusalem

Background: Social cognition, reward processing, and motivation are associated in ways which are not yet fully understood. For example, social and monetary reward learning share overlapping neural substrates in humans, and both forms of learning are impaired in schizophrenia. We hypothesized that social cognition impairments in schizophrenia impede ecologically meaningful reward processing and contribute to decreased motivation and reduced functioning.
Methods: Study 1 was an open-label trial of 24 hours of social cognitive training exercises delivered to 17 participants. Study 2 was a randomized controlled trial of 111 participants, randomized to receive 70 hours of either: a) intensive targeted social cognitive training plus auditory and visual training; or b) auditory and visual training alone.
Results: In Study 1, participants showed a significant improvement in measures of social cognition and social functioning, and in ratings of anticipatory pleasure.

In Study 2, both treatment groups showed significant improvement in multiple cognitive domains and in functional capacity. Only the group that received supplementary social cognitive training showed significant improvement in prosody identification and in anticipatory and consummatory pleasure. At 6-month follow-up, the total sample showed durable improvements in multiple cognitive domains, functional capacity, and symptoms. In the group that received social cognitive training, participants showed durable improvements in prosody identification and anticipatory pleasure; the latter was associated with improved social functioning.
Conclusions: Intensive training of social cognition impairments in people with schizophrenia lead to enduring gains in measures related to reward processing and motivation; such gains may have “sleeper” effects that lead to longer-term functional improvements.
Supported By: NIMH
Keywords: Schizophrenia, Social Cognition, Cognition, Cognitive Training, Motivation

SYMPOSIUM
Innovative Frameworks to Understanding Non-Suicidal Self-Injury
3:00 p.m. - 5:00 p.m.
Chair: Kathryn Cullen

148. Non-Suicidal Self-Injury: Neurobiological Findings From Animal Models

Darragh Devine[1]

[1]University of Florida

Background: Neuropsychiatric disorders are broadly defined and categorized according to clusters of behavioural symptoms. However, symptom expression can be heterogeneous within diagnostic categories and homogeneous across diagnostic categories. Accordingly, many recent investigations have focused upon identification and treatment of specific behavioural phenotypes. Non-suicidal self-injury (NSSI) is a phenotype that is highly prevalent in neuropsychiatric

disorders, including Borderline Personality Disorder. We are investigating developmental and experiential factors that confer vulnerability for NSSI using a rodent model.
Methods: Outbred rats are pre-screened for emotional responsiveness, exposed to emotional challenges, and then injected once daily for up to 5 days with the monoamine agonist pemoline. Self-biting is monitored during pemoline treatment.
Results: Individual rats differ in vulnerability to exhibit self-biting, and the outcomes can be predicted a priori, by evaluating innate behavioral and physiological responsiveness to a mild stressor. Stress hyper-responsive (HR) rats acquired self-biting behaviour during 6 days of pemoline treatment, whereas less stress-responsive (LR) rats did not ($n=18$; $p<0.05$). Vulnerability was elevated by emotional stress exposure (social defeat), or by administration of the anxiogenic drug FG7142 ($n=36$, $p<0.05$). Perhaps most importantly, social isolation during development increased vulnerability for pemoline-induced self-injury, and social enrichment was protective ($n=23$; $p<0.05$).
Conclusions: These findings highlight the role of innate emotional responses in vulnerability for self-injury and demonstrate that this vulnerability can be modified by environmental and pharmacological manipulations.
Supported By: Congressionally Directed Medical Research Program and the Research Opportunity Fund
Keywords: Non-Suicidal Self-Injury, Borderline Personality Disorder, Stress, Developmental

149. Differential Coherence Between Structural and Functional Connectivity in Adolescents With Versus Without Non-Suicidal Self-Injury

Midy Westlund Schreiner[1], Bonnie Klimes-Dougan[1], and Kathryn Cullen[1]

[1]University of Minnesota

Background: Neuroimaging research to date has indicated that non-suicidal self-injury (NSSI) is associated with aberrant brain connectivity. Structural and functional connectivity metrics do not always converge; the convergence between measures of functional and structural abnormalities are still unknown in adolescent NSSI. This study investigated the association, or coherence, of functional and structural connectivity within amygdala-centered neural circuits and how this coherence differs between adolescents with versus without NSSI.
Methods: Resting-state (rsfMRI) and diffusion MRI (dMRI) scans were acquired on adolescent females aged 13-21 years with and without NSSI. Functional connectivity (FC) values between amygdala and rostral anterior cingulate cortex (rACC) were extracted for each individual. We measured structural connectivity via assessing generalized fractional anisotropy (GFA) in the cingulum. We used general linear models (GLMs) to determine whether associations between these neural measures (coherence) differed between the two groups while controlling for age and IQ.
Results: Twenty-six adolescents with NSSI and 18 age-matched healthy controls (HC) without NSSI had complete and usable neuroimaging and IQ data. HC showed greater coherence (higher GFA associated with higher FC) between amygdala-rACC FC and cingulum GFA ($F=5.929$, $p=.020$).
Conclusions: Compared to NSSI, HC showed that higher FC between the amygdala and rACC, a region implicated in affective experience and regulation, was associated with higher GFA values of the cingulum, a white matter tract that serves the amygdala and rACC. This suggests that those with NSSI may have poorer organization between connectivity metrics, which may contribute to the deficits in effective emotion regulation that are characteristic of NSSI.
Supported By: National Institute of Mental Health, R21 MH091366 (Cullen)
Keywords: Resting-State Functional Connectivity, Diffusion Magnetic Resonance Imaging (dMRI), Non-Suicidal Self-Injury, Adolescence

150. Ecological Momentary Assessment of Psychological and Biological Antecedents and Consequences of Non-Suicidal Self-Injury

Lisa Stoerkel[1], Alexander Karabatsiakis[2], Johanna Hepp[1], Christian Schmahl[1], and Inga Niedtfeld[1]

[1]Central Institute of Mental Health Mannheim, [2]Ulm University

Background: Individuals practicing NSSI often describe a reduction of negative feelings and aversive tension through tissue damage, indicating an important role of the combination of operant learning and reinforcing neuronal mechanisms in the psychopathology of NSSI. Importantly, affected individuals are not able to reduce the self-harming behavior – even though they suffer from the consequences. Finally, it was supposed that NSSI has an effect on the endogenous opioid system, especially on ß-endorphin. The current study investigates possible psychological and biological antecedents and consequences of NSSI in daily life. We hypothesized that ß-endorphin levels are higher after NSSI compared to a control condition (high urge for NSSI). Additionally, negative affect as well as painfulness of NSSI should be related to β-endorphin level at the same time.
Methods: Over a study period of two weeks, we assessed data in daily life using ecological momentary assessment (smartphone app) five times per day. We used multilevel analysis to analyze our data.
Results: We included 45 participants with NSSI Diagnosis (DSM-5). Results show that negative affect and aversive tension show a significantly stronger decline after NSSI event than after control condition ($p<.001$). First data on ß-endorphin will be ready for presentation and discussion at the conference.
Conclusions: Our first results show that the relief after NSSI is not only due to regression to the mean. Furthermore, it underlines the findings in the field that NSSI is an effective strategy to regulate emotions and aversive tension. Relations between subjective and biological data will be discussed at the conference.
Keywords: Non-Suicidal Self-Injury, Ecological Momentary Assessment, Emotion Regulation, Opioid System

151. Peripheral β-Endorphin and Pain Sensitivity in Adolescent Non-Suicidal Self-Injury

Julian Koenig[1], Patrice Van der Venne[2], Elisa Drews[2], Peter Parzer[2], and Michael Kaess[3]

[1]Heidelberg University, [2]Centre for Psychosocial Medicine, University of Heidelberg, [3]University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern

Background: Non-Suicidal Self-Injury (NSSI) is associated with decreased sensitivity to experimentally induced pain. It has been suggested that β-endorphin, a peptide with analgesic effects, might be related to altered pain sensitivity in NSSI. However, this hypothesis has not yet been empirically addressed.
Methods: In a case-control study including female adolescents (12-17 years of age) with NSSI disorder according to DSM-5 section III (n = 94) and age-matched healthy controls (n = 34), we aimed to test for an association between peripheral β-endorphin and pain sensitivity. Thermal heat pain was applied to assess pain threshold and tolerance. Peripheral β-endorphin was determined from venous blood draws. All participants underwent detailed clinical assessment using structured interviews and self-reports.
Results: Adolescents with NSSI (43.27°C (3.77)) showed greater (t(127) = 2.07, p = .040) pain threshold compared to controls (41.77°C (3.36)). Levels of peripheral β-endorphin were lower (t(127) = 3.18, p = .002) in adolescents with NSSI (26.21 μg/ml (20.64)) compared to controls (39.02 μg/ml (19.45)). Peripheral β-endorphin was unrelated to pain threshold (r(129) = -.013, p = .882) or tolerance (r(129) = .053, p = .553).
Conclusions: Findings suggest that peripheral β-endorphin is unrelated to pain sensitivity in adolescent NSSI. Contradicting results from previous studies in adult NSSI, assessing β-endorphin derived from cerebrospinal fluid, we found evidence for lower peripheral β-endorphin in patients with NSSI. Implications for our understanding of NSSI and direction for future research are discussed.
Supported By: Dietmar Hopp Foundation
Keywords: Non-suicidal Self-Injury, Adolescents, β-Endorphin, Pain Perception

SYMPOSIUM
What's Next in the Genomics of Posttraumatic Stress Disorder: Developing Applications to Investigate Hundreds of Thousands of Individuals

3:00 p.m. - 5:00 p.m.
Chair: Renato Polimanti
Co-Chair: Caroline Nievergelt

152. Taking a Closer Look at PTSD Genomics: Rare Copy Number Variants and Extended Phenotyping

Adam Maihofer[1], Jonathan Coleman[2], Laramie Duncan[3], Andrew Ratanatharathorn[4], Israel Liberzon[5], Kerry Ressler[6], Karestan Koenen[7], and Caroline Nievergelt[8], PGC PTSD Workgroup

[1]UCSD School of Medicine, [2]Institute of Psychiatry, Psychology and Neuroscience, King's College London, [3]Stanford University, [4]Columbia University, [5]University of Michigan, [6]Harvard Medical School, McLean Hospital, [7]Harvard T.H. Chan School of Public Health, [8]University of California, San Diego

Background: The largest collection of genome-wide association studies (GWAS) of PTSD now include over 30,000 PTSD cases and 170,000 controls (PGC-PTSD Freeze 2). Meta-analyses on >23K cases of European and >4K cases of African ancestry identified 6 genome-wide significant loci. Heritability estimates (h2SNP) are in the range of 10-20%, explaining a significant, but incomplete proportion of the overall PTSD heritability. To refine our understanding of the genetic architecture of PTSD, we extended analyses on these data, including rare genetic variations derived from copy-number variants (CNV), and GWAS on quantitative PTSD phenotypes.
Methods: CNV calling was performed using the PGC CNV analysis pipeline, including PennCNV and iPattern. Rare CNVs (<1%) spanning at least 20KB were analyzed in PLINK and significance of CNV burden was determined using permutation tests. GWAS of PTSD symptoms was performed using linear regression and meta-analyzed using an inverse variance weighted fixed effects meta-analysis in METAL, and h2SNP were estimated using LD score regression.
Results: CNV analyses including 5,129 PTSD cases and 6,023 controls of European ancestry show a higher burden of gene deletions in cases than controls (p = 0.0023). There was no difference between PTSD cases and controls in regard to CNVs in specific genes or known psychiatric CNVs. In addition, h2snp calculated on PTSD symptoms and including trauma-exposure measures refine heritability estimates (>10% point-estimate increase) compared to dichotomous case-control analyses.
Conclusions: CNV results indicate rare genetic variation contributes meaningfully to PTSD risk. Further, heritability estimates using quantitative post-traumatic symptom scores are more robust, indicating the importance of extended phenotyping.
Supported By: R01MH106595
Keywords: PTSD - Posttraumatic Stress Disorder, Psychiatric Genetics, Diverse Populations, Copy Number Variation, SNP-Based Heritability

153. A Novel Framework for Well-Calibrated Analysis of Complex Traits in Admixed Individuals

Elizabeth Atkinson[1], Adam Maihofer[2], Karestan Koenen[3], Caroline Nievergelt[2], Benjamin Neale[4], and Mark Daly[5]

[1]Harvard Medical School, Massachusetts General Hospital, [2]University of California, San Diego, [3]Harvard School of Public Health, [4]Massachusetts General Hospital, [5]Broad Institute

Background: Many genetics studies exclude admixed individuals due to the challenges of accounting for their ancestry such that population substructure can bias results. This is especially problematic for psychiatric disorders including

PTSD, which has many sufferers of admixed descent and is extremely polygenic, meaning that accounting for local ancestral dosage is key to understand the genetic contribution of the many component sites of small effect that combine to result in the disorder.
Methods: Here, we present a novel framework to account for this issue, incorporate fine-scale population structure and improve phasing in admixed individuals, allowing them to be studied alongside homogenous samples by correcting for local ancestry. Incorporating local ancestry in addition to PCs accounts for subtle differences in admixture patterns that may differ among case and control cohorts, even if global ancestry fractions are the same.
Results: We apply our framework to several admixed American cohorts from the Psychiatric Genomics Consortium PTSD subgroup. We show this framework reduces false positives and boosts true signal to discover GWAS loci, gives increased precision when looking at variants across ancestry groups, and improves association signal resolution by leveraging differences in linkage disequilibrium patterns between populations to more narrowly map where signal is coming from.
Conclusions: This framework can solve issues related to admixture genomics activities, including in association testing and selection scans. It dramatically advances the existing methodologies for statistical genetic analysis of admixed individuals and allows for significantly better calibrated study of the genetics of complex psychiatric disorders such as PTSD in in underrepresented populations.
Supported By: NIH NRSA T32 MH 017119
Keywords: Ancestry, Psychiatric Genetics, PTSD - Posttraumatic Stress Disorder, GWAS, Diverse Populations

154. A Network Mendelian Randomization Analysis of Neuroticism, Trauma, and Psychopathology

Andrew Ratanatharathorn[1], Chia-Yen Chen[2], Karmel Choi[3], Shareefa Davie[4], Laramie Duncan[5], Adam Maihofer[6], Caroline Nievergelt[6], Renato Polimanti[8], and Karestan Koenen[1]

[1]Harvard School of Public Health, [2]Massachusetts General Hospital, [3]Harvard Medical School, [4]University of Cape Town, [5]Stanford University, [6]UCSD, [8]Yale University

Background: Neuroticism is a risk factor for both depression and posttraumatic stress disorder (PTSD) in prospective studies. However, it is unclear whether neuroticism is a causal risk factor for depression and PTSD, and in part responsible for their comorbidity, or whether neuroticism increases the likelihood of experiencing a traumatic event and later psychopathology. We undertook a two-sample Mendelian Randomization (MR) study using summary statistics from genome-wide association studies of Neuroticism (N≈ 63,000), PTSD (N≈125,000), depressive symptoms (N≈180,000), and trauma (N≈ 8,000) to determine the causal relations among the disorders.
Methods: Bidirectional Mendelian Randomization analyses of neuroticism with PTSD and neuroticism with depressive symptoms were conducted to assess causal relations between neuroticism and both disorders. Results were assessed for weak instrument bias and pleiotropic bias. A final set of MR analyses were conducted after removing pleiotropic SNPs. Multivariable MR with trauma as a mediating factor was conducted for significant associations.
Results: Neuroticism was not found to be causally associated with either PTSD (β = -1.23x10-04, p = 0.651) or depressive symptoms (β = 0.029, p = 0.109) nor was PTSD associated with neuroticism (β = -0.168, p = 0.949). Depressive symptoms were significantly associated with neuroticism (β = 0.199, p = 1.00x10-07) independently of experiencing a traumatic event (β = 0.199, p = 1.67x10-05).
Conclusions: MR analyses did not replicate observational associations between neuroticism, depression, and PTSD. Neuroticism-depression comorbidity was driven by depression mechanisms predisposing individuals for neuroticism though the effect of neuroticism on depression was in the expected direction.
Supported By: NIH R01MH106595
Keywords: PTSD - Posttraumatic Stress Disorder, Depression, Trauma Exposure, Neuroticism

155. Metabolome-Wide Mendelian Randomization Analysis of Trauma Response

Carolina Muniz Carvalho[1], Frank Wendt[1], Joel Gelernter[1], and **Renato Polimanti**[1]

[1]Yale University School of Medicine

Background: The behavioral consequences of trauma exposure results from a complex interaction of risk genes, biochemical changes, and other environmental risk factors. In the present study, we investigated the causal relationship of 123 circulating blood metabolites with respect to five problems that may occur in response to stressful experience assessed in the UK Biobank.
Methods: We conducted genetic correlation analysis, polygenic risk scoring (PRS), and Mendelian randomization using genome-wide data from the UK Biobank (N=157,357) and a nuclear magnetic resonance metabolomics study (N=24,925). Sensitivity analyses were conducted to exclude the presence of horizontal pleiotropy and heterogeneity affecting the MR results.
Results: LD score regression indicated glycoprotein acetyls (GP) as significantly correlated with trauma-response issues (rg=0.22-0.39, p=0.003). GP PRS appears to mostly predict two symptoms: “Felt irritable or had angry outbursts in past month” (Trauma-Irritable; p=2.92×10-4) and “Felt distant from other people in past month” (Trauma-Distant; p=1.45×10-5), but conversely, PRS based on these trauma-response issues also predicts GP levels (p=0.008). Conducting a Mendelian randomization analysis, we observed a causal effect of GP on Trauma-Distant (p=6.85×10-5) and Trauma-Irritable (p=7.21×10-4), but no reverse causation was observed. While no heterogeneity was present in the “GP→Trauma-Distant” relationship, significant heterogeneity was observed in the “GP→Trauma-Irritable” (Q p=0.002).
Conclusions: Our findings indicate that GP level may have a causal effect on the behavioral response to trauma. This result

is in line with a recent observational study that reported GP as significantly associated with lower general cognitive ability and increased risk of dementia, two well-known consequences of posttraumatic stress.
Supported By: VA National Center for PTSD Research
Keywords: Trauma Exposure, Metabolomics, Mendelian Randomization

SYMPOSIUM
The Role of Brain Microvascular Pathology in Neuropsychiatric Disorders
3:00 p.m. - 5:00 p.m.
Chair: Cynthia Calkin
Co-Chair: Alon Friedman

156. The Impact of Childhood Trauma on the Blood-Brain Barrier and the Risk of Suicide

Tatiana Falcone[1], Rachel Lovell[2], Damir Janigro[3], and Amit Anand[1]

[1]Cleveland Clinic Lerner School of Medicine, [2]Case Western Reserve University, [3]Flocel

Background: Adverse experiences during childhood, such as child abuse (CA), are associated with poor health over the lifespan. The impact of CA during critical developmental periods may have longstanding consequences. There is a strong correlation between exposure to trauma and suicide events in adolescents. Preliminary findings from our studies have revealed that adolescents with a history of childhood CA exhibit an increase in S100B levels regardless of diagnosis.
Methods: Levels of Blood-Brain barrier integrity biomarker were measured in a group of adolescents admitted to inpatient psychiatric at risk for suicide, with and without history of trauma as well as healthy adolescent controls. Patients n=90 controls = 26 no history of trauma, psychiatric illness or suicide attempts, Trauma was measured using the Life event check list (LEC) and the Adverse Child Experience (ACE)
Results: In a multivariate regression model, suicidality scores and trauma were the only two variables which were independently related to serum S100B levels. Patients with greater levels of childhood trauma had significantly higher S100B levels after controlling for intensity of suicidal ideation. Patients exposed to childhood trauma were significantly more likely to have elevated levels of S100B ($p < .001$) than patients without trauma, and patients with trauma had significantly higher S100B levels ($p < .001$) when compared to the control group. LEC (p 0.046), and BPRS-C suicidality scores ($p = 0.001$) significantly predicted S100B levels.
Conclusions: Childhood trauma, can potentially affect the levels of BBB biomarker S100B.

There is an important relationship between emotional trauma and suicide.
Supported By: MH093302
Keywords: Suicide, Adolescents, Blood-Brain Barrier, Biomarkers, Childhood Trauma

157. Retinal Imaging and Stem Cell Derived Brain Endothelial Cells: A Framework for Studying Blood Brain Barrier Dysfunction in Psychosis

Paulo Lizano[1], Rakesh Karmacharya[2], and Matcheri Keshavan[3]

[1]Beth Israel Deaconess Medical Center & Harvard Medical School, [2]Massachusetts General Hospital, [3]Harvard University

Background: The neurobiology of psychosis comprises of reductions in cortical thickness and cerebral perfusion. Since neurogenesis and vasculogenesis are coordinated, a defect in neurovascular development could result in poor functionality of neurons. To overcome limitations in brain imaging and human cellular models, we used retinal imaging and human induced pluripotent stem cells (iPSC) to study microvascular properties.
Methods: Optical coherence tomography angiography, was performed in 6 controls, 13 probands (bipolar I psychotic n=3, schizoaffective n=5, schizophrenia n=5), matched for age, gender, race, visual acuity and body mass index. In a separate cohort of schizophrenia and bipolar patients, human induced pluripotent stem cells were used to derive brain microvascular endothelial cells (BMEC).
Results: No significant differences were noted for microvascular density in probands (Cohen's d ranged from -0.74 to -0.14) or diagnostic groups (d = -1.1 to -0.1) compared to controls. We observed a trending effect for increased arterial tortuosity in probands (Left eye, p=0.09) and schizophrenia (Left eye, d=1.6, p=0.08) compared to controls. In probands, increased venous tortuosity was correlated with lower cognitive function (r=-0.75, p=0.03) and increased arterial tortuosity was correlated with PANSS positive score (r=0.69, p=0.02). We have successfully derived BMECs and are beginning to examine their cellular phenotypes.
Conclusions: The retinal imaging results presented here are preliminary, but the effect sizes, directionality of effect, and relationship with clinical measures are promising, and in line with the hypothesized role of microvascular dysfunction in psychosis. Future work will establish cellular and physiologic phenotypes of microvascular and blood brain barrier dysfunction in psychosis.
Supported By: Dupont Warren, KL2
Keywords: Psychosis Phenotype, Optical Coherence Tomography Angiography, Stem Cells, Brain Microvascular Endothelial Cells

158. Imaging Blood-Brain Barrier Pathology in Psychiatric Disorders

Lyna Kamintsky[1], Kathleen Cairns[1], Steven Beyea[1], Chris Bowen[1], Ronel Veksler[2], Cynthia Calkin[1], and **Alon Friedman**[1]

[1]Dalhousie University, [2]Ben-Gurion University of the Negev

Background: Dysfunction of the blood-brain barrier (BBB) was recently hypothesized to play a role in the pathogenesis of neuro-psychiatric disorders. While animals' studies revealed the mechanisms by which a leaky BBB leads to neuroinflammation and neural dysfunction, human data is scarce.

Methods: For BBB assessment, dynamic, a T1-weighted contrast-enhanced magnetic resonance imaging (DCE-MRI, 3T GE Discovery MR750) was performed in 36 bipolar patients and 14 controls (matched for sex and age). Participants underwent also diagnostic interviews, cognitive testing, anthropometric measurements and blood sampling.
Results: The extent of BBB pathology was highly variable among patients. Cluster analysis has identified a sub-group of 10 bipolar patients (28%) with extensive levels of BBB leakage ($p<0.0001$). This group consisted exclusively of bipolar patients with insulin resistance. They also had higher body-mass indices and elevated risk of cardiovascular disease ($p<0.05$), and also scored significantly worse on scales for depression, anxiety, global functioning, processing speed, and verbal learning and memory ($p<0.05$). No differences in the class of mood stabilizers between nominal and extensive BBB leakage groups were found. We found 6 brain regions associated with more severe depression, including the left accumbens.
Conclusions: We present direct evidence that BBB leakage is associated with insulin resistance and neuroprogression in patients with bipolar disorder. We assert that BBB imaging may prove a robust tool for diagnosing bipolar neuroprogression, monitoring disease course and assessing response to treatment. Future research is needed to explore novel treatment strategies that specifically target BBB integrity.
Supported By: CIHR
Keywords: Blood Brain Barrier, Brain Magnetic Resonance Imaging (MRI), Bipolar Disorder, Insulin-Resistance

159. Brain Microvascular Pathology is Associated With Bipolar Neuroprogression

Cynthia Calkin[1], Lyna Kamintsky[1], Kathleen Cairns[2], Ronel Veksler[3], Chris Bowen[1], Steven Beyea[1], and Alon Friedman[1]

[1]Dalhousie University, [2]Nova Scotia Health Authority, [3]Ben-Gurion University of the Negev

Background: Bipolar disorder affects ~5% of the population, with some patients progressing towards severe psychiatric, cognitive and functional outcomes referred to as "neuroprogressive". Dysfunction of the blood-brain barrier (BBBD) was recently hypothesized to play a role in neuroprogression by mediating neuroinflammation and neurodegeneration. Moreover, insulin resistance (IR) — also associated with BBBD — was identified as a risk factor for neuroprogression. The present study aimed to obtain the first ever characterization of BBBD in living bipolar patients, and to test whether pathological findings may be reflective of symptomatology.
Methods: We studied BBBD in 50 subjects using dynamic contrast-enhanced MRI. The accumulation rate of gadoteridol was calculated for each brain voxel, and the percent of brain voxels with elevated leakage was quantified for each subject. Blinded clustering (K-means) was used to identify subjects with extensive BBBD. Generalized linear model-based feed-forward selection was applied to identify brain regions most predictive of depression severity. Classification accuracy was assessed using receiver operating characteristic (ROC) analysis, while statistical comparisons were conducted using the Wilcoxon rank sum test.
Results: We identified extensive BBBD in 10/36 (28%) bipolar patients (and 0/14 age/sex-matched controls). All bipolar patients with extensive leakage also had IR, and worse psychiatric, cognitive and functional outcomes ($p<0.05$). We found depression to be associated with region-specific BBBD, with the nucleus accumbens best predicting depression severity.
Conclusions: IR elevates risk of extensive BBBD and neuroprogression, while region-specific BBBD reflects depression severity. BBB imaging may prove a robust tool for diagnosing bipolar neuroprogression, monitoring disease course and assessing response to treatment.
Supported By: NARSAD
Keywords: Bipolar Disorder, Neuroprogression, Blood-Brain Barrier, Insulin Resistance, Novel Neuroimaging

SYMPOSIUM
Imaging Effects of Electroconvulsive Therapy at the Human System Level: Megaanalyses From the GEMRIC Consortium
3:00 p.m. - 5:00 p.m.
Chair: Indira Tendolkar

160. Brain Changes Induced by Electroconvulsive Therapy are Broadly Distributed

Leif Oltedal[1], Olga Therese Ousdal[2], **Indira Tendolkar**[3], Hauke Bartsch[4], Ute Kessler[5], Ketil J. Oedegaard[5], Katherine Narr[6], and Anders M. Dale [4], GEMRIC

[1]Univeristy of Bergen, [2]Mohn Medical Imaging and Visualization Centre, Haukeland University Hospital, [3]Donders Institute for Brain, Cognition and Behaviour, [4]Center for Multimodal Imaging and Genetics, University of California, San Diego, [5]University of Bergen, Haukeland University Hospital, [6]University of California, Los Angeles

Background: Investigations of Electroconvulsive therapy (ECT) have revealed structural brain changes (volume increase) in the hippocampus, amygdala, striatum and some cortical areas. It is not well known if such changes are specific to a few regions or more globally distributed.
Methods: Individual subject data from 14 sites; 328 patients (age range 19-92; ~ 60 % female) and 95 controls (age range 20-78; ~ 60 % female), was available. T1 weighted images were corrected for scanner specific gradient non-linearities and processed in FreeSurfer and Quarc for unbiased estimates of regional anatomical change. Volume change was evaluated in standard Regions of Interest (ROIs) as provided by FreeSurfer and in weighted means of ROIs for gray matter, white matter and ventricles.
Results: The ECT-associated structural brain changes occur broadly: The cortical volume increased by 1.0 % ($t = 17.5$, $df = 298$, $p < 0.001$) and the subcortical gray matter volume increased by 1.5 % ($t=24.0$, $df = 294$, $p < 0.001$). The ventricle volume decreased by 4.9 % ($t = -12.8$, $df = 298$, $p < 0.001$) and this change correlated to the increase in subcortical gray matter ($rho = -0.4$, $p < 0.001$). White matter volume remained unchanged (-0.02 %, $p = 0.4$). Changes in weighted ROIs were

modulated by the number of treatments but was not associated with clinical improvement.
Conclusions: ECT induces volume increases that are broadly distributed in cortical and subcortical gray matter regions while the ventricle volume is reduced. The changes may be more broadly distributed than previously thought.
Supported By: Western Norway Regional Health Authority, Haukeland University Hospital and the University of Bergen.
Keywords: Electroconvulsive Therapy (ECT), Major Depression, Structural MRI

161. The Relationship Among Electric-Field Distributions, Neuroimaging Findings and Clinical Outcomes in ECT

Miklos Argyelan[1], Leif Oltedal[2], Benjamin Wade[3], Zhi-De Deng[4], Indira Tendolkar[5], Georgios Petrides[1], Anil Malhotra[1], and GEMRIC, Chris Abbott[6]

[1]Zucker Hillside Hospital, [2]University of Bergen, [3]UCLA, [4]National Institute of Health/NIMH, [5]Donders Institute for Brain Cognition and Behaviour, [6]University of New Mexico, Albuquerque

Background: Electric-field (E-Field) modeling provides a novel approach for investigating causal links between ECT and neuroimaging and clinical outcome.
Methods: We analyzed N=151 (age: 57.3±17.1) patients who underwent right unilateral ECT for depression (followed with MADRS) and had two brain MRIs (baseline and at the end of the ECT course). Quarc (Holland and Dale 2011) was used for unbiased estimation of subcortical and cortical volume change. We estimated ECT induced E-Field with ROAST v1.1 (Huang et al. 2017). We analyzed the relationship between volume change and E-Field in 85 ROIs with the following linear model: $\Delta Vol \sim E\text{-}Field + ECT\# + age$ (ECT#: number of ECT). We also conducted a voxel-wise analysis between E-Field maps and clinical outcome: $\Delta MADRS \sim E\text{-}Field + ECT\# + age$.
Results: The average MADRS improvement was 61.3 ± 34.0%.

E-Field values correlated with volume changes in five regions (Left Hippocampus, Left and Right Amygdala, Left Entorhinal Cortex, Left Superior Temporal Gyrus) dominantly in the left side ($p<0.05$ FDR corrected). Detailed analysis revealed that volume changes were higher on the right side, but they did not correlate with E-Field due to a ceiling effect. In agreement with our previous report (Oltedal et al., 2018) volume changes did not correlate with clinical outcome.

E-Field correlated the clinical change in the left posterior hippocampus, the ventromedial prefrontal cortex (vmPFC) and the posterior cingulate cortex (cluster corrected $p<0.05$ on an uncorrected $p<0.001$).
Conclusions: We found that the cingulate cortex, vmPFC and left posterior hippocampus could be a potential target for increased personalized E-Field application to achieve a better clinical outcome.
Keywords: Depression, Electroconvulsive Therapy (ECT), Electrical Field Modeling, MRI Brain Imaging, Personalized Medicine

162. Antidepressant Response Along Latent Symptom Dimensions Associated With Longitudinal Structural Covariance in Electroconvulsive Therapy

Benjamin Wade[1], Gerhard Hellemann[2], Randall Espinoza[3], Roger Woods[1], Shantanu Joshi[1], Ronny Redlich[4], Anders Jørgensen[5], Chris Abbott[6], Leif Oltedal[7], and Katherine Narr[3]

[1]University of California, Los Angeles, [2]UCLA Semel Institute for Neuroscience and Human Behavior, [3]UCLA Brain Mapping Center, University of California Los Angeles, [4]University of Muenster, [5]Psychiatric Center Copenhagen, [6]University of New Mexico, Albuquerque, [7]University of Bergen

Background: Major depressive disorder (MDD) is highly prevalent and symptomatically heterogeneous. The Hamilton Depression Rating Scale (HDRS) total score is commonly used to evaluate clinical improvement, though different neural systems may underlie particular symptom profiles. We used data-driven methods and novel graph theory to evaluate how improvements in symptom dimensions relate to structural covariance patterns over electroconvulsive therapy (ECT) in a large multisite ECT cohort.
Methods: We included 111 MDD patients (age=52.16±14.67; 68 female) with pre- and post-ECT HDRS-17 and MRI assessments from four Global ECT-MRI Research Collaboration sites. We used exploratory factor analysis (EFA) of baseline HDRS-17 items to identify symptom dimensions. FreeSurfer-based cortical thickness and subcortical volume estimates were extracted and used to calculate longitudinal structural connectivity metrics for each subject. Random forest (RF) regression was used to predict individual symptom dimension changes using patterns of connectivity and demographics.
Results: EFA identified three symptom dimensions: somatic disturbances (F1), core mood/anhedonia (F2), and insomnia (F3). Correlation between RF-predicted and true symptom dimension changes was significant (all $p<0.0001$): F1 ($r=0.46$), F2 ($r=0.64$), and F3 ($r=0.59$). Improvement along F1 associated with structural divergence between the left anterior cingulate, ventro-limbic, and sensory association cortices. Divergence between the right accumbens, mediotemporal, and frontotemporal networks characterized improvement in F2. Left putamen and frontal-mediotemporal covariance characterized F3 improvement.
Conclusions: We used machine learning to identify distributed patterns of structural connectivity associated with improvements in latent symptom dimensions over ECT. Symptom dimensions uniquely related to overlapping connectivity patterns suggesting that targeted neuromodulation of specific networks will affect specific symptom profiles.
Supported By: 2018 NARSAD Young Investigator Grant; NIMH R01 MH092301; NIMH U01 MH110008; German Research Foundation (DFG) FOR2107; Centers of Biomedical Research Excellence (COBRE)
Keywords: Major Depressive Disorder (MDD), Electroconvulsive Therapy (ECT), Machine Learning, Connectivity, Structural MRI

163. Individual Prediction of Electroconvulsive Therapy Response Using Multicenter Neuroimaging Data: For the GEMRIC Consortium

Willem Bruin[1], Rajat Thomas[1], Annemiek Dols[2], and **Guido van Wingen**[2]

[1]Academic Medical Centre, University of Amsterdam, [2]VU University Medical Center

Background: Electroconvulsive therapy (ECT) is the most effective intervention for severe depression. Initial studies have identified neuroimaging biomarkers that may enable personalized treatment. However, sample sizes were small and replication across larger multicenter datasets is required. Therefore, we aimed to develop robust imaging markers based on multicenter data from the Global ECT-MRI Research Collaboration (GEMRIC).
Methods: Structural T1 and resting-state fMRI data from 166 depressed patients were obtained from seven sites in North America and Europe. All participants underwent scanning and clinical assessment pre- and post-ECT. Treatment response was defined as 50% reduction in MADRS or HDRS score. Voxel-based morphometry was used to extract gray matter images from T1 scans. Independent component analysis was used to extract resting-state networks from fMRI data, and between-network correlations were computed. Multivariate classification analyses were performed using linear support vector machine (libsvm) with 50 cross-validation iterations with random selection of 80% data for training and 20% for testing, stratified for class and site.
Results: The final sample included 106 ECT responders and 60 ECT non-responders. Response classification accuracy was higher using functional network correlations (AUC mean (SD): 0.75(0.08)) than when using gray matter images (AUC mean(SD): 0.65(0.07)).
Conclusions: These preliminary results show that the response to ECT can be predicted for individual patients using neuroimaging data. The large variability of the multicenter data suggests that these biomarkers are robust, indicating that future development of a clinical decision support tool might be feasible.
Supported By: NWO/ZonMW Vidi 016.156.318
Keywords: Electroconvulsive Therapy (ECT), Depression, Neuroimaging, Machine Learning

SYMPOSIUM
Computational Approaches to Behavioral Treatments for Affective Disorders

3:00 p.m. - 5:00 p.m.
Chair: Joel Stoddard
Co-Chair: Melissa Brotman

164. Retraining the Bipolar Brain: Preliminary Results From a Trial of Computerized Cognitive Remediation for Cognitive Flexibility in Children With Bipolar Disorder

Daniel Dickstein[1], James Blair[2], Jeffery Epstein[3], Chad Jenkins[4], Anthony Spirito[5], and Ellen Leibenluft[6]

[1]Bradley Hospital/Brown University School of Medicine, [2]Boystown National Research Hospital, [3]Cincinnati Children's Hospital Medical Center, [4]University of Michigan, [5]Brown University School of Medicine, [6]National Institute of Mental Health, National Institutes of Health

Background: We need better, brain-mechanism targeted treatments for bipolar disorder in children and adolescents, given its substantial impairment despite our best treatments. Previously, we showed children with bipolar disorder have impaired brain/behavior mechanisms underlying cognitive flexibility–defined as the ability to adapt to changing rewards and punishments–as indexed by reversal learning tasks. Here, we present the rationale and first look at results from a trial of computerized cognitive remediation for cognitive flexibility in bipolar youth.
Methods: Children ages 7-17 years old participated in a study approved by the IRB's of Bradley Hospital and Brown University. We first conducted a stage 1A trial to see if our twice weekly 8-week cognitive remediation would engage relevant fronto-striatal circuitry. We then conducted a stage 1B double-blind randomized pilot study using two variants of our computerized cognitive remediation.
Results: Our stage 1A trial in n=12 BD youth showed that our computer-assisted cognitive remediation with increasing difficulty (probabilistic feedback) was feasible, acceptable, and engaged frontal circuitry. Our stage 1B trial has enrolled n=32 BD youth with 2 more recruitment months. We will then test feasibility, acceptability, and circuit differences between the skill-building and non-skill-building variants of our cognitive remediation.
Conclusions: Our stage 1A trial results show that computer assisted cognitive remediation for cognitive flexibility is feasible, acceptable, and engages the target circuit. At SOBP, we will present the first look at results of our stage 1B trial to test if these findings are specific to the skill-building variant of our computer-assisted cognitive remediation, or not.
Supported By: R21MH096850, R33MH096850
Keywords: Bipolar Disorder, Cognitive Remediation, Child, Adolescents

165. A Model of Attention Learning and its Implications for Anxious Disorders

Matt Jones[1] and **Samuel Paskewitz**[1]

[1]University of Colorado Boulder

Background: Affective disorders have been linked to dysfunction in reward processing or attention. These processes have been hypothesized as involved in the mechanisms of treatment response to exposure-based therapies. Basic research in associative learning has shown attention to a cue modulates the rate of learning for cue-reward associations, and the predictive value of cues affects attention. We present a novel attention-learning model that accounts for these effects simultaneously, with important implications for learning-based interventions for affective disorders.
Methods: We present and empirically validate a novel model of attention learning, CompAct. CompAct mathematically

operationalizes cue competition for resource-limited attention, and its interaction with associative learning. We test CompAct using a standard train-transfer learning task in two experiments with replications in four independent, unselected online samples (Ns = 30, 60, 60, 139). We then present the development of a novel affective-attention learning paradigm.
Results: Attention to cues, operationalized as rate of association learning in the transfer phase, is moderated by cue validity (ps < .05) and reward magnitude (ps < .05) during the training phase. Both predictions follow from CompAct. Additional simulations demonstrate CompAct accounts for all known benchmarks in the field of attention learning, including correlation effects, highlighting, and Pearce-Hall (uncertainty) effects.
Conclusions: Given its explanatory power, CompAct is a major advance in attention-learning modeling. CompAct has potential to measure clinically relevant individual differences in salience of threat cues and attention flexibility. These connections may inform interventions such as exposure therapy, enabling assessment of their mechanism of action and prediction of individual response to treatment.
Keywords: Affective Disorders, Attention Learning, Associative Learning, Exposure Therapy, Reinforcement Learning

166. A Computational Model to Measure Mechanisms of Interpretation Bias Training for Treating Disruptive Mood Dysregulation Disorder

Simone Haller[1], Matt Jones[2], Daniel Pine[1], Ellen Leibenluft[1], Melissa A. Brotman[1], and Joel Stoddard[3]

[1]NIMH, [2]University of Colorado Denver, [3]University of Colorado Anschutz Medical Campus, Children's Hospital

Background: Disruptive Mood Dysregulation Disorder (DMDD) is associated with the tendency to interpret ambiguous social cues as threatening. Interpretation bias training (IBT) increases benign interpretations of ambiguous face-emotions via computerized feedback. It may reduce irritability/aggression, which are core features of DMDD. In an open and randomized trial, we test the efficacy of IBT and model learning mechanisms. We hypothesize that relative to healthy youth, those with DMDD have impairments in the ability to learn new, positive associations of ambiguous face-emotions that predict treatment response.
Methods: Study 1. Youth (n=24) with either DMDD or healthy comparisons completed 4 sessions of once-daily IBT. Validated in separate trial, a computational model incorporated reinforcement learning, generalization, and choice. It measured learning rates for happy (benign) and angry (hostile) judgements.
Results: Relative to HV youths, youth with DMDD learned more slowly [F(1,21) = 7.1, p= 0.015] and required more sessions to learn new, positive associations to ambiguously angry faces [F(1,58)= 4.61, p=0.036]. Learning rates did not differ for predominantly happy faces.
Conclusions: Study 2. In a double-blind trial of IBT, youth with DMDD (n=40) were randomized to either active or sham IBT. Data collection will complete November 2018. We will examine whether learning rates calculated by the computational model predict treatment response to IBT.

Together, these data will examine DMDD-associated differences in learning and their relationship to IBT effectiveness. The findings may be able to help optimize IBT treatment response, specifically who the treatment may be efficacious for and the 'dosage' necessary to achieve learning of new associations.
Supported By: NIMH/DIRP
Keywords: Affective Disorders, Youth, Cognitive Training, Computational Modeling, Disruptive Mood Dysregulation Disorder (DMDD)

167. The Impact of Emotion Judgments on Mood – Evidence From a Trial of Interpretation Bias Training

Anna Van Meter[1], Joel Stoddard[2], Ian Penton-Voak[3], Christen Deveney[4], and Marcus Munafò[3]

[1]The Feinstein Institute for Medical Research, [2]University of Colorado Anschutz Medical Campus, Children's Hospital, [3]University of Bristol, [4]Wellesley College

Background: People with bipolar disorder (BD) often have a negative bias when interpreting others' emotions, which could lead to unpleasant and/or less frequent social interactions and depressed mood. If correct, this theory implies that shifting one's perception to see others' emotions as more positive should improve social functioning and mood.

Goals were to (1) evaluate theory-based mathematical models of choice to measure emotion judgments, (2) determine whether Interpretation Bias Training (IBT) can shift emotion judgments, (3) test the association between emotion judgments and clinical outcomes.
Methods: Young people (16-25) with BD were recruited for three sessions of IBT (randomized to active or sham). Active IBT trains towards more happy judgments of faces on the sad/happy continuum. Sham IBT reinforces a person's native bias. Two months after IBT sessions, outcomes were evaluated. Model fits to IBT (judgments only) were evaluated in an unselected sample (N=376).
Results: Forty-three participants consented, 34 completed the trial. Negative emotion bias shifted more in the active than sham group (Cohen's d=1.49, p<.001). Comparative judgment models with logistic functions provided reasonable fit.

In a linear mixed model, fixed effects for group (p=.027) and group-by-time (p=.031) were significant; the intervention group had a larger decrease in depressed mood (p=.027), and a larger increase in familial social support (p=.011).
Conclusions: Results converge with prior work that IBT improves mood, and reinforce the use of mathematical models to test and inform theory; the association between emotion judgments and mood supports the hypothesis that seeing others' emotions more positively could enhance interactions and improve mood.
Supported By: Einstein-Montefiore Institute of Clinical and Translational Research
Keywords: Bipolar Disorder, Cognitive Remediation, Emotional Facial Processing

SATURDAY, MAY 18, 2019

PLENARY
Cognitive Systems, Decision Making and Disease Risk: Genetic and Computational Frameworks
8:00 a.m. - 11:30 a.m.
Chair: Scott Langenecker

168. Learning and Decision Making Across Healthy and Disease States

Yael Niv

Princeton University

Recent years have seen immense progress in understanding decision making and learning processes in the animal and human brain, and how these work in concert with other cognitive processes such as attention and memory. Key to this progress has been the use of computational frameworks that allow hypotheses to be stated precisely, and tested rigorously. Importantly, computational models allow us to measure and quantify dynamic processes at the level of an individual person, with widespread implications for psychiatric diagnosis and treatment. In this talk, I will describe some of these recent advances, focusing in particular on interactions between learning and attention that we have been studying in my lab.
Keywords: Computational Psychiatry, Reinforcement Learning, Attention Learning, Extinction Learning And Recall, Decision Making

169. New Technology for Learning About Genetic Effects on Brain Cells and Brain Tissue

Steven McCarroll

Harvard Medical School

Psychiatric disorders have long offered the following scientific conundrum: heritability and specific results point to an organic basis, presumably in brain tissue; but brain tissue from patients presents few if any overt cellular or molecular clues about pathophysiological mechanisms. I will describe the development of new single-cell technologies and analytical methods for unlocking the molecular information that is hidden in brain tissues, and early insights from applying these approaches to the human brain.
Keywords: Brain Structure

170. What Can Machine Learning and Neuroimaging Techniques Bring to Psychiatry?

Janaina Mourao-Miranda

University College London

Over the last years artificial intelligence and machine learning have hugely impacted many areas, such as advertising, finance and medicine. These techniques can find hidden patterns in high dimensional and complex data enabling predictions not previously possible. Among all medical areas, psychiatry can potentially be the one that will be most transformed by artificial intelligence and machine learning due to the current lack of biomarkers. Advanced machine learning models that can combine information from neuroimaging techniques with complementary knowledge from clinical assessments and general patient information have the potential to identify reliable biological markers and improve patient characterization in psychiatry. In this talk, I will present some pioneering examples of how machine learning has been applied to improve diagnosis and prognosis of psychiatric disorders based on neuroimaging. I will also discuss how machine learning models can help us to identify a brain-behaviour latent space which has the potential to improve characterization of mental health disorders and identify people at risk of developing these disorders.
Keywords: Mental Health, Machine Learning, Neuroimaging

171. Decision-Making and Computational Psychiatry: An Explanatory and Pragmatic Perspective

Martin Paulus

Laureate Institute for Brain Research

The past twenty years have seen a surge of interest in understanding decision-making in mathematics, psychology, economics, social sciences, and also in psychiatry. Two complementary approaches have emerged as the theoretical underpinning for decision processes: within the framework of reward and value, decision-making has been conceptualized as the selection of actions that maximize gains and minimize losses; in comparison within a Bayesian framework, decision-making is the process of selecting an action based on inference that provides the most predictive outcome within an uncertain world. Thus, dysfunctional decision-making can be understood as a breakdown of adaptive value representation or as the consequence of making improper inferences about the true state of the world. Together, these frameworks provide powerful explanatory approaches to conceptualize processing dysfunctions in psychiatric conditions that can be transdiagnostic and quantitative. Indeed, both value-based dysfunctions and incorrect inferences have been identified for a variety of psychiatric disorders ranging from substance use to schizophrenia. More research will be necessary to ground these processing dysfunctions in neurobiology that can be the target for novel interventions. At the same time and within a pragmatic framework, there has been a surging interest in the use of machine learning to generate individual level predictions that have clinical utility. These approaches have capitalized on advances in statistical learning to move beyond establishing general relationships between variables of interest to using many variables and statistical models that optimize the tradeoff between precision and robustness when predicting individual psychiatric outcomes. These approaches have yielded predictions for medication selection, relapse or recurrence of disorder status, and even risk for suicide. However, the lack of a conceptual processing model underlying these approaches have limited our understanding of these prediction

tools. In this review, examples of both approaches will be presented, strengths and limitations will be highlighted, and opportunities for future research will be emphasized. Taken together, decision-making has been a useful construct to integrate both explanatory and pragmatic approaches in psychiatry to improve our understanding of these disorders and making research results useful for clinicians.
Keywords: Risky Decision-Making, Choice Mechanisms, Prediction

SYMPOSIUM
Novel Findings on the Gut-Brain Axis
12:30 p.m. - 2:30 p.m.
Chair: Mirjana Domakonda

172. Child Weight Gain Trajectories Associated With Oral Microbiota Composition

Sarah Craig[1], Daniel Blankenberg[2], Alice Parodi[3], Ian Paul[4], Leann Birch[5], Jennifer Savage[1], Michele Marini[1], Jennifer Stokes[4], Anton Nekrutenko[1], Matthew Reimherr[1], Francesca Chiaromonte[1], and Kateryna Makova[1]

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Background: Gut and oral microbiota perturbations have been observed in obese adults and adolescents, but less is known about their influence on weight gain in young children. Herein, we examined associations between oral and gut microbiota and weight gain in infants to determine whether there are differences between children with rapid vs. non-rapid weight gain. We also explore relationships between maternal oral microbiota and infant weight trajectories. Lastly, we assessed the impact of diet on oral/gut microbiota.
Methods: We analyzed the gut and oral microbiota of 226 two-year-olds with 16S rRNA gene sequencing. Weight and length were measured at seven time points and used to identify children with rapid weight gain (a strong risk factor for childhood obesity), and to derive growth curves with innovative Functional Data Analysis (FDA) techniques.
Results: Children's growth curves were associated negatively with diversity ($p = 4.1 \times 10-2$) and positively with Firmicutes-to-Bacteroidetes ratio of the oral microbiota ($p = 1.5 \times 10-3$). We demonstrated an association between the gut microbiota and child growth, but only when considering the effect of diet on the microbiota ($p = 0.020$). Lastly, we identified several bacterial genera that are associated with child growth patterns.
Conclusions: These results suggest that by the age of two, the oral microbiota of children with rapid weight gain may have already begun to establish patterns often seen in obese adults. They also suggest that the gut microbiota, while strongly influenced by diet, at age two does not harbor obesity signatures many researchers identified in later life stages.
Supported By: This project is supported by grants R01DK088244 and R01DK99364 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This project is also supported by the funds from the Eberly College of Sciences at PSU, by the Penn State Institute of Cyberscience, by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (through Grant UL1TR000127). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additionally, this project is funded, in part, under a grant with the Pennsylvania Department of Health using Tobacco Settlement and CURE funds. The Department specifically disclaims responsibility for any analyses, interpretations, or conclusions.
Keywords: Obesity, Pediatrics, Childhood

173. Preliminary Evidence for Changes in Neurocognitive Function After Adolescent Bariatric Surgery

Alaina Pearce[1], Eleanor Mackey[2], J. Bradley Cherry[3], Alexandra Olson[4], Xiaozhen You[5], Sheela N. Magge[2], Michele Mietus-Snyder[2], Evan Nadler[2], and Chandan Vaidya[5]

[1]The Pennsylvania State University, [2]Center for Translational Sciences, Children's Research Institute, Children's NHS, [3]Georgetown University, [4]Center for Translational Sciences, NHS, [5]Georgetown University, Children's Research Institute, Children's NHS

Background: Pediatric obesity is associated with neurocognitive deficits that impact important developmental and academic trajectories. A meta-analysis we conducted showed pediatric obesity is associated with worse executive and reward function, and recent data suggest poorer self-regulation in very young children is predictive of future weight gain. Unknown is whether these deficits are a cause or consequence of obesity, or whether they may be reversed with weight-loss. To better understand the role of obesity in cognitive deficits, we conducted a pilot study examining changes in brain and cognitive functioning following vertical sleeve gastrectomy (VSG) in adolescents.
Methods: Thirty-six adolescents, 10 scheduled for VSG, 14 wait-listed for VSG (WL), and 12 healthy controls (HC), underwent fMRI twice 4 months apart (pre- and post-surgery for VSG), during executive and reward tasks, in addition to behavioral testing for reward-related decision making.
Results: VSG showed larger improvements in executive and reward-related performance than HC and WL groups. After surgery, VSG showed significant weight loss ($p<0.001$), while WL showed weight gain ($p=0.005$). A Group x Time interaction ($p<0.05$ corrected) showed prefrontal and striatal activation during working memory and reward anticipation, respectively, was reduced to similar levels as HC adolescents after VSG. In contrast, WL increased prefrontal activation during working memory, and no change in during reward anticipation.
Conclusions: These data provide preliminary evidence for VSG induced functional brain changes in adolescents with severe obesity, suggesting neural plasticity may be related to metabolic change.
Supported By: NIDDK
Keywords: Obesity, Bariatric Surgery, Brain Imaging, fMRI, Adolescents

174. Pre-Surgical fMRI Brain Activation Predicts 12-Month Post-Bariatric Surgery Outcomes

Godfrey Pearlson[1], Michael Stevens[2], Krishna Pancholi[2], Mirjana Domakonda[2], Hedy Kober[3], and Pavlos Papasavas[2]

[1]Yale University School of Medicine, [2]Hartford Hospital / Institute of Living, [3]Yale University

Background: For morbidly obese adults who fail to lose significant weight with diet/exercise and have secondary medical problems, bariatric surgical represent effective alternatives. Post-surgical success varies widely, but pre-surgical prediction of outcome using traditional medical, hormonal, sociological, personality or psychiatric data is inaccurate.
Methods: N= 65 individuals BMI>35 were recruited from a Surgical Weight Loss Center and imaged pre-surgically in a Siemens Skyra 3T MRI. fMRI tasks included: 1. Resting State, 2. Gustatory Food Cues (GFC) to milkshake, 3. Monetary Incentive Delay (MID), 4. Regulation of Craving (RoC), 5. Affective Perception, 6. Visual Social Food Cues (SFC). 12m post-surgery follow-up assessed % total weight loss (%TWL) and key medical indices. fMRI tasks modeled 26 pre-selected, non-overlapping regions-of-interest (ROIs) in FSL-FEAT. Stepwise linear regression explored the relationship of ROI values to %TWL and change in fasting glucose, hemoglobin A1c, triglycerides, sleep apnea & hypertension, all values $p<0.05$ multiple-comparison corrected.
Results: 69% total variance in %TWL ($F=12.099$; $p=3.5065E-10$) was explained by combined fMRI brain activity in caudate, thalamus, hippocampus, anterior cingulate & orbitofrontal cortices during, MID, SFC, GFC and RoC tasks. No other hormonal, personality or psychiatric data entered the stepwise regression model. fMRI data predicted 54% of a more complex, PCA-derived outcome measure, comprising %TWL, quality of life and the above health information.
Conclusions: Consistent with a prior smaller pre-surgical fMRI study, we successfully predicted 69% of 12-month post-surgical %TWL using pre-hoc specified brain regions. Brain imaging measures may be useful in triaging bariatric surgical candidates to determine those needing additional pharmacologic or counseling support.
Supported By: IOL/ Hartford Hospital research award and NIDDK 1R01DK113408
Keywords: Obesity, Brain Imaging, fMRI, Bariatric Surgery, Cognitive Neuroscience, Obesity

175. Targeting the Gut-Brain Axis to Regulate Preference and Striatal Response to Fat

Maria Jorina van Kooten[1], Mary Burke[2], A.G. DiFeliceantonio[2], J. Dalenberg[2], M.G. Veldhuzien[2], E. Garcia[2], R.M. Masheb[3], I.E. de Araujo[2], and **Dana Small**[4]

[1]Yale School of Medicine, University of Groningen, [2]Yale School of Medicine, [3]Yale School of Medicine, VA Connecticut Healthcare, [4]Yale University

Background: High fat diet (HFD) leads to disrupted striatal dopamine function and alterations in fat preference. One mechanism by which this occurs is depletion of gut lipid messengers, including oleoylethanolamine (OEA), which when replenished rescues dopamine response and increases preference for low fat emulsions via the generation of vagal afferent signals (Tellez et al., 2013). Using a supplement containing the OEA precurser N-oleyl-phosphatidylethanolamine and epigallocatechin-3-gallate (NOPE+EGCG), we tested whether this effect translates to humans and whether supplementation improves outcomes on a behavioral weight loss trial.
Methods: 67 individuals were randomized to a 9.5-month supplementation regimen with NOPE+EGCG or placebo and outcomes were assessed after supplementation alone (6 weeks), after a weight loss trial (4 months), and after a weight maintenance period (4 months). Neural response to milkshake was measured using fMRI.
Results: Directly replicating findings in rodents, compared to placebo, 6-weeks supplementation with NOPE+EGCG reduced fat intake and preference and increased dorsal striatal response to milkshake (Tellez et al., 2013). Additionally, individuals supplementing with NOPE+EGCG, lost more weight overtime, achieving 5% weight loss following the trial and 8% loss following the maintenance period. Critically, this effect depended on history of saturated fat intake at enrollment, such that those eating a HFD benefited most from the supplement.
Conclusions: Consistent with findings in mice, our results demonstrate that targeting fatty acid-derived gut-brain communication can influence striatal response to fat, fat preference and fat intake and may have therapeutic potential for weight loss and regulation of striatal circuits in individuals consuming HFD.
Supported By: NIH/NCI R01
Keywords: Gut-Brain Axis, Obesity, Novel Treatments, Fatty Acid

SYMPOSIUM
Assessing the Risks and Benefits of Antipsychotic Medication on Brain and Body: Data From a Double Blind Randomized Placebo-Controlled Clinical Trial, and Convergent Data From an Animal Model

12:30 p.m. - 2:30 p.m.
Chair: Ellen Whyte

176. Sustaining Remission of Psychotic Depression: The Stop-PD II Study

Ellen Whyte[1], Alastair J. Flint[2], Anthony Rothschild[3], Benoit H. Mulsant[4], George Alexopoulos[5], Patricia Marino[5], Samprit Banerjee[6], Matthew Rudorfer[7], and Barnett Meyers[6]

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Background: Acute treatment guidelines for unipolar psychotic major depression (PD) recommend electroconvulsive therapy or the combination of antidepressant and antipsychotic medications. Unfortunately, relapse and recurrence are common. Little is known about continuation pharmacologic treatment in PD, specifically whether antipsychotic medication needs to be continued once an episode of PD responds to combination pharmacotherapy. This issue has great clinical significance – premature discontinuation of the antipsychotic medication has the potential risk of early relapse of this severe and potentially lethal disorder whereas its unnecessary continuation can expose a patient to adverse effects.
Methods: STOP-PD II was a NIMH-funded, multicenter randomized placebo-controlled trial that assessed the risks and benefits of continuing antipsychotic medication in adults once the episode of PD had responded to combination treatment with an antidepressant (sertraline) and an antipsychotic (olanzapine).
Results: Among 126 remitted participants, the time to relapse was significantly shorter for participants randomized to antidepressant monotherapy compared to those randomized to combination therapy (X2 = 17.8, dF=1, p< 0.0001); the frequency of relapse was 54.8% (n=34/62) and 20.3% (n=13/64), respectively, over 36 weeks. There was a significant difference between groups in trajectories of weight (F=116.78, dF = 1,1422, p<0.0001) and total cholesterol (F=13.15, dF = 1,311, p=0.0003), with a decrease in these variables in the antidepressant monotherapy group and an increase in weight in the combination therapy group. The groups did not differ in the trajectory of plasma glucose.
Conclusions: In this study, combination therapy was associated with a reduced risk of relapse but at the expense of ongoing weight gain.
Supported By: NIMH
Keywords: Psychotic Depression, Antipsychotics, Metabolic Side Effects, Relapse Prevention

177. Effects of Antipsychotic Medication on Brain Structure: Data From a Double-Blind, Randomized, Placebo-Controlled Trial

Aristotle Voineskos[1], Alastair Flint[2], Nicholas Neufeld[1], Erin Dickie[1], Ellen Whyte[4], Matthew Hoptman[5], Anthony Rothschild[6], Barnett Meyers[7], George Alexopoulos[8], and Benoit Mulsant[1]

[1]Centre for Addiction and Mental Health, University of Toronto, [2]University Health Network, [4]University of Pittsburgh School of Medicine, [5]Nathan Kline Institute for Psychiatric Research, [6]Center for Psychopharmacologic Research & Treatment, University of Massachusetts Medical School, [7]Weill Cornell Medical College, [8]Weill Medical College of Cornell University-The New York-Presbyterian Hospital

Background: We report new data from an NIMH-funded four site study which capitalizes on the only placebo-controlled study of an antipsychotic with neuroimaging. The main aim of the neuroimaging study is to compare the effects of olanzapine vs. placebo on brain structure, which is of public health importance.
Methods: Participants were recruited at four academic centers. As part of a multimodal protocol, a T1-weighted scan, and DTI scan were obtained at randomization and then at either sustained remission (36 weeks later) or relapse. Brain structure comparisons were made first between those who sustained remission, and then with all participants for a treatment group by time interaction using a linear mixed model.
Results: 72 follow-up scans were completed at either sustained remission or relapse (mean duration 12 weeks). In those who sustained remission, the olanzapine exposed group demonstrated a reduction compared to the placebo group F=15.2, p=0.0004 (left hemisphere cortical thickness). When including those who relapsed (55% relapse rate in placebo group vs. 20% relapse in olanzapine group), there were significant treatment group by time interactions for left hemisphere cortical thickness (t=3.2, p=0.002), i.e. those who relapsed in the placebo group experienced reduction in cortical thickness.
Conclusions: To our knowledge, this is the first prospective placebo-controlled longitudinal antipsychotic neuroimaging study in humans. Our results show that longer-term olanzapine treatment is associated with potentially deleterious effects on cortical thickness. However, in those who experience early and sudden relapse, not treated with olanzapine, there is also a deleterious effect of illness on brain structure.
Supported By: NIMH R01MH099167
Keywords: MRI, Depression., Antipsychotics, Clinical Trials

178. Brain Network Biomarkers of Remitted Psychotic Depression

Nicholas Neufeld[1], Antonia Kaczkurkin[2], Aristeidis Sotiras[2], Erin Dickie[1], Benoit Mulsant[1], Barnett Meyers[3], George Alexopoulos[3], Anthony Rothschild[4], Ellen Whyte[5], Matthew Hoptman[6], Alastair Flint[7], Christos Davatzikos[2], Theodore Satterthwaite[2], and Aristotle Voineskos[1]

[1]Centre for Addiction and Mental Health, [2]University of Pennsylvania, [3]Cornell University, [4]University of Massachusetts, [5]University of Pittsburgh, [6]Nathan Kline Institute, [7]University of Toronto and UHN

Background: Little is known about the neurobiological basis of major depressive disorder with psychotic features ("psychotic depression"). This preliminary case-control study addresses this knowledge gap by using structural magnetic resonance imaging to compare structural covariance networks in patients with remitted psychotic depression and healthy controls.
Methods: We scanned patients who participated in the Study of Pharmacotherapy of Psychotic Depression (STOP-PD) II randomized controlled trial and healthy controls. All patients had achieved remission of both depressive and psychotic symptoms with olanzapine and sertraline. Structural (cortical thickness) covariance networks were derived using non-negative matrix factorization, an unsupervised multivariate

pattern analysis technique, and a general linear model was employed to compare patients and controls.
Results: Our sample included patients (n=87, mean age [SD]=55.0 [15.0]) and controls (n=155, mean age[SD]=44.8 [18.4]). Compared to controls, patients demonstrated significantly decreased ($p<0.05$, False Discovery Rate (FDR) corrected) cortical thickness in structural covariance networks that, medially, encompassed bilateral ventromedial prefrontal, cingulate, paracingulate, and parahippocampal cortices and, laterally, encompassed bilateral ventrolateral prefrontal, parietal, temporal, and insular cortices. A structural covariance network encompassing the bilateral insular, posterior cingulate, and parahippocampal cortices showed the largest effect when comparing patients and controls (t=4.611, p=0.0002, FDR corrected).
Conclusions: These results suggest that, compared to controls, patients with remitted psychotic depression treated with an antipsychotic and an antidepressant present with decreased cortical thickness, particularly in a structural covariance network that includes regions involved in interoception, self-directed thought, and memory.
Supported By: B.S.M (5U01MH062518), A.J.R. (5U01MH062624), E.M.W (5U01MH062565), A.J.F (5U01MH062446), and A.N.V (5R01MH099167).
Keywords: Structural MRI, Psychotic Depression, Biomarkers, Remission

179. Effects of Chronic Haloperidol Treatment on Brain Volume in a Rat Model in of Infection-Mediated Neurodevelopmental Disorders

Marie-Caroline Cotel[1], Zsuzsa Lindenmaier[2], Ewelina Lenartowicz[1], Sridhar Natesan[1], Jason Lerch[2], and **Anthony Vernon**[1]

[1]Institute of Psychiatry, King's College London, [2]University of Toronto

Background: Pre-clinical evidence suggests chronic antipsychotic exposure leads to decreased cortical thickness. However, these findings are in naïve animals, confounding any extrapolation regarding the effects of antipsychotics on cortical thickness changes in the brains of medicated schizophrenia patients. To address this, we investigated cortical thinning in a rat model for schizophrenia following chronic antipsychotic treatment.
Methods: Adult offspring from control (CON; saline, i.v.; GD15; n=5) and maternal immune activation (MIA) exposed dams (poly (I:C); 4 mg/kg i.v. GD15; n=5) were randomly allocated to one of four groups CON/vehicle; CON/haloperidol; MIA/vehicle and MIA/haloperidol (all n=10; haloperidol 0.5 mg/kg/d s.c., 28 days). At the end of treatment, animals were culled and perfused with 4% PFA, with the brain left in the cranium. T2-weighted ex vivo MR images were acquired and analysed using an automated rat cortical thickness pipeline. Differences between groups in cortical thickness (corrected for total brain volume) were assessed using linear models in R and corrected for multiple comparisons using the False Discovery Rate (5%).
Results: Prefrontal and parieto-temporal lobe cortical thickness were significantly increased in MIA offspring treated with vehicle ($p<0.05$; $q<0.05$). Significant MIA*treatment interactions were found only for the parieto-temporal lobe thickness, with haloperidol decreasing cortical thickness in the MIA offspring ($p<0.05$; $q<0.05$).
Conclusions: These data show that chronic treatment with haloperidol results in region-specific cortical thinning in a relevant animal model for schizophrenia, as previously seen in naive animals and human patients. This provides a framework to investigate the functional relevance of these changes and their underlying mechanisms.
Supported By: Medical Research Council New Investigator Grant
Keywords: Antipsychotics, Schizophrenia, Cortical Thinning, Structural Neuroimaging, Maternal Immune Activation

SYMPOSIUM
Genetic, Cellular, and Circuit Substrates of the Differential Behavioral Response to Ovarian Steroids
12:30 p.m. - 2:30 p.m.
Chair: David Rubinow
Co-Chair: Peter Schmidt

180. Premenstrual Dysphoric Disorder (PMDD): Neuroanatomical Hubs and Cellular Substrates of Risk

Peter Schmidt[1], Shau-Ming Wei[1], Howard Li[2], Goff Allison[3], Sarah Rudzinskas[1], Jessica Hoffman[1], Neelima Dubey[1], Cheryl Marietta[3], Pedro Martinez[1], Lynnette Nieman[4], David Rubinow[5], Karen Berman[1], and David Goldman[3]

[1]NIMH, [2]Harvard Medical School, [3]NIAAA, NIH, [4]NIDDK/NIH, [5]University of North Carolina

Background: Premenstrual Dysphoric Disorder (PMDD) represents the convergent effects of ovarian steroid triggers and susceptibility to affective dysregulation. We investigate the possible neurofunctional and cellular substrates of this behavioral sensitivity to ovarian steroids.
Methods: Women with PMDD (n=20) and controls (n=43) underwent resting state H215O-PET during three hormone conditions: induced-hypogonadism, estradiol (E2) and progesterone (Prog) to explore interactions between diagnosis and hormone conditions in the brain. Concurrently, lymphoblastoid cells (LCLs) from women with PMDD (n=10) and controls (n=9), and neuroprogenitor cells (NPCs) (n=4/group) were derived and exposed to E2 or Prog. RNA-seq and network analyses identified differentially expressed genes (DEGs) and networks, including ESC/E(Z). qRT-PCR was performed in a replication sample of LCLs (n=24/group)
Results: There was a significant diagnosis-by-hormone interaction in the subgenual cingulate ($F_{2,57}=7.4$, $P_{FDR}<.05$): compared with controls, women with PMDD had significantly decreased resting rCBF during E2 and Prog ($P<.03$ both comparisons) but not during hypogonadism. LCLs showed increased baseline mRNA expression in PMDD over controls within the 13 ESC/E(Z) gene-family including increased expression in MTF2, PHF19, and SIRT1 ($P<0.05$), and these

findings were confirmed with qRT-PCR and by RNA-seq in NPCs. DEGs were observed after Prog in controls but not PMDD (EED, EZH2, MTF2, P<0.05) and after E2 in PMDD but not controls (JARID2, P<0.05). Finally, preliminary network analysis of E2-exposed LCLs implicates DEGs involved in intracellular calcium regulation (NUCB1, GCC2, TRPM7; P<.01) in PMDD.
Conclusions: The differential behavioral sensitivity in women with PMDD is paralleled by rCBF (in vivo) and cellular transcription (in vitro) responses to ovarian steroids.
Supported By: The NIMH Intramural Research Program/NIH/HHS
Keywords: Premenstrual, Subgenual Anterior Cingulate Cortex, Epigenome

181. Variations in Sex-Steroid Regulated Genes: Ovarian Steroid Hormones Modulate Working-Memory Related Brain Function in Women

Shau-Ming Wei[1], Erica Baller[2], Philip Kohn[1], J. Shane Kippenhan[1], Bhaskar Kolachana[1], Steven Soldin[3], David Rubinow[4], Peter Schmidt[1], and Karen Berman[1]

[1]NIMH, NIH, [2]University of Pennsylvania, [3]NIH/CC, [4]University of North Carolina

Background: Regulatory actions of ovarian steroids on genes relevant to brain function are well-documented. Here, we employed a hormone-manipulation paradigm to test for interactions between ovarian hormones and specific sex steroid-regulated genes on brain function.
Methods: Working memory-related regional cerebral blood flow (rCBF) and BOLD signal change were measured with H215O-PET and fMRI, respectively, in healthy women during three pharmacologically-controlled hormone conditions: GnRH agonist-induced ovarian suppression, estradiol addback, and progesterone addback. For each of the three hormone conditions, a discovery dataset was obtained with rCBF PET in 39 women genotyped for BDNF Val66Met and COMT Val158Met, and for BDNF genotype, a confirmatory dataset was obtained with fMRI in 27 women.
Results: A hormone-by-BDNF interaction was observed on working memory-related hippocampal function (PET: F2,37=9.11, p=0.05 SVC for FWE; fMRI: F2,26=5.43, p=0.02 uncorrected): there was atypical hippocampal recruitment in Met-carriers but only in the presence of estradiol. Additionally, a hormone-by-COMT interaction was found in the right dorsolateral prefrontal cortex ([DLPFC]; PET: F2,68=9.34, p=0.00026): during estradiol only, a COMT genotype dose-related, step-wise DLPFC activation pattern was observed: Met homozygotes had the highest activation, followed by heterozygotes and then Val homozygotes.
Conclusions: The fact that the BDNF-by-estradiol interaction was present in the hippocampus and not the DLPFC, whereas the COMT-by-estradiol interaction was present in the DLPFC and not the hippocampus suggests regional specificity that reflects where in the brain these genes have particular functional relevance. These findings also suggest that genomic variation in sex steroid-regulated genes could contribute to the differential behavioral sensitivity to estradiol in some women.
Supported By: NIMH IRP, NIH
Keywords: Ovarian Steroids, Genetic Variants, PET, BOLD fMRI, Working Memory

182. Differential Gene Expression in Response to Estradiol Withdrawal in Perimenopausal Depression

Sarah Rudzinskas[1], Jessica Hoffman[1], David Rubinow[2], David Goldman[3], and Peter Schmidt[1]

[1]NIH/NIMH, [2]University of North Carolina, [3]NIH/NIAAA

Background: Perimenopausal women are 1.5-3x more likely to report major or minor depressions compared with premenopausal or postmenopausal women. Evidence suggests that heightened sensitivity to changes in estradiol (E2) contribute to the onset of perimenopausal depression (PMD). Clinical studies show both the therapeutic benefits of E2 in PMD and the symptom-provoking effects of E2-withdrawal in women with past PMD.
Methods: We created lymphoblastoid cell lines (LCLs) derived from blood samples from women with a past PMD (n=8), or asymptomatic controls (n=9), and exposed them to 3 different experimental conditions: vehicle, E2, or E2-withdrawal. LCLs were then collected, and RNA-sequencing was performed for changes in gene expression and other pathway analyses.
Results: We found 534 (p,uncor<0.05) differentially expressed genes (DEGs) in LCLs between ACs and women with PMD after E2-withdrawal. Of these DEGs, CXCL10 (p,uncor<1.55x10-5), linked to cardiovascular disease, is significantly upregulated in the cells of women with past PMD, especially in the E2-withdrawal treatment condition. In contrast, CYP7B1 (p,uncor<5.6x10-4), of interest due to its involvement in the metabolism of DHEA and pregnenolone, is also significantly upregulated in PMD, but in all treatment conditions. Furthermore, several molecular networks appear to be significantly altered in women with PMD.
Conclusions: Our results support the hypothesis that the differential responsivity to E2-withdrawal in PMD could be linked to dynamic gene expression changes on a cellular level and suggests that both intrinsic genetic differences as well as differential sensitivity to E2-withdrawal could underlie PMD.
The elevated CXCL10 suggests a possible contributor to the increased cardiac risk associated with PMD.
Supported By: NIH/NIMH, NIH/NIAAA
Keywords: Perimenopause, Estradiol, Depression, RNA-seq, Differential Susceptibility

183. Epigenetic Intersection of BDNF Val66Met Genotype with Premenstrual Dysphoric Disorder Transcriptome in a Cross-Species Model of Estradiol Add-Back

Jordan Marrocco[1], Nathan Einhorn[1], Howard Li[2], Karen Berman[2], David Goldman[3], Francis Lee[4], Peter J. Schmidt[2], and Bruce McEwen[1]

[1]The Rockefeller University, [2]National Institute of Mental Health, [3]NIAAA/National Institute of Mental Health, [4]Weill Cornell Medical College

Background: Natural fluctuations in circulating ovarian steroids across the menstrual cycle are associated with negative emotions. Mice with a single nucleotide polymorphism of the human BDNF gene (Val66Met), show a negative behavioral response to ovarian hormone fluctuations, resembling that of women with premenstrual dysphoric disorder (PMDD) to estrogens.
Methods: Heterozygous BDNF Met (Het-Met) mice and wild type (WT) mice (n=12/group) were ovariectomized and administered E2 or vehicle in drinking water for six weeks. The ventral hippocampus was dissected and processed for RNA-seq (n=3/group). Women of ages 18 to 48 years were included in the clinical study. Lymphoblastoid cell lines (LCLs), created from control women and women with PMDD, were treated or not with estradiol, and processed for RNA-seq (n=5/group). A comparative DESeq2 analysis pipeline was used to quantify both species' raw reads and obtain p-values ($p<0.05$, Benjamini-Hochberg FDR), and fold change (>1.3).
Results: We identified a number of common orthologues that were induced by E2 in both species. A GO analysis of commonly regulated genes revealed two major epigenetic clusters, namely, transcription and covalent chromatin modification. Common epigenetic genes were entered into GeneMANIA to correlate genes in the same interaction network. This network included 15 epigenetic modifiers, as well as 4 genes of the ESC/E(Z) complex, an effector of response to ovarian steroids.
Conclusions: BDNF Met genotype intersected the epigenome of women with PMDD, showing a cluster of epigenetic modifiers by which ovarian steroids may produce negative behavioral effects. Epigenetic markers conserved across species may be relevant for novel diagnostic and therapeutic interventions.
Supported By: Hope for Depression Research Foundation
Keywords: BDNF Val66Met, Premenstrual Dysphoric Disorder, Epigenetics, Cross Species, RNA Sequencing

SYMPOSIUM
Identifying and Influencing Large-Scale Networks Underlying the Risk of Suicide in Mood Disorders

12:30 p.m. - 2:30 p.m.
Chair: Kathryn Cullen

184. Subspecialization Within Default Mode Nodes

Danilo Bzdok[1]

[1]RWTH Aachen University

Background: In the present investigation, we conduct several computational experiments to probe the structural and functional link of the DMN with higher-order brain networks. We explore organizational details of the DMN architecture by combining a recently completed DMN atlas and 10,129 brain-scanned individuals from the UK Biobank - the currently largest biomedical population dataset.
Methods: Multimodal brain-imaging was obtained from the latest data release of the UK Biobank which included structural-, diffusion- and resting-state magnetic resonance imaging in 10,129 individuals. We used a recently established DMN atlas compromising 26 subnodes across dorsomedial [dmPFC] and ventromedial prefrontal cortex [vmPFC], posteromedial cingulate cortex [PMC], temporoparietal junction [TPJ], and hippocampus [HC] to acknowledge the accumulating evidence that the individual nodes of the DMN functionally further segregate into distinct subnodes.
Results: In brain structure, the fornix fiber tract emerged as best predicted by DMN volumes explaining up to 37% +/- 2 of the variance in independent participants (Fig. 1a, b). Here, the DMN subregions most important to the prediction were the PMC- 2, posterior TPJs, and the vmPFC-1.

In brain function, our CCA findings highlighted the anterior TPJ as a primary hub for governing the interplay between the DMN and major brain networks.
Conclusions: We identified the anterior TPJs as critical for large-scale functional network coupling. Moreover, each examined node was shown to embed subregions associated with fornix-carried hippocampal space-time inputs and adjacent subregions governing functional coupling between major cortical networks.
Supported By: This work was supported by the International Research Training Group (IRTG 2150) of the German Research Foundation (DFG)
Keywords: Machine Learning, Systems Neuroscience, Personalized Medicine

185. Probing the Functional Connectivity Default-Mode Network and Intrinsic Activity of the Anterior Cingulate Cortex of the Adolescent Suicidal Brain

Anthony Gifuni[1], Henry Chase[2], Mary Phillips[2], Johanne Renaud[1], and Fabrice Jollant[3]

[1]McGill University, [2]University of Pittsburgh, [3]Université Paris-Descartes

Background: Social rejection is a frequent proximal trigger for suicidal behaviors in adolescents. However, the neural basis of increased suicidal risk following a social stress remains poorly defined. Changes in functional connectivity in the default-mode network have been related to the development of social cognition in adolescents, while activity in the ACC has been associated with social rejection.
Methods: Three groups were recruited: 1) depressed adolescents with a history of suicidal attempt (N=34), 2) depressed adolescents adolescent without suicidal attempt (N=25), and 3) healthy controls (N=26). Each subject underwent resting state fMRI and task-based MRI with the Cyberball Task, a paradigm that simulates social rejection. Seed-based methods and wavelet-based analysis of intrinsic neural activity were employed to characterize DMN activity and the intrinsic activity of the ACC.
Results: Seed-based connectivity preliminary analysis indicated that depressive disorders in adolescents are

associated with increased connectivity between the posterior cingulate cortex and the anterior cingulate cortex ($p=0.003$, df(1,80), uncorrected). While PCC-ACC functional connectivity did not distinguish adolescents based on prior suicidal behaviors, the variability of intrinsic dorsal ACC activity was higher in mid-range frequencies in individuals with a history of suicide attempt ($p<0.05$).

Conclusions: Within a DMN network with higher PCC-ACC connectivity, the intrinsic variability in the ACC at rest might be a potential biomarker associated with the propensity to attempt suicide in depressed adolescents. Questions remain whether activity in the resting state reflects brain reactivity to social rejection in adolescents at risk of suicide.

Supported By: Manulife, FQRS

Keywords: Suicide Attempts, Functional Connectivity, Functional Neuroimaging, Adolescent Depression

186. Longitudinal Decreases in Suicidal Ideation are Associated With Increases in Salience Network Coherence in Depressed Adolescents

Jaclyn Schwartz[1], Tiffany Ho[1], Sarah Ordaz[1], and Ian Gotlib[1]

[1]Stanford University

Background: Suicidal ideation (SI) is a significant predictor of suicide attempt; SI itself, however, is difficult to predict. Given that SI begins in adolescence when brain networks are maturing, it is important to understand associations between longitudinal changes in network functioning and changes in severity of SI.

Methods: Depressed adolescents (N=33, ages 14-17 years) were administered the Columbia-Suicide Severity Rating Scale to assess SI and completed resting-state fMRI at baseline (T1) and 6 months later (T2). We computed network coherence in the executive control (ECN), default mode (DMN), salience (SN), and non-relevant noise networks and examined associations between changes in severity of SI and changes in brain network coherence from T1 to T2.

Results: A greater reduction in severity of SI was associated with a greater increase in SN coherence from T1 to T2 ($\beta=-.50$, $t=-3.05$, $p=.006$) controlling for severity of T1 SI and depression. There were no associations between SI and the other networks.

Conclusions: Although more time-points are necessary to elucidate finer-grained trajectories of SI and trajectories of SN coherence, our finding that reductions in SI are associated with increases in SN coherence extends previous cross-sectional results documenting a negative association between SI severity and SN coherence. Given the regulatory role of the SN in coordinating activation of ECN and DMN in response to salient information, the association between SN coherence and SI severity suggests that adolescents with reduced SN coherence more easily engage in harmful thoughts. Therefore, the SN may be a relevant target for intervention approaches with depressed adolescents.

Supported By: American Foundation for Suicide Prevention (grant number PDF-1-064-13); Brain & Behavior Research Foundation (grant number 23582); the Klingenstein Third Generation Foundation (Fellowship Award); the National Institutes of Health (grant numbers R21-MH101545, R37-MH101495, K01-MH106805)

Keywords: Resting State Functional Connectivity, Suicidal Ideation, Adolescence, Salience Network, Longitudinal

187. Developing Approaches to Identify and Modulate Components of Altered Resting State Default Mode Connectivity in Suicidal Individuals

Henry Chase[1], Ardesheer Talati[2], Myrna Weissman[2], Jonathan Posner[2], Simona Graur[1], Michele Bertocci[1], Randy Auerbach[1], and Mary Phillips[1]

[1]University of Pittsburgh, [2]Columbia University, New York State Psychiatry Institute

Background: Neural signatures of suicidal risk may reflect a combination of suicide-specific and non-specific illness related factors, and successful identification of a marker may assist the development of treatments. We examined whether default mode network (DMN) connectivity can be decomposed into components reflecting familial risk for depression and suicidal ideation (SI), and whether DMN connectivity can be modulated using transcranial direct current stimulation (tDCS) via the left ventrolateral prefrontal cortex (VLPFC).

Methods: Study 1 (S1): Resting state (rs) fMRI data were obtained in 85 individuals (53 high familial risk/32 low risk; 46 SI history/39 no SI history). Study 2 (S2): RsfMRI data were obtained in 50 individuals (25 euthymic bipolar/25 healthy controls) following 17.5min of cathodal 1mA stimulation to LVLPFC or left somatosensory cortex (LSS) using tDCS across separate sessions. S1/S2: Data were analyzed using standard seed-based methods and wavelet-based analysis of intrinsic neural activity.

Results: S1: Heightened familial risk of depression was associated with greater ventral posterior cingulate cortex (PCC) versus dorsal PCC connectivity with the anterior cingulate cortex (ACC: $F(1,78)=9.76$, $p=0.003$). Suicidal ideation was associated with reduced intrinsic activity in the ACC ($F(1,78)=4.15$, $p=0.045$). S2: Cathodal stimulation to the LVLPFC reduced PCC-ACC functional connectivity compared to the LSS condition ($F(1,48)=4.23$, $p=0.045$).

Conclusions: We report differentiation of specific markers of suicide from non-specific predictors of depression risk, and that the underlying circuits may be modulated by tDCS. Together, this suggests that it may be possible to develop strategies for treatment development using a combination of information about underlying neural circuitry and targeted interventions.

Supported By: R01-MH036197 (to MMW); 1R21MH108421-01A1 (to MLP/HWC)

Keywords: Suicidal Ideation, Functional Neuroimaging, Resting State Functional Connectivity, Transcranial Direct Current Stimulation (tDCS)

SYMPOSIUM
Large Scale Imaging Studies of Rare Copy Number Variants: Brain Imaging From Enigma and Other Large-Scale International Studies
12:30 p.m. - 2:30 p.m.
Chair: Paul Thompson

188. ENIGMA-CNV: Unraveling the Effects of Rare Copy Number Variants on Brain Structure

Ida Sønderby[1], Bragi Walters[2], Dennis van der Meer[3], Srdjan Djurovic[3], Ingrid Agartz[3], Lars T. Westlye[3], Sebastien Jacquemont[4], Hreinn Stefansson[2], Paul Thompson[5], and Ole A. Andreassen[3], European 16p11.2 Consortium, ENIGMA-CNV working group

[1]NORMENT, University of Oslo, Oslo University Hospital, [2]deCODE genetics, [3]Norwegian Centre for Mental Disorder Research, [4]University of Montreal, [5]Keck School of Medicine, University of Southern California

Background: ENIGMA-CNV aims to identify the effect of CNVs on brain MRI measures. The 1q21.1 CNV predisposes to e.g. delayed development and schizophrenia and deletion carriers display microcephaly and duplications carriers macrocephaly. Frequency, UK biobank: 0.027 % (deletion).
Methods: Structural T1-MRI data from ENIGMA-CNV and the UK biobank were analyzed (FreeSurfer) and CNVs called (PennCNV). Subcortical volumes, cortical area and thickness were normalized correcting for age, age squared, gender, scanner and intracranial volume (ICV). Dose response (deletion = 1, non-carrier = 2, duplication = 3) was analyzed in a linear model on the normalized brain values.
Results: We found a positive dose-response effect of copy number on intracranial volume (β=1.52, P=1.4E-26) and total surface area (β=0.81, P = 1.5E-08) with the highest effect on the frontal lobe and a small, significant negative dose response on caudate and hippocampus (β=-0.44, P=0.0026; β -0.5, P=0.00064) (deletion= 30, non-carriers=24,575, duplications=19). The results on cortical surface area were replicated in an Icelandic sample (2 deletions, 6 duplications). In the largest analysis to date on 15q11.2 (91 deletions, 129 duplications, 29,773 non-carriers), we showed a positive dose response for cortical surface area (β=0.23, P=0.00063) and a negative dose response for average cortical thickness (β=-0.29, P=1.6E-5).
Conclusions: The mechanism behind the head circumference change in 1q21.1 distal CNV carriers seems to be an increase in cortical surface area which may indicate an effect on early development of the (dorsal) telencephalon. This underlines the value of large-scale collaboration such as ENIGMA-CNV for studies of rare genetic variants implicated in brain pathology.
Supported By: Research Council of Norway, South East Norway Health Authority, Kristian Gerhard Jebsen Stiftelsen
Keywords: CNV, Brain Structure, ENIGMA Consortium

189. The Effect of Penetrance of CNVs for Intellectual Disability and Schizophrenia on Brain Structural Phenotypes

Mark Drakesmith[1], Greg Parker[2], Stefanie Linden[2], Elliott Rees[2], Nigel Williams[2], Michael Owen[2], Jeremy Hall[2], Marianne Van Den Bree[2], and David Linden[2]

[1]CUBRIC, Cardiff University, [2]Cardiff University

Background: Genomic copy number variants (CNVs) are amongst the most highly penetrant genetic risk factors for neuropsychiatric disorders. The scarcity of carriers of individual CNVs and their phenotypical heterogeneity limits investigations of the associated neural endophenotypes. To address this, we applied a novel design based on CNV penetrance for schizophrenia (Sz) and developmental delay (DD) that allows us to identify the most relevant structural sequelae of these disorders.
Methods: 21 adult participants carrying neuropsychiatric risk CNVs (including 22q11.2, 15q11.2, 1q21.1, 16p11.2, and 17q12) and 15 controls (n=36) underwent T1-weighted structural and diffusion MRI. Various micro- and macro-structural proprieties of the major white-matter pathways were investigated using DTI, NODDI and tractography. Further morphometric grey-matter measurements were made using FreeSurfer. Imaging measurements were correlated with penetrance scores for Sz/DD, correcting for multiple comparisons.
Results: Structural properties of the cingulum bundles were associated with penetrance for both Sz and DD, in particular curvature (Sz:p=0.026; DD:p=0.035) and intracellular volume fraction (Sz: p=0.019; DD: p=0.064) Further principle component analysis showed altered interrelationships between the volumes of several mid-line white matter structures (Sz:p=0.055; DD:p=0.027). In particular, the ratio of volumes in the splenium and body of the corpus callosum was significantly associated with both penetrance scores (Sz:p=0.037; DD;p=0.006).
Conclusions: Our results are consistent with the notion that significant alteration in developmental trajectories of mid-line white-matter structures constitutes a common neurodevelopmental aberration contributing to risk for Sz and DD. These does not manifest in gross brain morphological changes, but in more subtle alterations in the morphological interrelationships in mid-line white-matter structures.
Supported By: Wellcome Trust
Keywords: White Matter Microstructure, Tractography, Volumetric Neuroimaging, Neurodevelopmental Trajectories, Copy Number Variant

190. Novel Diffusion MRI Measures in 22q Deletion Syndrome: Large-Scale International Studies by the ENIGMA-22q Consortium

Julio Villalón[1], Christopher Ching[2], Talia Nir[1], Neda Jahanshad[1], Deydeep Kothapalli[1], Daqiang Sun[2], Amy Lin[2], Jennifer Forsyth[3], Leila Kushan[3], Ariana Vajdi[2], Maria Jalbrzikowski[4], Therese van Amelsvoort[5], Geor Bakker[5], Wendy R. Kates[6], Kevin M. Antshel[7], Wanda Fremont[6], Linda Campbell[8], Kathryn McCabe[8], Daly Eileen[9], Gudbrandsen Maria[9], Clodagh Murphy[9], Declan. G.M. Murphy[9], Michael C. Craig[9],

Beverly Emanuel[10], Donna McDonald-McGinn[10], Kosha Ruparel[11], Eric Schmitt[11], Tony Simon[12], Paul M. Thompson[1], and Carrie Bearden[5]

[1]Keck School of Medicine, USC, [2]Semel Institute for Neuroscience and Human Behavior; University of California-Los Angeles, [3]UCLA, [4]University of Pittsburgh, [5]Maastricht University, [6]SUNY Upstate Medical University, [7]Syracuse University, [8]University of Newcastle, [9]Institute of Psychiatry, Psychology & Neuroscience King's College London, [10]Children's Hospital of Philadelphia, [11]University of Pennsylvania, [12]University of California Davis

Background: Diffusion MRI (dMRI) is now widely used to study white matter (WM) microstructure in neurogenetic disorders, including 22q11.2 deletion syndrome (22q11DS) - a condition associated with increased rates of developmental neuropsychiatric disorders, autism spectrum disorders and psychosis.
Methods: To better understand brain abnormalities associated with 22q11DS, we evaluated 249 participants with 22q11DS and 224 age-matched healthy controls (HC) (age range: 8-35 years) with dMRI at eight centers worldwide. We mapped group differences - in atlas-defined brain regions of interest - for four diffusion anisotropy measures to better define their consistency across centers.
Results: We found significant differences for all anisotropy measures, in a widespread but not always coinciding pattern. The tensor distribution function fractional anisotropy (TDF-FA) - a measure of fiber coherence - showed greatest group differences (greater anisotropy in 22q11DS than HC). Fractional anisotropy based on the tensor model (FA) showed the second largest effect sizes; some regions showed higher mean values in 22q11DS, but others lower. Generalized fractional anisotropy (GFA) showed the opposite pattern to TDF-FA; most regions showed lower anisotropy in 22q11DS versus HC. Anisotropic power maps (AP) showed lowest effect sizes, with mixed patterns of effects across regions.
Conclusions: Different mathematical metrics can detect different profiles of group differences, even in large, well-powered population studies. Biophysical models derived from multi-shell dMRI and histological validations are beginning to help us understand these differences. 22q11DS is a promising model to study differences in WM microstructural measures; group differences are relatively large and animal models exist for histological validation.
Supported By: U54 EB020403; RO1 MH085953 and R01MH100900
Keywords: 22q11.2 CNV, Diffusion Magnetic Resonance Imaging (dMRI), ENIGMA Consortium

191. Mirror Effects of 4 Neurodevelopmental CNVs on Functional Connectivity and Implication for Idiopathic Autism

Clara Moreau[1], Sebastian Urchs[2], Catherine Schramm[3], Amy Lin[4], Leila Kushan[4], Alan C. Evans[2], John D. Lewis[2], Simons VIP Consortium[5], Carrie Bearden[4], Pierre Bellec[6], and Sebastien Jacquemont[1]

[1]University of Montreal, [2]Montreal Neurological Institute, McGill University, [3]CHU Sainte Justine, [4]University of California, Los Angeles, [5]Simons Foundation, [6]CRIUGM

Background: CNVs at the 16p11.2 and 22q11.2 loci are among the most frequent risk factors for autism and schizophrenia. Our aims are 1) To characterize their individual impact on functional connectivity (FC). 2)To investigate whether these CNV-associated patterns are observed in a heterogeneous group of idiopathic autism at a level consistent with the risk conferred by each genetic variant. 3) To explore the similarity of spatial patterns of FC alterations associated with each CNV.
Methods: Resting-state fMRI data were preprocessed on 105 carriers and 128 controls subjects from Simons VIP and UCLA, using Niak pipeline. FC profiles of each CNV were correlated to patterns observed in 309 autism and 363 control subjects from the ABIDE dataset. A linear model was fitted to each connection with genetic status, motion, sex and site as explanatory factors. Connectivity patterns were compared to the autism cohort using spatial correlation of the individual connectome with the CNV derived pattern of connectivity alterations.
Results: The 16pDel is associated with a significant overall increase in connectivity while the 22qDel exhibits an opposite general profile. An enrichment of CNVs individual profiles is reported in the ASD sample. A functional covariance pattern between 16pDel and 22qDel is observed in Fronto-parietal, Limbic, and Anterior DMN networks.
Conclusions: Despite the opposing pattern of FC alteration exhibited by DEL carriers at each locus, we find an enrichment of both in an idiopathic autism sample. This is likely conferred by the similar relative distribution of FC alterations with the observed convergence of covariance connectivity patterns between 16pDel and 22qDel.
Supported By: NIH RO1 MH085953, NIH Big Data to Knowledge (BD2K) award (U54 EB020403) and SFARI Explorer Award to CEB, Brain Canada, Compute Canada
Keywords: CNV, Functional Connectivity, ASD, Schizophrenia, Imaging

SYMPOSIUM
Neuromodulation With Near-Infrared Light: Cell Survival, Neurophysiology, Cognition and Mood
12:30 p.m. - 2:30 p.m.
Chair: Paolo Cassano
Co-Chair: Dan Iosifescu

192. Photobiomodulation Therapy for Parkinson's Disease: Translating the Evidence in Animal Models to Humans

John Mitrofanis[1]

[1]The University of Sydney

Background: Parkinson's disease is a neurological disorder with signs of resting tremor, akinesia and rigidity. These

manifest after a progressive death of many midbrain dopaminergic neurones. Although available therapies can reduce these signs, the progression of neuronal death has proved difficult to stop. Red to infrared light therapy (λ=600 -1070nm), known also as photobiomodulation, is emerging as an effective therapy that is capable of stabilising dying neurones in a range of neurological conditions, from Alzheimer's to Parkinson's disease.

Methods: Focus will be on several issues relating to the use of photobiomodulation in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated animal models of Parkinson's disease, including the use of a transcranial approach, together with use of a novel intracranial method of delivery. Mice (n=40) and monkeys (n=25) were assessed either clinically (monkeys) and with an open-field behavioural test (mice and monkeys) and their brains were processed for routine immunohistochemistry and stereological analysis

Results: There were significant differences in the clinical signs (monkeys: ANOVA, F=16, $p<0.0001$) and locomotive behaviour of mice (ANOVA, F=10.6; $p<0.05$) and monkeys (ANOVA, F=23, $p<0.0001$) between controls, MPTP and photobiomodulation-treated MPTP animals. There were also significant differences in the number of midbrain dopaminergic neurones in mice (ANOVA, F=4.9; $p<0.001$) and monkeys (ANOVA, F=22, $p<0.0001$) between controls, MPTP and photobiomodulation-treated MPTP animals

Conclusions: There is evidence that photobiomodulation reduces clinical signs, improves behaviour and offers neuroprotection to the midbrain dopaminergic cells in animal models of the disease, from mice to monkeys. I will discuss the prospect of using the therapy in patients

Supported By: Michael J. Fox, Tenix corp, Salteri family

Keywords: Parkinson's Disease, Transcranial Photobiomodulation, Neuroprotection

193. Neurophysiological Enhancements of the Human Brain by Transcranial Photobiomodulation Using 1064-nm Laser

Xinlong Wang[1], Hashini Wanniarachchi[1], Francisco Gonzalez-Lima[2], and **Hanli Liu**[2]

[1]The University of Texas at Arlington, [2]University of Texas at Austin

Background: Transcranial photobiomodulation (tPBM) using near infrared or infrared light has shown promises to improve human memory and cognition. However, underlying mechanisms of tPBM are not well understood.

Methods: To investigate tPBM-induced changes in neurophysiology in the human brain non-invasively, we performed multi-mode optical (n=11) and electrophysiological (n=23) measurements from healthy human subjects (total n=34) before, during, and after tPBM was applied on the right side of the forehead of each participant. The laser to deliver tPBM was at 1064 nm with a power density of ~250 mW/cm2, an aperture of 4 cm in diameter, and a duration of 8 minutes. A broadband near infrared spectroscopy device was placed near the stimulation site to quantify tPBM-induced upregulation in both metabolic and hemodynamic activities, while a 64-channel EEG system was utilized to record electrophysiological responses across the entire human head.

Results: After careful, rigorous data analysis, we show that the 1064-nm laser was able to significantly (n=11; paired t-test; $p<0.05$) neuro-modulate or upregulate cerebral concentrations of oxygenated hemoglobin (HbO) and oxidized cytochrome-c-oxidase (oxCCO), as compared to those under the placebo stimulation. It is also interesting to observe that the increase of HbO was linearly proportional to the increase of oxCCO. In addition, our 64-channel EEG data revealed that cerebral oscillations at both alpha and beta bands were significantly (n=23; paired t-test; $p<0.05$) enhanced, with improved brain connectivity across the entire brain/head.

Conclusions: As the first time, this study clearly revealed neurophysiological enhancements by tPBM on metabolic, hemodynamic, and electrophysiological activities across the human brain.

Supported By: This study is supported in part by an NIH BRAIN Initiative grant, RF1MH114285.

Keywords: Photobiomodulation, Electrophysiological Measurements, Hemodynamic Measurements, Neurophysiological Activities, Laser Stimulation

194. Transcranial Photobiomodulation in Healthy Subjects: Cognitive Enhancement

Francisco Gonzalez-Lima[1], Douglas Barrett[1], Celeste Saucedo[1], Courtney Alexander[1], Hanli Liu[2], and Andreana Haley[1]

[1]The University of Texas at Austin, [2]University of Texas at Arlington

Background: Transcranial infrared laser stimulation (TILS), a form of brain photobiomodulation, uses infrared light to boost cerebral oxygen metabolism. When targeted to the right prefrontal cortex, we have found that TILS improve executive function, rule-based category learning, attention and memory in young healthy adults. TILS may have cognitive enhancing effects on sustained attention and working memory in healthy younger adults and older adults with age-related cognitive decline.

Methods: In this ongoing project, four studies with N=154 participants, included younger adults (n=100, 18-35 years old) and older adults (n=54, 45-90 years old). CW 1,064-nm laser stimulation used power of 3.4 W in an area of 13.6 cm2, corresponding to 250 mW/cm2 irradiance, or sham/placebo. Two right forehead sites were stimulated, 60 J/cm2 per site. A psychomotor vigilance task (PVT) measured sustained attention and a delayed match-to-sample task (DMS) measured working memory. Cognitive measures were done blinded before and after one or multiple weekly laser sessions.

Results: Cognitive performance after TILS in younger adults was significantly enhanced compared to placebo (ANOVA $p<0.05$, 2-tailed) including improved reaction time during sustained attention (PVT), memory retrieval latency and number of correct responses (DMS). In older adults, after 4-6 TILS sessions, 63% improved on the PVT and 56% improved on the difficult DMS task. These percentages were significantly greater than placebo effects (chi-square $p<0.05$, 2-tailed). We found no adverse effects.
Conclusions: TILS to the right prefrontal cortex significantly improved cognition in healthy young adults. TILS also appears effective for reversing age-related cognitive decline in older adults.
Supported By: Supported by the Oskar Fischer Fund and NIH grants (R21 AG050898 and 1RF1MH114285).
Keywords: Cognitive-Aging, Laser Stimulation, Cognitive Remediation, General Cognitive Ability, Cognitive Decline

195. Transcranial Photobiomodulation for Mood Disorders: Clinical Efficacy and Tolerability

Paolo Cassano[1]

[1]Massachusetts General Hospital

Background: Transcranial photobiomodulation (t-PBM) with near-infrared light (NIR) consists of delivering NIR to the scalp, to reach non-invasively the adjacent cortical areas. t-PBM modulates cortical excitability and improves cerebral perfusion and oxygenation.
Methods: A double-blind, sham-controlled study on the tolerability and antidepressant efficacy of adjunct t-PBM NIR (823nm) delivered to R-L-dlPFC, twice a week for 8 weeks, in subjects with MDD. Baseline (BOCF) and last observation carried forward (LOCF) and completers analyses were performed (Mann-Whitney U test).
Results: The mean change in HAM-D17 total score in subjects receiving t-PBM NIR was significantly greater than sham with the BOCF [NIR ($n=10$) -10.8 ± 7.55 vs. sham ($n=11$) -4.4 ± 6.65; $z=1.982$, $p=.047$)] and in completers [NIR ($n=6$) -15.7 ± 4.41 vs. sham ($n=7$) -6.1 ± 7.86; $z=2.158$, $p=.031$)]. However, the threshold for significance was not reached with the LOCF [NIR ($n=10$) -10.8 ± 7.55 vs. sham ($n=9$) -5.33 ± 7.04; $z=1.556$, $p=.119$)]. More subjects in the NIR t-PBM group experienced side-effects ($\chi2 = 3.60$; $df = 1$; $p = 0.058$). The rate of side-effects described by participants as "severe" in intensity was low and similar between groups ($\chi2 = 0.56$; $df = 1$; $p = 0.45$). No participants experienced a serious adverse event. Changes in weight and blood pressure across groups were not significant, except for a marginal increase in diastolic blood pressure in the t-PBM NIR group. The mean improvement in sexual function was significantly greater in the t-PBM NIR group.
Conclusions: t-PBM with NIR could be a novel intervention for patients with MDD, with a fairly benign side-effect profile. Replication in larger samples is warranted.
Supported By: Brain and Behavior Research Foundation (NARSAD), Photothera Inc.
Keywords: Depression, Neuromodulation, Transcranial Photobiomodulation, Low Level Light Therapy, Near-Infrared

SYMPOSIUM
Advance of Science in the RDoC Paradigm
12:30 p.m. - 2:30 p.m.
Chair: William Carpenter Jr.
Co-Chair: Bruce Cuthbert

196. Neurobiology of the Anxiety and Mood Disorders: An RDoC Analysis

Peter Lang[1], Margaret Bradley[1], and Nicola Sambuco[1]

[1]University of Florida

Background: The research addresses the RDoC research Domain, Negative Valence Systems' acute "fear" construct, assessing reactivity in anxious and depressed patients as they process "fear" challenges. The ultimate research aim is to classify patients' disorders "based on dimensions of observable behavior and neurobiological measures."
Methods: Research participants were: Diagnosed principal anxiety/mood disorders ($N= 450$), healthy controls ($N= 50$). Fear challenges: 1) imagery of text-prompted emotionally arousing events, 2) viewing emotionally evocative pictures. Recorded measures included EEG, MRI, and somatic/autonomic reflexes (e.g., startle, facial muscle action), and non-paradigm-dependent state measures: Cell data (telomere length), cortisol (hair samples), blood pressure, body mass index, and questionnaires assessing anxiety, depression, trauma history, and life dysfunction.
Results: Analyses of telomeres and MRI structural data are presented, as these measures relate to disorder severity, and questionnaire battery results. Questionnaire analysis yielded three significant factors: Negative Affect (measures of anxiety/depression), Anxious Arousal (physical symptoms) and reported Trauma/Stress-event history. Reduction in telomere length predicted a significant increase in Negative Affect and Trauma report, both in raw (p's<.02) and residual (p's<.02) data analyses that controlled for age—but not for reports of anxiety-related physical symptoms. Greater trauma history was, furthermore, significantly related to a parallel decrease brain structural thickness in insula ($r=-.35$) and inferior frontal gyrus ($r=-.28$). Orbital frontal cortex thickness was also reduced, as both Trauma and Negative Affect increased ($r's=-.21$).
Conclusions: Cluster analyses of these neurobiological variables suggest patient groupings with different co-varying measures, independent of diagnosis, but relating significantly to reports of negative affect and life dysfunction.
Supported By: R01-MH098078; R01-MH094386
Keywords: Research Domain Criteria (RDoC), Telomere, Negative Affect, Trauma, MRI

197. Spanning Levels in the RDoC Matrix: Does Working Memory Work?

Robert Bilder[1], Agatha M. Lenartowicz[1], Jesse Rissman[2], Sandra K. Loo[1], Jean-Baptise Pochon[3], Kristen Enriquez[1], Holly Truong[3], Carrie Bearden[1], Catherine Sugar[2], and Gerhard Hellemann[1]

[1]Semel Institute for Neuroscience & Human Behavior at UCLA, [2]UCLA, [3]David Geffen School of Medicine

Background: The Research Domains Criteria (RDoC) initiative specified constructs including working memory (WM) by features at different levels of analysis. We examined associations among multiple indicators of WM using MRI, EEG, neurocognitive, symptom, and disability assessments.
Methods: We examined (1) CareSeeking (CS, n=106) and (2) NonCareSeeking (NCS, n=44) individuals using clinical, cognitive, EEG and MRI (sMRI, rs-fMRI, activation-fMRI, and DTI) assessments. We used dimension reduction strategies and general linear models to examine covariance within and across levels of analysis.
Results: The CS group had more mental disorders including Major Depressive Disorder (50% CS vs 21% NCS), Anxiety Disorders (25% CS vs 14% NCS), and psychotic disorders (7.5% CS vs 0% NCS). Symptom measures explained 75% of the variance in disability but neurocognitive measures shared less than 10% of variance with disability and were redundant with clinical ratings. sMRI measures accounted for 13% and gray matter volume alone shared 7% of variance with disability. Associations among neurocognitive, EEG and MRI variables were moderate, with typical multivariable associations sharing 10% of variance between sets of variables within each level.
Conclusions: Results suggest that "multilevel" models of RDoC dimensions face challenges, including limited strength of associations across levels. While we observed robust associations of basic indicators like total gray matter volume reduction with the severity of disability, this effect was not mediated via EEG, fMRI or cognitive measures. Patterns of association among neurocognitive, EEG and fMRI measures may define meaningful functional neuroanatomic dimensions, but so far their relations to higher level symptoms, syndromes, and disability are unclear.
Supported By: R01MH101478
Keywords: Working Memory, Electroencephalography (EEG), Brain Magnetic Resonance Imaging (MRI), Neurocognition, Everyday Functioning

198. Mapping Neuro-Behavioral Relationships in Dimensional Geometric Embedding (N-BRIDGE) via Pharmacology, Computation and Clinical Neuroimaging: Unifying Categories and Dimensions Along the Psychosis Spectrum

Alan Anticevic[1]

[1]Yale University

Background: A challenge in neuropsychiatry lies in matching patients with effective treatments. Most studies operate under the assumption that categorical diagnoses and/or pre-existing clinical assessments are the 'gold standard' for describing behavioral - and therefore neural - symptom variation. Attempts to characterize the neural substrates of these predefined variables yield limited success, suggesting an inadequate neuro-behavioral mapping. This problem is particularly present along the psychosis spectrum.
Methods: We describe a multivariate neuro-behavioral framework under which behavior can be mapped to features of specific neural systems in a data-driven way. We leverage neural (fMRI-derived) and behavioral data from 436 psychosis-spectrum patients that were publicly available via the NIMH Data Archive. We relate these effects to pharmacological neuroimaging experiments manipulating NMDA glutamate receptor via ketamine (N=40) and the 5-HT receptor via LSD (N=24).
Results: We identify dimensions of maximal behavioral variation in patients by performing data reduction across all behavioral assessments. We demonstrate that latent behavioral dimensions capture neural variation via global brain connectivity ($p<.05$ whole-brain corrected). We show that this framework can inform the identification of pharmacological targets for developing drugs for subject-specific symptom profiles in relation to ketamine and LSD effects.
Conclusions: Characterizing how and which sets of symptoms map to neural circuitry is a key step towards developing targeted and effective treatments for psychiatric disorders. We propose the Neuro-Behavioral Relationships In Dimensional Geometric Embedding (N-BRIDGE) framework as a key step towards unified mapping between the geometry of data-driven behavioral variation and the geometry of data-driven neural variation, thus integrating categories and continuous dimensions.
Supported By: NARSAD Independent Investigator; 5R03MH105765; 5R01MH108590
Keywords: Psychosis Spectrum, Neuroimaging, Computational Modeling, Neuropharmacology, Ketamine

199. RDoC-Informed Translation of Genomic Discoveries to an Outpatient Child Psychiatry Cohort

Alysa Doyle[1], Pieter Vuijk[2], Giulio Genovese[3], Joanna Martin[4], Michael Capawana[1], Sheila O'Keefe[1], Ashley Dumont[3], Jordan Smoller[1], Roy Perlis[1], and Ellen Braaten[1]

[1]Harvard Medical School/Massachusetts General Hospital, [2]Center for Genomic Medicine/ Massachusetts General Hospital, [3]Stanley Center for Psychiatric Research, [4]Cardiff University

Background: For a range of psychiatric diagnoses, studies have identified a polygenic component of risk, reflecting the aggregate influence of potentially thousands of small-effect common genetic variants. As anticipated by NIMH's RDoC framework, scores based on this polygenic component do not track precisely with DSM diagnostic boundaries. Yet, such scores may still have clinical value as objective risk indicators and tools for risk stratification. Here, we report an RDoC-informed investigation of polygenic risk scores (PRS) for ADHD and bipolar disorder (BPD) for this purpose in an outpatient child psychiatry cohort.
Methods: Data are from the Longitudinal Study of Genetic Influences on Cognition, which ascertains youth consecutively referred for evaluation. The study has enrolled over 1300 youth, ages 7 to 18, characterized with clinical diagnoses and dimensions of psychopathology and cognition. In N=470

genotyped youth, we used hierarchical regression and mixed models to relate ADHD and BPD PRS to select phenotypes.
Results: ADHD PRS associated with ADHD-related phenotypes and with aggression and working memory (R2 ~2.2-27%, all p's<.01), which share ADHD liability and have implications for clinical outcome. BPD PRS associated with mania symptoms in adolescents (R2 ~2.9-5.0%, p<.05) , raising the possibility that scores could aid in identifying pre-symptomatic children. Youth and adolescents with high ADHD and BPD PRS, respectively, showed distinctive clinical profiles, with impairment on symptoms relevant to but also beyond their derivative conditions.
Conclusions: Consistent with RDoC tenets, genomic discoveries may extend our conceptualization of the structure of psychopathology and hold potential as objective risk indicators in the child clinical setting.
Supported By: Stanley Center for Psychiatric Research, NIH R03MH106862
Keywords: Polygenic Risk Score, Child and Adolescent Psychiatry, Research Domain Criteria (RDoC), ADHD, Bipolar Disorder

SYMPOSIUM
Cell Signaling and Cell Communication: New Frameworks for Vulnerability to Mood Disorders
12:30 p.m. - 2:30 p.m.
Chair: Eleni Tzavara
Co-Chair: Naguib Mechawar

200. Dissecting the Transcriptomic and Phenotypic Complexity of PTSD With Transcriptomic Imputation and Bayesian Machine Learning

Yue Li[1], Vasiliki Michopoulos[2], Adriana Lori[2], Abigail Lott[2], Bekh Bradley[2], Tanja Jovanovic[2], Kerry Ressler[3], Manolis Kellis[1], and **Nikolaos Daskalakis**[3]

[1]MIT, [2]Emory University, [3]Harvard Medical School/McLean Hospital

Background: PTSD occurs in some trauma-exposed individuals, but its molecular basis remains uncharacterized. Previously, we have associated genetically regulated gene expression across tissues with PTSD (Huckins et al. 2018). Here, we study the relationship between genetically-regulated transcriptional variation, and phenotypic variation in PTSD, in a cohort of 9400 inner-city, low-socioeconomic-status, primarily-African-American patients of the Grady Memorial Hospital.
Methods: Each individual was ascertained phenotypically using interview-based assessments, self-reports and lab tests. In addition, we imputed gene expression across 48 tissues using GTEx project's eQTL maps. To study the comorbidity patterns of transcriptomic and phenotypic information across individuals, we used MixEHR, a Bayesian unsupervised learning method (Li & Kellis, 2018).
Results: We identified latent disease topics of high probability of PTSD diagnosis that were concordant with symptom severity and childhood trauma. We found enrichments for genes and tissues in the disease topics across multiple tissues. Top tissues with the highest PTSD associations are basal ganglia, amygdala, substantia nigra, and pituitary, which have been associated with emotion regulation and PTSD. We also constructed a ranked list of PTSD genes across multiple disease topics. The top genes were: MXRA8 is important in the maturation and maintenance of blood-brain barrier; ATP6AP1L is implicated in the glucocorticoid receptor pathway and neural responses to stress; and AP3S2 is essential for vesicles delivery into neurites and nerve terminals.
Conclusions: By combining transcription imputation across the body with Bayesian machine learning in a trauma-exposed sample, we discovered tissue-types and genes that yield new biological insights into the genetic and phenotypic architecture of PTSD.
Supported By: NIH KL2, NARSAD Young Investigator, McLean Hospital Brooking Fellowship
Keywords: PTSD - Posttraumatic Stress Disorder, Systems Biology, Bayesian Modeling, Transcriptomic Imputation, Childhood Trauma

201. Stress Resilience vs. Vulnerability in Mood disorders, an Integrative Biological Approach

Caroline Menard[1], Madeline Pfau[2], Georgia Hodes[2], Veronika Kana[2], Victoria Wang[2], Sylvain Bouchard[2], Aki Takahashi[2], Meghan Flanigan[2], Hossein Aleyasin[2], Katherine LeClair[2], William Janssen[2], Benoit Labonte[2], Eric Parise[2], Zachary Lorsch[2], Sam Golden[3], Mitra Heshmati[2], Carol Tamminga[4], Gustavo Turecki[5], Matthew Campbell[6], Zahi Fayad[2], Cheuk Ying Tang[2], Miriam Merad[2], and Scott Russo[2]

[1]University Laval, [2]Icahn School of Medicine at Mount Sinai, [2]Albert Einstein, [3]National Institute on Drug Abuse, [4]UT Southwestern Medical Center, [5]McGill University, [6]Trinity College

Background: Chronic stress is associated with neurovascular and immune changes and individual differences in these adaptations underlie resilience vs vulnerability to stress and the establishment of depressive symptoms. However, to date the mechanisms by which these systems interact with the brain to induce maladaptive behaviors remain largely unknown.
Methods: The strength of our approach is a reverse translational strategy that consists in studying stress responses in mice to unravel novel biological mechanisms underlying mood disorders in humans. We combine behavioral experiments to functional, molecular and imaging studies and validate rodent findings in human samples.
Results: We found reduced expression of the endothelial cell tight junction protein claudin-5 (Cldn5) and abnormal blood vessel morphology in nucleus accumbens (NAc) of stress-susceptible but not resilient mice (n=9-14/group, p=0.0014). CLDN5 expression was also decreased in NAc of depressed patients (n=10-15/group, p=0.0117). Cldn5 downregulation was sufficient to induce depression-like behaviors following subthreshold social stress (n=12/group, p=0.0386) whereas chronic antidepressant treatment rescued Cldn5 loss and promoted resilience (n=12-16/group, p=0.0201). Reduced BBB integrity in NAc of stress-susceptible or mice caused infiltration of the peripheral cytokine interleukin-6 (IL-6) into

brain parenchyma and subsequent expression of depression-like behaviors (n=7-10/group, p=0.0405).
Conclusions: These findings suggest that chronic social stress alters BBB integrity through loss of tight junction protein Cldn5, promoting peripheral IL-6 passage across the BBB and depression. By understanding how chronic stress affects the neurovasculature and immune system we may be able to augment current antidepressant treatments or design new therapeutic strategies.
Supported By: NIH (S.J.R.), NARSAD Young Investigator Grant (C.M.)
Keywords: Depression, Stress, Blood-Brain Barrier, Immune System, Resilience

202. Impaired Astrocyte-Oligodendrocyte Gap Junction Coupling in the Anterior Cingulate Cortex of Depressed Suicides

Naguib Mechawar[1], Arnaud Tanti[2], and Gustavo Turecki[2]

[1]Douglas Institute; McGill University, [2]Douglas Institute

Background: Interactions between astrocytes and oligodendrocytes, which are notably implicated in proper axon myelination, involve gap junctions made through heterotypic coupling of astrocyte-specific (Cx30 and Cx43) and oligodendrocyte-specific (Cx32 and Cx47) connexins. The objective of this study was to assess this coupling in the anterior cingulate cortex (ACC) of depressed suicides (DS).
Methods: Postmortem ACC samples from DS and matched controls (CTRL) were labeled with immunofluorescence and examined at the confocal microscopy to map and quantify the expression of Cx30 along oligodendrocytes (CTRL = 11; DS = 12) myelinated fibers (CTRL = 10; DS = 17) and blood vessels (CTRL = 9; DS = 18) in the grey matter. RNAseq data (CTRLs = 26; DS = 27) used to screen for gap junction-related changes in gene expression were validated by qPCR (CTRL = 19-23; DS = 33-38). For molecular experiments, DESeq2 was used to perform general linear models with age, gender, and RNA integrity number as covariates, and unpaired two-tailed t-tests were used to compare groups for all other p values reported.
Results: DS samples showed a decreased expression of Cx32 and Cx47 ($P = 0.04$ and $P = 0.03$ respectively), as well as of several key mediators of gap junction assembly ($0.001<P<0.05$). These changes were associated with decreased Cx30 puncta mapping to oligodendrocytes ($P = 0.001$) and myelinated fibers ($P = 0.03$), suggesting lower gap junction channel coupling in DS.
Conclusions: These results could account for the impairments in oligodendrocyte function and myelination that have been documented in depression and suicide.
Supported By: CIHR
Keywords: Depression And Suicide, Anterior Cingulate Cortex, Oligodendrocytes, Astrocytes, Gap Junctions

203. ELK-1, Trauma and Negative Life Event Exposure

Raoul Belzeaux[1] and El Chérif Ibrahim[2]

[1]AP-HM, [2]INT Aix Marseille Université

Background: Trauma and life stress are considered as major environmental factors in psychiatric disorders. Recently, we have identified the transcription factor ELK-1, an effector of the glucocorticoid/ERK pathway, as a major key in pathophysiology of Major Depression and antidepressant response, and an interesting biomarker of antidepressant response. Mechanisms associated with ELK-1 variation are still unclear.
Methods: To explore stress-related and trauma-related ELK-1 variation and to explore physiological and biological factors (age, gender, immunometabolic status e.g. BMI, C-reactive protein) associated with ELK-1 variation, we followed a cohort of 85 healthy subjects and 47 patients with a Major Depressive Episode. ELK-1 mRNA was measured in peripheral mononuclear blood cells using qRT-PCR. Trauma was evaluated with childhood trauma questionnaire and recent negative life events with Paykel questionnaire.
Results: In healthy subjects, we found that history of childhood trauma (but not of recent negative life event) was associated with lower ELK-1 mRNA in blood (p=0.033). We found a negative correlation between number of trauma and ELK-1 mRNA. In these subjects, we found also a negative correlation between age and ELK-1 mRNA and after correction for age, we confirmed the impact of childhood trauma on ELK-1 expression. Interestingly, the opposite profile was seen in patients.
Conclusions: Our results suggest that ELK-1 has different deregulation after childhood trauma in healthy controls than in patients with depression. This result suggests that resilience to early life stress maybe related to ELK-1 regulation. Further prospective analyses are ongoing, including immune-metabolic analyses related to this cell signaling pathway.
Supported By: PHRC National DGOS
Keywords: Childhood Trauma, Healthy Subjects, Gene Expression

SYMPOSIUM
Embracing Resilience in Psychopathology: Novel Theories, Brain Mechanisms and Research Applications

12:30 p.m. - 2:30 p.m.
Chair: Janna Cousijn

204. The Challenges of Transiting From Adolescence Into Adulthood: Resilience Factors in a Critical Life Period

Haakon Engen[1], Kenneth S.L. Yuen[1], Miriam Kampa[1], Anita Schick[1], Alexandra Sebastian[1], Andrea Chmitorz[1], Oliver Tüscher[1], Michele Wessa[2], Göran Köber[3], Harald Binder[3], and **Raffael Kalisch**[1]

[1]Johannes Gutenberg University Medical Center, [2]Johannes Gutenberg University, [3]University of Freiburg Medical Center

Background: Emerging adulthood is marked by frequent new onset of stress-related mental problems or exacerbation of

existing problems. Prevalence of depression and anxiety in this age range is on the rise. The study aims at identifying resilience mechanisms that protect individuals against the development of life transition-related impairments, based on positive appraisal style theory of resilience (Kalisch et al, Behav Brain Sci 2015).
Methods: Young adults (N=200, study inclusion 18 years) are regularly monitored over several years for adverse life events and daily hassles (stressors) and mental health changes, using a new online tool. A dedicated extensive lab battery (behavior, MRI, biosamples, psycho-social variables) is applied every 1.75 years to assess potential protective functions.
Results: First results indicate that composite neural/behavioral indices of volitional (cognitive) reappraisal (standardized beta=.5), response inhibition (beta=.37) and reward sensitivity (beta=.49) (all p<.001) at baseline exert a dampening influence on increases in mental health problems related to stressor exposure early in the transition phase, suggesting protective function.
Conclusions: In the field of resilience, there is a dire need for prospective-longitudinal research with frequent and repeated monitoring of stressors, mental health changes and potential resilience mechanisms (Kalisch et al, Nat Hum Behav 2017). The value of this approach will be discussed, and other exemplary ongoing studies will also be presented. Results from these types of studies will identify targets for risk diagnosis and mechanistically based preventive intervention.
Supported By: Ministry of Science, State of Rhineland-Palatinate, Germany; European Union Horizon 2020 research and innovation programme (grant no 777084).
Keywords: Reappraisal, Cognitive Control, Reward Sensitivity, Resilience and Vulnerability, Stress

205. Role of Norepinephrine-Mediated Mesolimbic Homeostatic Plasticity in Resilience to Social Stress

Hongxing Zhang[1], Carole Morel[1], Sarah Montgomery[1], Jun-Li Cao[2], and **Ming-Hu Han**[1]

[1]Icahn School of Medicine at Mount Sinai, [2]Xuzhou Medical University

Background: Homeostatic plasticity in ventral tegmental area (VTA) dopamine neurons projecting to nucleus accumbens (NAc) play a key role in mediating resilience to social stress. Further, there is an association between stress resilience and the activity of locus coeruleus (LC)-norepinephrine neurons projecting to the VTA. However, the precise circuit connection and the underlying adrenergic receptors responsible need to be elucidated.
Methods: In a well-established chronic social defeat stress (CSDS) model of depression, we employed projection-specific electrophysiological, optogenetic, and molecular profiling techniques to investigate the functional role and molecular basis of the LC-VTA circuit in mediating resilience to social defeat stress.
Results: We found that LC norepinephrine neurons projecting to the VTA exhibit enhanced firing activity in the resilient group as compared to stress-naïve control and susceptible mice ($F_{2,40}=13.46$, $p<.0001$). Optogenetically mimicking this firing adaptation by activating these neurons in susceptible mice reverses depression-related behaviors ($F_{2,124}=8.70$, $p<.001$), and establishes cellular and ion channel-mediated homeostatic plasticity ($F_{2,39}=26.38$, $p<.0001$), which is seen in the resilient mice. Circuit-specific molecular profiling studies reveal that α1 and β3 adrenergic receptors are highly expressed in VTA dopamine neurons projecting to the NAc ($t_2=24.80$, $p<.05$), and pharmacologically activating these receptors induces similar pro-resilient phenotypes at the ion channel, cellular and behavioral adaptations ($F_{12,420}=4.53$, $p<.0001$). Oppositely, intra-VTA micro-infusion of α1 and β3 receptor antagonists blocks the optogenetic stimulation-induced cellular and behavioral effects ($F_{3,42}=6.33$, $p<.005$).
Conclusions: These observations provide highly consistent molecular, cellular and behavioral evidence for the underlying mechanisms by which a LC-VTA-NAc circuit functions as a stress resilient pathway in the brain.
Supported By: R21, IMHRO, NARSAD
Keywords: Resilience, Locus Coeruleus, Adrenergic Receptor, Ventral Tegmental Area, Depression

206. Resilient Brain Responses to Social Exclusion

Laura Moreno-Lopez[1], NSPN Consortium[2], and **Anne-Laura Van Harmelen**[1]

[1]University of Cambridge School of Clinical Medicine, [2]University of Cambridge, University College London

Background: Half of all children and adolescents' experiences childhood adversity (CA; ranging from parental psychopathology, peer victimisation to abuse and neglect). Improved understanding of the neurobiological factors that contribute to resilience after CA is crucial to reduce CA related mental illness. Here we examined resilient brain responses to social exclusion in young adults.
Methods: Participants from a prospective study (ages 14,15,17) with depressive symptoms in the top or bottom 25% on 2 out of the first 3 assessment waves were invited at age 25. N=66 individuals underwent social exclusion during MRI (Cyberball task; Williams & Jarvis, 2006). Resilient functioning at age 25 was quantified as "positive psychological functioning relative to the degree of childhood adversity experiences" (see van Harmelen et al., 2017).

We used SPM12 in MATLABR2017b, and conducted a multiple regression analysis with resilient functioning, age, gender, socioeconomic status and CA on both whole brain and ROI (insula, ACC, DMPFC and DLPFC) responses to the contrast 'No-ball exclusion vs. Ball inclusion' at pFWE<.05 (whole brain) or pFWE-SVC<0.05 using structural masks for the ROIs.
Results: Resilient functioning was positively associated with right insula and right DLPFC activity to social exclusion (Insula: x=40, y=0, z=-10; k=10; t=3.51; pFWE-SVC<0.05; DLPFC: x=32, y=12, z=44; k=31; t=3.32; pFWE-SVC<0.05).

Conclusions: Resilient functioning after childhood adversity is associated with increased Insula and DLPFC response to social exclusion. The DLPFC and Insula facilitate cognitive control, emotion regulation and interoceptive awareness; as such our findings offer an important first step in our understanding of the neurobiology of resilient functioning after CA.
Supported By: Royal Society Dorothy Hodgkin Fellowship.
Keywords: Resilience, Social Exclusion, Childhood Adversity, DLPFC, Insula

207. Unravelling the Adolescent Paradox of Risk and Resilience to Alcohol Addiction: A Translational Perspective

Janna Cousijn[1], J. Leon Kenemans[2], Louk J.M.J. Vanderschuren[3], and Heidi M.B. Lesscher[3]

[1]University of Amsterdam, [2]Helmholtz Institute, Utrecht University, [3]Utrecht University

Background: Although the prevalence of alcohol addiction rapidly rises during adolescence, most reduce their drinking when reaching adulthood. This adolescent paradox of risk and resilience is poorly understood and studies directly comparing adolescent and adult drinkers are missing. The goal of this translational rat-human study is to unravel age-related differences in the neuropsychological mechanisms underlying heavy alcohol use in adolescents versus adults.
Methods: In the human study, the relation between neuropsychological functioning (executive functioning, impulsivity, approach-avoidance behaviour, craving, drinking motives) and alcohol use was compared between light to heavy drinking adolescents (16-17 years; n=45) and adults (30-35 years; n=45). In parallel, the relation between control over alcohol use (conditioned suppression) and alcohol use was compared between light to heavy drinking adolescent (n=84) and adult (n=84) rats.
Results: Only craving, impulsivity, and social, enhancement and coping drinking motives were positively related to alcohol use (all p's<0.01). Although adolescents scored higher on impulsivity (p<0.001) and enhancement motives (p<0.01), the relation between these variables and alcohol use did not differ between age groups. In rats, the relation between conditioned suppression and alcohol use differed between adolescents and adults. Adults consumed more alcohol (p<0.05) and showed a negative correlation between consumption and suppression. This relation was absent in adolescents, among which heavy drinkers still showed suppression.
Conclusions: This first study suggests a complex interplay between age, neuropsychological functioning and alcohol use. Tentatively, impulsivity and enhancement drinking motives may put adolescents at increased risk, however, they may be less prone to lose control over alcohol use compared to adults.
Supported By: DoY-grant Utrecht University; Amsterdam Brain & Cognition project grant
Keywords: Alcohol, Adolescence, Neuropsychology, Translational Research, Resilience and Vulnerability

SYMPOSIUM
The Complexity and Importance of the Central Nucleus of the Amygdala in Anxiety and Addiction

12:30 p.m. - 2:30 p.m.
Chair: Ned Kalin
Co-Chair: Rothem Kovner

208. Transcriptional Profiling of Primate Central Nucleus of the Amygdala Neurons: A Role for PKCd Neurons in Early Life Anxious Temperament

Rothem Kovner[1], Tade Souaiaia[2], Andrew Fox[3], Patrick Roseboom[4], Delores French[4], Jonathan Oler[1], James Knowles[2], Julie Fudge[5], and Ned Kalin[4]

[1]University of Wisconsin-Madison, [2]State University of New York-Downstate, [3]University of California Davis, [4]University of Wisconsin School of Medicine and Public Health, [5]University of Rochester Medical Center

Background: Children exhibiting stable and extreme anxious temperament (AT) are at risk to develop anxiety and depression. We identified the central nucleus of the amygdala (CeA) as a key player underlying the neural circuity of at-risk children and nonhuman primates with extreme AT. However, the cellular and molecular underpinnings of primate AT are not well understood. Research presented here combines laser capture microscopy (LCM) and RNA-sequencing (RNA-Seq) to characterize AT-related molecular alterations in CeA microcircuits.
Methods: Using LCM, approximately 600 CeL neurons were collected from each of n=47 AT-phenotyped young monkeys and RNA-Seq was performed. Multiple regression analysis investigated the relationship between exonic transcripts and AT. Interesting AT transcripts were selected for further anatomical validation.
Results: One exciting finding was the demonstration that Protein Kinase C delta (PKCd) mRNA expression is significantly and positively associated with AT (t= 3.280, p=0.017). In rodents, CeA PKCd neurons are involved in threat processing and conditioned fear learning. To provide a translational link to these rodent studies, we characterized the localization and distribution of PKCd in the primate CeA (n=3). Results demonstrated that PKCd localization was cytoplasmic, PKCd neurons accounted for 59% of neurons, and were evenly distributed across the CeA anterior-posterior extent.
Conclusions: These results point to a role for CeA PKCd mRNA in AT. This is particularly exciting in the context of the rodent studies and points to PKCd and PKCd neurons within the CeA microcircuit as being mechanistic targets for nonhuman primates AT studies that could serve to develop novel anxiety-related treatments.
Supported By: R01MH081884
Keywords: Anxiety Disorders, Non-Human Primate, Amygdala, Translational research

209. The Role of Central Amygdala CRF Neurons in the Regulation of Fear Acquisition and Extinction

Larry Zweifel[1]

[1]University of Washington

Background: Central amygdala (CeA) that release the stress-associated neuropeptide CRF (CeA-CRF) play an important role in setting a gain control for the acquisition of fear memories. More recently we have sought to determine these neurons influence fear extinction. Through the examination of the immediate fear extinction deficit, in which formation of an extinction memory is impaired if extinction occurs immediately following the acquisition of the fear memory, we have found the CeA-CRF neurons encode an early fear memory trace that actively antagonizes the formation of an extinction memory.
Methods: To determine how CeA-CRF neurons encode fear memory acquisition and the relationship of this activity to extinction, we tracked these neurons using in vivo miniscope imaging of calcium transients. We selectively manipulated these neurons using optogenetics and DREADD receptors. Neurons were manipulated during either immediate extinction (20 min post acquisition), delay extinction (24 h post acquisition), or reinstatement.
Results: Longitudinal imaging of CeA-CRF neurons during habituation, fear acquisition, extinction, and extinction recall reveals that these neurons rapidly acquire a fear memory trace ($n = 6$ mice). During immediate extinction CeA-CRF neurons maintain responsiveness to the CS that persists during extinction recall. During delay extinction CeA-CRF neurons ($n = 3$ mice) lose CS responsiveness. Transient inhibition of CeA-CRF neurons with Jaws ($n = 11$ mice) during CS presentation in immediate extinction promotes extinction memory formation. A single optogenetic activation of CeA-CRF neurons following delay extinction promotes reinstatement.
Conclusions: This work details important neural substrates underlying the persistence of fear and fear reinstatement.
Supported By: P50MH106428
Keywords: CRF, Fear Extinction, Longitudinal Brain Imaging

210. Central Amygdala Neurotensin Neurons in Consumption and Reward

Maria Luisa Torruella Suarez[1], Jessica Vandenberg[1], Gregory Tipton[1], Brennon Luster[1], Kedar Dange[1], Gunjan Patel[1], Jenna McHenry[1], J. Andrew Hardaway[1], Pranish Kantak[1], Nicole Crowley[1], Jeffrey DiBerto[1], Sara Faccidomo[1], Clyde Hodge[1], Garret Stuber[1], and **Zoe McElligott**[1]

[1]UNC-Chapel Hill

Background: The central nucleus of the amygdala (CeA) modulates several affective behaviors, including consummatory and appetitive behaviors. We are only beginning to understand how certain populations/circuitry contribute to these behaviors.
Methods: To investigate the role CeA neurotensin (NTS) neurons in the consumption of alcohol/reward, we utilized an NTS-cre mouse with site directed viral strategies (caspase virus and channelrhodopsin) to manipulate the neurons.
Results: To investigate CeA NTS neurons in alcohol consumption we lesioned these neurons (NTSCeA::casp). NTSCeA::casp mice showed significant decreases in ethanol consumed across all weeks as compared to NTSCeA::eYFP (Two-way ANOVA: interaction, $F(6,126)=0.4321$, $p=0.8564$; week, $F(6,126)=2.539$, $p=0.0235$; ablation, $F(1,21)=11.19$, $p=0.0031$). We next examined the CeA NTS neurons' projection to the parabrachial nucleus. Animals performed an operant task for optical stimulation (Wilcoxon matched-pairs signed rank test: control $W= -20$, $p= 0.3379$; ChR2 $W= -89$, $p=0.0005$). Finally, we investigated if stimulation alters consumption of ethanol. Optical stimulation increased ethanol consumption (Wilcoxon matched-pairs signed rank test: control $W=-20$, $p=0.4131$; ChR2 $W=61$, $p=0.0327$) and decreased food consumption (Two-way ANOVA: interaction $F(1,22)=4.313$, $p=0.0497$; virus type, $F(1,22)=0.5391$, $p=0.4705$; stimulation, $F(1,22)= 7.387$, $p=0.0126$). When given a water/food option, stimulation did not alter consumption of either.
Conclusions: These data suggest that 1. NTS neurons play a key role in promoting the consumption of alcohol, 2. activation of the projection from the CeA to the PBN is reinforcing, and 3. stimulation of this pathway is sufficient to increase alcohol consumption. Ergo, this pathway may be liable to adaptation and plasticity in alcohol and substance use disorders and warrants further investigation.
Supported By: K01 AA023555; P60 AA011605; F31 AA026183; Alcohol Beverage Medical Research Foundation; NC TRacS 5550KR71419
Keywords: Central Nucleus Of The Amygdala, Ethanol, Parabrachial, Reward, Optogenetics

211. Role of the Central Nucleus of the Amygdala in the Dark Side of Drug Addiction: A Neuroendocrine Connection

George Koob[1]

[1]NIAAA National Institutes of Health

Background: Addiction involves the construct of negative reinforcement as a motivational driving force in particularly the withdrawal/negative affect stage of the addiction cycle. The purpose of this presentation is to present the hypothesis that neuropeptide/neuroendocrine interactions in the central nucleus of the amygdala drive this dark side of addiction.
Methods: Alcohol-dependent animals are trained to respond for alcohol 6-8 h into withdrawal. For the opioid studies, animals with intravenous catheters are allowed to intravenously self-administer heroin under extended access conditions. All animals for these studies were male subjects, with a sufficient sample size required by power analyses. The data were analyzed using repeated-measures analysis of variance. Values of $p < 0.05$ were considered statistically significant.
Results: The results showed that brain stress systems, including corticotropin-releasing factor (CRF) and glucocorticoids, are recruited and dysregulated during compulsive drug (alcohol and opioid) taking. Alcohol- and opioid-induced, glucocorticoid-mediated differential regulation of stress

systems led to hypothalamic-pituitary-adrenal axis tolerance, contributed to a hypofunctional reward system, and sensitized the brain stress systems in the central nucleus of the amygdala. CRF1 receptor antagonism and chronic glucocorticoid receptor antagonism decreased dependence-induced compulsive-like alcohol seeking and compulsive-like escalated intravenous heroin self-administration. Glucocorticoid receptor plasticity in hypothalamic and extrahypothalamic CRF systems may mediate these effects.
Conclusions: Plasticity in the brain pain emotional systems in the central nucleus of the amygdala is triggered by acute excessive drug intake, is sensitized during the development of compulsive drug taking with repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of compulsive drug seeking.
Supported By: NIH
Keywords: Central Nucleus Of The Amygdala, Alcohol, Heroin, Stress, Corticotropin-Releasing Factor

SYMPOSIUM
Modeling, Dissecting, and Controlling Circuits of Perseverative Behavior
3:00 p.m. - 5:00 p.m.
Chair: Alik Widge

212. Dissecting Lateral Orbitofrontal Cortex Contributions to Distinct Perseverative Behaviors Using In Vivo Calcium Imaging in a Preclinical Mouse Model Relevant to OCD

Elizabeth Manning[1], Xiaojun Li[1], Sean Piantadosi[1], and Susanne Ahmari[1]

[1]University of Pittsburgh

Background: Neuroimaging studies implicate orbitofrontal cortex (OFC) dysfunction in perseverative behaviors across different mental illnesses. For example, patients with obsessive compulsive disorder (OCD) show OFC hyperactivity during symptom provocation, whereas impaired OFC recruitment is observed during tasks probing perseverative decision-making including reversal learning. In vivo imaging in the Sapap3 knockout mouse (KO), which displays OCD-relevant perseverative grooming and decision-making, can be used to determine whether overlapping or distinct activity patterns in OFC contribute to these behaviors.
Methods: Mice were injected with virus encoding fluorescent calcium indicator (AAV5-hysn-GCaMP6f) and implanted with gradient-index (GRIN) lenses in lateral OFC (lOFC) to visualize neural activity using Inscopix miniature microscopes (n=10KO/8 wildtype (WT) littermate controls). Calcium imaging was performed during grooming assessment and reversal learning and aligned to behaviors of interest (initiation/termination of grooming, correct/incorrect responses).
Results: A larger population of lOFC neurons are suppressed at the time of grooming termination in Sapap3-KOs vs. WTs (18% vs. 9%, p=0.03); % suppressed neurons is positively correlated with increasingly disorganized grooming in KOs (R=0.66, p=0.003). During reversal learning a subset of KOs (n=5) show elevated incorrect responding, which doesn't correlate with perseverative grooming. This perseverative decision-making is positively correlated with the percentage of neurons suppressed by incorrect responses (R=0.65, p=0.007).
Conclusions: In vivo imaging data suggests that Sapap3-KOs show excessive suppression of lOFC activity associated with perseverative grooming and decision-making. Ongoing analysis will provide new insight about the specific patterns of OFC neural dysfunction associated with distinct perseverative behaviors, which could help guide neuromodulatory strategies targeting OFC activity in OCD patients.
Supported By: R21MH116330
Keywords: Obsessive Compulsive Disorder (OCD), Mouse Model, Calcium Imaging, Reversal Learning, Compulsive

213. Effects of Deep Brain Stimulation in Cognitive Flexibility Using an OCD Animal Model

Adriano Reimer[1], Meng-Chen Lo[1], Maria F. Murillo[2], and Alik S. Widge[1]

[1]University of Minnesota, [2]Massachusetts General Hospital

Background: Deficits in cognitive flexibility are found in several psychiatric disorders, such as Obsessive-Compulsive Disorder (OCD) and depression. These deficits seem to result from disturbances of the corticostriatal circuits. Deep brain stimulation (DBS) targeted to the ventral capsule/ventral striatum seems to influence corticostriatal circuitry, possibly ameliorating inflexibility.
Methods: We used an operant set-shifting paradigm to evaluate behavioral flexibility in Long-Evans rats. We modeled inflexibility with meta-Chlorophenylpiperazine (5-HT2A/C-agonist, mCPP), which in pre-clinical studies induces repetitive/perseverative behaviors. Further, we evaluated the effects of DBS of the dorsal part of the ventral striatum on the flexibility of normal and mCPP-treated animals. Animals received 1) mCPP only (2.0 mg/kg), 2) DBS-only (100-300 μA for 1 h prior to and during the test), 3) a combination drug and DBS intervention. DBS and/or drug were administered on alternate days during daily testing sessions.
Results: mCPP impaired animals' flexibility, increasing reaction time (RT, t=20.59, p<0.01, for regression coefficient, trials=5892, n=7) and the number of errors (t=5.13, p<0.01). DBS at 300 μA improved flexibility (reduced RT, t=-6.13, p<0.01) with unchanged accuracy (t=-1.47, p=0.14), but in only half the cohort (omnibus RT effect, t=-1.74, p=0.08, trials=16263, n=8). DBS did not reverse mCPP-induced inflexibility (RT, t=-1.63, p=0.35; errors, t=-2.91, p=0.02).
Conclusions: DBS had modest effects on flexibility in this animal model. This may result from individual differences in electrode placement (currently being explored) or from mCPP affecting flexibility through mechanisms outside cortico-striatal circuits. Continued investigation will help to define corticostriatal circuits' influence and DBS potential benefits on flexibility.
Supported By: This work is supported by the Brain & Behavior Research Foundation, the Harvard Brain Initiative, Bipolar Disorder Fund, and a private donation from Dr. Michael Jenike
Keywords: Cortico-Striatal-Thalamic-Cortical Circuit, DBS, Cognitive Flexibility, Obsessive Compulsive Disorder (OCD)

214. Deep Brain Stimulation in OCD: Subthalamic Versus VC/VS Stimulation

Annemieke Apergis-Schoute[1], Himanshu Tyagi[2], Harith Akram[2], Tom Foltynie[2], Patricia Limousin[2], Lynne Drummond[2], Naomi A. Fineberg[3], Keith Matthews[4], Marjan Jahanshahi[2], Trevor W. Robbins[5], Barbara J. Sahakian[5], Ludvic Zrinzo[2], Marwan Hariz[2], and Eileen M. Joyce[2]

[1]University of Leicester, [2]University College London, [3]University of Hertfordshire, [4]University of Dundee, [5]University of Cambridge

Background: Deep brain stimulation (DBS) is an emerging treatment for disorders marked by perseveration, including depression and OCD. We compared the efficacy of ventral capsule/ventral striatal (VC/VS) and anteromedial subthalamic nucleus (amSTN) DBS in the same OCD patients and tested for mechanistic differences on mood and cognitive flexibility and associated neural circuitry.
Methods: Six patients with treatment-refractory OCD (5 male;YBOCS $>$ 32) entered double-blind counterbalanced phases (12 weeks amSTN or VC/VS DBS), followed by open phases when amSTN and VC/VS were stimulated together. OCD, mood and cognitive flexibility (ID/ED) were assessed. Diffusion-weighted and intraoperative MRI scans were performed for tractography from optimally activated electrode-contacts. Baseline and 12-week were compared via two-tailed t-tests
Results: Y-BOCS improved following both amSTN and VC/VS DBS (Baseline versus amSTN: $p < 0.001$; Baseline versus VC/VS: $p < 0.001$; amSTN versus VC/VS: $p = 1.00$). Changes in MADRS scores differed from baseline for both amSTN and VC/VS. The amSTN effect was greater than VC/VS (Baseline versus amSTN: $p = 0.023$; Baseline versus VC/VS: $p < 0.001$; amSTN versus VC/VS: $p = 0.001$). Changes in ExtraDimensional errors were significant for amSTN but not VC/VS DBS (Baseline versus amSTN: $p = 0.003$; Baseline versus VC/VS: $p = 0.157$; amSTN versus VC/VS: $p = 0.018$).

Tractography streamlines from amSTN-VTAs were connected to the lateral OFC, dACC, dlPFC and medial forebrain-bundle. Average streamlines from VC-VTAs were connected to the mOFC, mediodorsal thalamus, amygdala, hypothalamus and habenula.
Conclusions: VC/VS and amSTN are equally effective targets for severe treatment-refractory OCD. Differential improvements in mood and cognitive flexibility and their associated connectivity suggests that DBS at these sites modulate distinct brain networks.
Supported By: The study was funded by MRC grant MR/J012009/1 and Wellcome Trust award to TR (WT 104631/Z/14/Z)
Keywords: Deep Brain Stimulation, Obsessive Compulsive Disorder (OCD), Cognitive Flexibility, Subthalamic Nucleus, VC/VS

215. Recording and Disrupting Cortical-Striatal Hyperconnectivity in Obsessive-Compulsive Disorder

Mustafa Taha Bilge[1], Alexander Rockhill[1], Anish Kanabar[1], Aishwarya Gosai[1], Emily Hahn[1], Cristina Cusin[1], Thilo Deckersbach[1], Ziv Williams[1], Darin Dougherty[1], and **Alik S. Widge**[2]

[1]Harvard Medical School/Massachusetts General Hospital, [2]University of Minnesota

Background: It has been proposed that Deep Brain Stimulation (DBS) works through altering brain networks that are implicated in psychiatric illness. In the case of obsessive-compulsive disorder (OCD), it is argued that a Cortico-Striatal-Thalamo-Cortical (CSTC) network is hyperconnected, leading to perseverative thought and behavior. We aim to disrupt this hyperconnectivity in CSTC by simultaneously stimulating striatal and cortical parts of this network via DBS.
Methods: One participant diagnosed with OCD was implanted with DBS leads in Ventral Capsule/Ventral Striatum (VC/VS) and Supplementary Motor Area (SMA). The Activa PC+S system was programmed to record Local Field Potentials (LFP) from VC/VS and SMA throughout a 6-month period. Clinical questionnaires assessing OCD severity and mood were administered.
Results: Coherence between VC/VS and SMA in the theta and low-gamma band correlated with depression severity, as assessed by Montgomery-Asberg Depression Rating Scale (MADRS) ($r=0.65$ and $r=0.64$, for theta and low-gamma bands, respectively. ps < 0.03), yet the YBOCS correlations failed to reach significance for all frequency bands. After an optimization session for cortical stimulation, z-scores for alpha band power in SMA increased from 0.36 to 2.06, and alpha band power in VC/VS increased from -0.27 to 1.77). Subjectively, coherence-disrupting stimulation produced marked acute improvement in OCD symptoms and ruminative thoughts.
Conclusions: Our results support the linkage of CSTC hyperconnectivity to perseverative thoughts and actions. Further, they demonstrate a clinically viable protocol for disrupting that connectivity. Even brief stimulation appears able to reset parts of the CSTC network, a phenomenon we are now investigating further.
Supported By: NIH; UH3NS100548-01
Keywords: Deep Brain Stimulation, Obsessive Compulsive Disorder (OCD), Coherence, Theta Band

SYMPOSIUM
Microbiota-Gut-Brain Axis: A Research Update
3:00 p.m. - 5:00 p.m.
Chair: Chadi Calarge
Co-Chair: Vicki Ellingrod

216. Gut Microbiota Indole Production and Depressive-Like Symptoms: A Fecal Transplantation Study in Mice

Laurent Naudon[1], Catherine Philippe[2], Magali Monnoye[2], Moez Rhimi[2], Sylvie Rabot[2], and Chadi Calarge[3]

[1]French National Center for Scientific Research (CNRS), [2]French National Institute for Agricultural Research, [3]Baylor College of Medicine

Background: Recently, our group has shown that overproduction of a bacterial metabolite, indole, triggered anxiety and depressive-like behaviors in rats and mice. Therefore, we

investigated whether differences in indole production exist between adolescents with and without major depressive disorder (MDD) and whether this difference could play a role in the emergence of symptoms, in an animal model.
Methods: The amount of indole was assessed in fecal samples from a cohort of 15 to 20 year-old adolescents, 2/3 of whom had MDD. Next, fecal samples from participants with MDD having high (n=4, HI) and low indole-producing potential (n=4, LI) were used to inoculate germ-free mice. Six weeks later, HI (n=21) and LI (n=17) mice underwent depression-relevant behavioral tasks: nesting, splash, sucrose, tail suspension and forced swim tests.
Results: The amount of fecal indole varies in the cohort (n=194) from 28 to 877 nmol/g. Fecal indole concentration was higher in HI vs LI mice 2- and 6-weeks post inoculation ($p<0.001$). The analysis of cecal SCFA shown that their total production is higher in HI vs LI mice ($P<0.001$). No significant differences were observed between HI and LI mice in the behavioral tests. However, in a memory test, the HI mice performed better at distinguishing a new from an old object.
Conclusions: This study demonstrates the feasibility of transferring indole production, a bacteria-dependent function, from humans to mice. Future studies should test whether alternative paradigms, such as unpredictable chronic mild stress, are better suited to examine the role indole plays in the emergence of depressive-like symptoms.
Supported By: R01MH090072; BBRF
Keywords: Gut Microbiota, Depression, Fecal Transplantation, Indole, Mice

217. The Role of the Microbiome in Complex Phenotypes of Pediatric Autism Spectrum Disorder

Ruth Ann Luna[1], Kent Williams[2], Robin Kochel[1], Craig Powell[3], Carol Redel[1], James Versalovic[1], and Tor Savidge[1]

[1]Baylor College of Medicine, [2]Nationwide Children's Hospital, [3]The University of Texas- Southwestern

Background: The microbiome-gut-brain axis is emerging as a potential central driver of autism spectrum disorder (ASD) phenotypes, and microbial-based interventions are proving effective in experimental animal models. Here, we will describe the largest study of the gut microbiome and metabolome as it relates to behavioral and GI phenotypes in pediatric ASD.
Methods: Extensive clinical history was obtained as well as data from several behavioral surveys and a two-week diary detailing diet, stooling pattern, and GI pain. Stool specimens were collected from pediatric subjects with ASD (n=145), unaffected siblings (n=48), and unrelated healthy typically developing children (n=219). Microbiome characterization and global metabolomics were performed. Multiple bioinformatics and biostatistical approaches were utilized to identify individual organisms and metabolites of interest.
Results: Differences in both bacterial composition and diversity were observed across groups. The greatest shifts in the gut microbiome were associated with GI pain, with distinct differences noted in the ASD group that reported pain. Statistically significant differences ($p<0.05$) in the relative abundances of several of these organisms were previously reported in ASD. These organisms were also associated with specific behavioral patterns and overall severity as well as with a variety of metabolites, including metabolic pathways associated with glutamate and tryptophan metabolism.
Conclusions: Distinct differences exist in the gut microbiome and metabolome of children with ASD compared to their typically developing peers. Within ASD, subgroups can be identified based on complex phenotypes composed of behavioral characteristics, GI symptoms, and microbiome/metabolome profiles, and these multi-omic profiles will aid in developing selection criteria for future microbially-mediated therapeutic interventions.
Supported By: Autism Speaks
Keywords: Gut Microbiome, Autism Spectrum Disorder, Functional Gastrointestinal Disorders

218. Gut Microbiota Varies With Atypical Antipsychotic Treatment and Probiotics in a Bipolar and Schizophrenia Cohort

Stephanie Flowers[1], Nielson Baxter[2], Kristen Ward[2], A. Zarina Kraal[2], Melvin McInnis[2], Thomas Schmidt[2], and Vicki Ellingrod[2]

[1]University of Illinois at Chicago, [2]University of Michigan

Background: Previous studies have identified shifts in gut microbiota associated with AAP-treatment, which may link AAPs to metabolic burden. Dietary prebiotics, like resistant starch (RS) may be beneficial in obesity and glucose regulation, but little is known mechanistically about its ability to modify gut microbiota in AAP-treated individuals. This investigation was undertaken to mechanistically delineate the effects of AAP-treatment and RS on gut microbiota in a psychiatric population.
Methods: Microbiome DNA obtained from stool samples from participants with a serious mental illness were subject to 16S rRNA gene sequencing. Inter- and Intra- group diversity measures were performed by PERMANOVA and Inverse Simpson Diversity Index, respectively. Differentially abundant organisms were detected using linear discriminant analysis of effect size.
Results: We recruited 37 participants (57% male, age (mean) = 52.2 +/- (12.5), 57% receiving AAPs) for this study. While no significant difference in overall microbiota composition was detected at baseline between AAP users and non-users, non-AAP users showed increased fractional representation of Alistipes. AAP-treated females exhibited decreased diversity when compared with non-AAP-treated females. Although the microbiome of AAP-treated participants varied with RS administration, an increased abundance of the Actinobacteria phylum was observed.
Conclusions: These data suggest that AAP treatment associates with specific representation of gut microbiota, particularly in female AAP-treated patients where reduced species richness was observed. Additionally, variable microbiome responses to RS supplementation was seen with significant increase in starch degraders.
Supported By: NIMH (R01MH082784); T2 (MICHR; UL1TR002240)
Keywords: Atypical Antipsychotics, Schizophrenia, Bipolar Disorder, Gut Microbiome, Metabolic Syndrome

219. Host-Microbiome Interaction: A Putative Mechanism of Antipsychotic-Induced Weight Gain

Erika Nurmi[1], Jude McElroy[1], Gerhard Hellemann[1], Christopher Laughlin[1], James McCracken[1], Chadi Calarge[2], and Lauren Seaman[1]

[1]University of California Los Angeles, [2]Baylor School of Medicine

Background: Antipsychotic-Induced Weight Gain (AIWG) is a common, serious adverse drug effect, to which children are especially vulnerable; however, the mechanism remains unclear. Studies in rodents and humans have argued for a central role of gut microbes in AIWG and, in parallel, of bile acids (BAs) in obesity. Therefore, we hypothesized that gut microbes could drive AIWG by altering BA signaling. Specifically, conversion of liver-derived CDCA to UDCA by certain gut bacteria reverses downstream effects on metabolic pathways.
Methods: To test the relationship between BAs and AIWG, plasma BAs were measured in 30 children with and without AIWG before and after 8 weeks of risperidone treatment.
Results: We observed an increase of primary BAs (CDCA and CA) with treatment (p=0.01), 3X greater in subjects with clinically significant weight gain. Conversely, the secondary BA UDCA was protective. The ratio of change in CDCA to change in UDCA correctly predicted AIWG status in 11/12 (92%) participants whose ratios changed (p=0.001), with a sensitivity of 100% and specificity of 86%. In line with our hypothesis, a similar pattern of BA changes paralleled a decrease in bacteria capable of converting CDCA to UDCA in a small, independent, prospective sample of risperidone-treated children (n=4).
Conclusions: In our pilot sample, risperidone treatment resulted in unfavorable microbiome and BA changes associated with AIWG. A replication study is in progress. If replicated, this model could advance our understanding of obesity and drug-induced weight changes, potentially guiding readily-available clinical interventions to prevent metabolic side effects.
Supported By: NIMH N01MH70010
Keywords: Psychopharmacological Treatment, Adverse Effects, Weight Gain, Antipsychotics, Children

SYMPOSIUM
Excitation-Inhibition Balance as a Stepping Stone for Stratification and Rational Interventions in Neurodevelopmental Disorders

3:00 p.m. - 5:00 p.m.
Chair: Hilgo Bruining
Co-Chair: Alan Anticevic

220. Non-Invasive Estimation of Excitation-Inhibition Balance Facilitates Physiological Dissection of Autism Spectrum Disorder

Hilgo Bruining[1], Erika Juarez-Martinez[2], Jan Sprengers[2], Dorinde Marije van Andel[2], Sonja Simpraga[3], Simon-Shlomo Poil[4], Eva Dellares[3], Huibert Mansvelder[3], Bob Oranje[2], Richard Hardstone[5], and Klaus Linkenkaer-Hansen[3]

[1]UMC Utrecht, [2]Brain Center Rudolf Magnus, UMC Utrecht, [3]Center for Neurogenomics and Cognitive Research, (CNCR), VU University Amsterdam, [4]NBT Analytics BV, [5]Neuroscience Institute, New York University School of Medicine

Background: Imbalances in neural excitation and inhibition (E/I) are implicated in the pathogenesis of Autism Spectrum Disorder (ASD) but could so far not be confirmed through non-invasive clinical measurements. Based on the framework of critical-state dynamics, we recently introduced a method to estimate E/I ratios from the joint analysis of power and long-range temporal correlations (LRTC) measured with conventional EEG. In this part of the symposium, we present the application of this biomarker in a large sample of children with ASD versus age-matched typically developing children.
Methods: We measured LRTCs and E/I in the alpha band in unmedicated children with ASD (n=110, aged 6.6-15.9, M=10.36, 73.6% male, TIQ 55-145, M=101.85, ADOS-2 M=9.5) and typically developing children (n=30, aged 7.4-14.5, M=10.24, 50% male, TIQ 90-145, M=120.41). All EEGs were visually inspected, and abnormalities were graded according to the classification system of Luders & Noachtar's.
Results: We investigated eyes-closed rest recordings of 64-channel EEG. ASD patients showed more EEG abnormalities (NL= 59, grade I=17, grade II=25, grade III=9) than TDs (NL=30). LRTCs were enhanced in all scalp regions (Wilcoxon Rank-Sum Test, p <.001), which translated to enhanced variability of E/I ratios in ASD (F (1, 138) =18.1, p=< .001). E/I variability could be dissected by epileptiform abnormalities that were associated with reduced E/I ratios (Wilcoxon Rank-Sum Test, p<.001).
Conclusions: These findings provide a clinical validation of a non-invasive estimation of E/I heterogeneity in ASD and indicate that epileptiform abnormalities lead to compensatory changes in neural inhibition.
Keywords: Autism Spectrum Disorder, Excitation/Inhibition Balance, EEG, Critical-State Dynamics

221. Behavioural and Neurophysiological Outcomes of the Bumetanide in Autism Medication and Biomarker (BAMBI) Trial

Jan Sprengers[1], Bob Oranje[2], Dorinde Marije van Andel[2], Erika Juarez-Martinez[2], Sonja Simpraga[3], Klaus Linkenkaer-Hansen[3], and Hilgo Bruining[2]

[1]UMC Utrecht, [2]Brain Center Rudolf Magnus, UMC Utrecht, [3]Center for Neurogenomics and Cognitive Research, (CNCR), VU University Amsterdam

Background: Disruptions in the balance of excitation-inhibition (E/I) ratios are indicated as a common pathway in Autism Spectrum Disorder (ASD). This implication may have important consequences for treatment developments as several existing agents can shift E/I balance. Bumetanide is an E/I-shifting candidate due to its putative actions on chloride homeostasis and GABAergic transmission. In this part of the symposium, we present the effects of bumetanide on behavioural and neurophysiological measures as part of the forthcoming results

of the Bumetanide in Autism Medication and Biomarker (BAMBI) trial.
Methods: The BAMBI trial is a placebo-controlled randomized trial consisting of 3 months treatment (2dd1mg bumetanide or placebo) in children aged 7-15 years with unmedicated ASD, followed by 1-month washout period. The SRS-2 is the primary endpoint and secondary endpoints include behavioural questionnaires, neurocognitive test-battery, event-related potential (ERP) and resting state EEG paradigms, including a novel E/I estimation biomarker. Patients were included between June 2016 and August 2018.
Results: The last study visit is scheduled in December 2018, then treatment allocation will be unblinded and results analysed. Ninety children (age M=10.5; 70.7% male; TIQ 55-145, M=101.3, ADOS-2 M=9.16) participated. Analyses of the primary endpoint and secondary EEG endpoints after treatment and wash-out periods will be presented as well as machine learning indices to delineate responders from non-responders through step-wise inclusion of EEG parameters, including the E/I biomarker.
Conclusions: The BAMBI findings are pivotal to test replicability of previous behavioural bumetanide RCTs and to move forward to more personalized applications of rational agents using diagnostic companions.
Supported By: 'goed gebruik geneesmiddelen' grant from Zon-MW
Keywords: Randomized Control Trial, Autism Spectrum Disorder, Bumetanide, Excitation/Inhibition Balance, Prediction of Response

222. Cognitive Outcomes of the Bumetanide in Autism Medication and Biomarker (BAMBI) Trial

Dorinde Marije van Andel[1], Jan Sprengers[1], Erika Juarez-Martinez[1], Sonja Simpraga[2], Bob Oranje[1], Klaus Linkenkaer-Hansen[2], Maretha de Jonge[1], and Hilgo Bruining[1]

[1]Brain Center Rudolf Magnus, University Medical Center, [2]Center for Neurogenomics and Cognitive Research, (CNCR), VU University Amsterdam

Background: Disruptions in the balance of excitation-inhibition (E/I) ratios are implicated as a common pathway in Autism Spectrum Disorder (ASD). This implication may have important consequences for treatment developments as several existing agents can shift E/I balance. Bumetanide is an E/I-shifting candidate due to its putative actions on chloride homeostasis and GABAergic transmission. In this part of the symposium, we present effects of bumetanide on cognitive measures as part of the forthcoming results of the BAMBI trial.
Methods: The BAMBI trial is a placebo-controlled randomized trial consisting of 3-months treatment (2dd1mg bumetanide or placebo) in children aged 7-15 years with unmedicated ASD, followed by a 1-month washout period. Ninety patients were included between June 2016 and August 2018 and treatment allocation will be unblinded December 2018.
Results: At baseline, patients showed faster baseline reaction times (n=86; z=2.17, p=.03; d=.23; two-tailed z-tests) but less accuracy (n=86; z=-2.52, p =.01; d=-.27). Response inhibition paradigms showed a similar pattern for reaction time and number of false alarms (respectively n=73; z=5.77, p<.001; d=.68 and z=-15.26, p=<.001; d=-1.79). Memory deficits were apparent in both visual working (WNV-RO: n=69; z=-3.05, p<.005; d=-.37) and long-term memory (RVDLT DR: n=71; z=-3.22, p=.001; d=-.38). Analyses of these cognitive endpoints will be presented after treatment as well as machine learning indices created to delineate responders from non-responders on the basis of cognitive profiles.
Conclusions: The BAMBI findings are pivotal to test replicability of previous bumetanide RCTs and to move forward to more personalized applications of rational agents using diagnostic companions.
Supported By: 'Goed Gebruik Geneesmiddelen' grant from Zon-MW
Keywords: Randomized Control Trial, Autism Spectrum Disorder, Bumetanide, Excitation/Inhibition Balance, Cognition

223. Using Computation, Pharmacology and Neuroimaging to Characterize Excitation-Inhibition Imbalance in Neuropsychiatric Illness

Alan Anticevic[1]

[1]Yale University

Background: The functioning of excitatory (E) and inhibitory (I) neural circuit computations plays a pivotal role in supporting human thought and behavior. The pattern and timing E/I balance changes across neural circuits has been hypothesized as a core mechanism that cuts across neuropsychiatric diagnoses such as autism spectrum disorders and psychosis spectrum disorders (ASD).
Methods: We combine computational modeling, pharmacological manipulations and non-invasive functional neuroimaging to understand the mechanism underlying altered E/I balance in neuropsychiatric disease. We collected resting-state neuroimaging data in 40 participants following administration of ketamine and 24 participants under LSD, which are known to modulate E/I balance via glutamate and serotonin-mediated mechanisms respectively. In turn, we map these findings to clinical data cross the psychosis and the ASD spectra (BNSIP vs. ABIDE) to investigate if specific groups of patients resemble the pattern of neuropharmacological effects.
Results: We find that ketamine vs. LSD induce dissociable brain-wide patterns of dysconnectivity, which we simulate via computational large-scale biophysical modeling approaches. We observed that LSD reduced associative, but concurrently increased sensory-somatomotor brain-wide and thalamic connectivity, whereas ketamine exhibited largely the opposite pattern. In turn, we identified sub-groups of patients along the psychosis and ASD spectra that quantitatively capture pharmacological effects.
Conclusions: These data suggest that mapping neuropharmacological mechanisms of putative E/I imbalance may provide a powerful way for iteratively closing the gap across levels of analysis, from cells and circuits to neural systems and

ultimately altered behavior. These effects could drive rational development of neurobiological therapies for disrupted neural circuits across psychosis and ASD spectra.
Keywords: Ketamine, E/I Balance, Glutamate, Acute Psychosis, ASD

SYMPOSIUM
Biological Variables Moderating Immune Dysregulation in Mood Disorders: Age- And Sex-Differences

3:00 p.m. - 5:00 p.m.
Chair: James Murrough
Co-Chair: Ebrahim Haroon

224. Sex Differences in Association of Inflammation and Suicidality: Findings From Two Separate Cohorts of Patients With Major Depressive Disorder

Manish Jha[1], **Abu Minhajuddin**[2], Cherise Chin Fatt[2], Joseph Trombello[2], Taryn Mayes[2], Tracy Greer[2], and Madhukar Trivedi[2]

[1]Icahn School of Medicine at Mount Sinai, [2]University of Texas Southwestern Medical Center

Background: Role of inflammation in suicidality has gained recent attention. However, it is unclear whether the association between suicidality and inflammation differs on the basis of sex.
Methods: Participants of Establishing Moderators and Biosignatures of Antidepressant Response in Clinical care (EMBARC) study with plasma c-reactive protein (CRP) available at baseline (n=219) were included. Gender-stratified mixed model analyses tested baseline-CRP (categorized as <3 and ≥3 mg/L)-by-visit (weeks-0, 1, 2, 3, 4, 6, and 8) interactions for changes in suicide propensity and ideations (using Concise Health Risk Tracking scale). Data from Combining Medications to Enhance Depression Outcomes (CO-MED) trial were used for replication.
Results: In EMBARC, there was a significant baseline-CRP-by-visit interaction for changes in suicide propensity in males (p=0.046) but not in females (p=0.412) even after controlling for age, race, ethnicity, site, body mass index, and age of onset. While suicide propensity scores were similar at baseline (p=0.751), males with CRP ≥3 mg/L (n=10) at baseline had significantly higher scores at week 8 (p=0.050) than those with CRP <3 mg/L (n=65). Pre-treatment CRP did not predict changes in suicidal ideations in either males (p=0.743) or females (p=0.308). In CO-MED trial, while suicide propensity scores were similar at baseline, males with CRP ≥3 mg/L (n=14) had higher suicide propensity from weeks 6-12 (Cohen's d =0.67-1.34) than those with CRP <3mg/L (n=35).
Conclusions: High baseline CRP predicted persistently elevated suicide propensity after acute-phase antidepressant treatment in males but not in females in two separate cohorts. Future research should consider sex-differences in mechanisms linking inflammation and suicidality.
Supported By: NIMH U01MH092221; NIMH U01MH092250; NIMH N01 MH-90003; Center for Depression Research and Clinical Care; Hersh Foundation; Jordan Harris Foundation
Keywords: Inflammation, C-reactive Protein, Suicidality, Major Depression, Sex Differences

225. Sex Differences in the Peripheral Immune Signatures of Stress Susceptibility and Resilience

Jennifer Rainville[1], Flurin Cathomas[2], Scott Russo[2], and **Georgia Hodes**[1]

[1]Virginia Polytechnic Institute and State University, [2]Icahn School of Medicine at Mount Sinai

Background: Little is known about mechanisms contributing to the higher incidence of inflammatory and stress-related illness, such as mood disorders, in females. Here, we compared peripheral cytokine profiles in males and females from two different stress-based mouse models, variable stress and social defeat stress
Methods: Subjects were exposed to 6 days (n = 40) of variable stress or 10 days social defeat stress (n = 58). Cytokine protein levels from plasma were detected using multiplex enzyme-linked immunosorbent assays.
Results: In both paradigms, we observed greater immune regulation by stress of females compared to males. Some cytokines, (G-CSF and GM-CSF) were significantly down regulated following variable stress ($F_{1,34} = 5.5$, $p < 0.05$/ $F_{1,31} = 6.49$, $p < 0.05$) but upregulated following social defeat stress ($F_{2,52} = 8.7$, $p < 0.001$/ $F_{2,51} = 4.87$, $p < 0.05$) particularly in stress susceptible females. Others such as Eotaxin were significantly upregulated in males and down regulated in females for variable stress ($F_{1,36} = 25.13$, $p < 0.0001$) and social defeat stress ($F_{2,54} = 5.87$, $p < 0.01$). More cytokines correlated with behavior in variable stress (GM-CSF r= -0.37, IL-9 r = 0.46, IL-10 r= 0.36, IL-12 r= 0.33) than social defeat stress (IFN-γ r= 0.33).
Conclusions: We found that different rodent stress paradigms produced variation in how they regulate peripheral cytokines. Across both stressors' females produced larger immune responses to stress than males. These data suggest that not all stressors have the same effects on circulating levels of cytokines.
Supported By: NARSAD
Keywords: Stress, Sex Differences, Animal Models, Cytokines And Chemokines

226. 'Inflammaging' in Depression - Morphological, Metabolic and Behavioral Consequences

Ebrahim Haroon[1], Xiangchuan Chen[1], Agnes H. Kim[1], Bobbi Woolwine[1], Trusharth Patel[1], Jennifer C. Felger[1], and Andrew Miller[1]

[1]Emory University

Background: 'Inflammaging' is a state of chronic, low-grade increases in inflammation seen during aging. Monocyte chemoattractant protein (MCP)-1 - a chemokine that signals

peripheral immune cell trafficking to sites of inflammation - is increased in immune disorders and is emerging as a promising marker of inflammaging. Using this marker, we examined structural brain changes associated with inflammaging in depressed subjects.
Methods: 41 medication-free depressed subjects underwent blood and cerebrospinal fluid (CSF, n=35 only) sampling for inflammatory markers along with structured behavioral and neurocognitive assessments. Structural MRI and magnetic resonance spectroscopy (MRS) scans were obtained using a Siemens-3T Trim Trio scanner. Group-wise comparisons and linear effects were examined after controlling for sex, BMI, race, depression-severity, and total brain volume. FDR-correction was used to limit false-positive errors, and Cohen's 'd' to estimate effect sizes.
Results: K-means clustering was used to divide the sample into inflammaging (n-22) and comparison (n=20) groups. C-reactive protein, MCP-1, and soluble tumor necrosis factor receptor type-2 were all elevated in the CSF (but not plasma) of the inflammaging group (d>0.7). Greater volume decreases impacting total and subcortical (SCgray) gray matter, left/right caudate, and left/right putamen regions (d-range=0.50-1.18) were associated with inflammaging group status. Linear models indicated that MRS-based estimates of left basal ganglia myo-inositol (astroglial marker) negatively predicted SCgray (b=-0.39, d=0.92) and SCgray*inflammaging group interaction negatively predicted performance on Stockings of Cambridge test of executive abilities (b=-0.61, d=1.06).
Conclusions: Aging impacts inflammation-associated pathophysiologies in depression. Identifying exaggerated inflammaging in depressed patients can lead to personalized treatments employing immunomodulatory, neuro- and glioprotective interventions.
Supported By: R01MH H107033, K23MH091254, R01MH112076, R01MH087604
Keywords: Accelerated Aging, Psychoneuroimmunology, Synaptic Plasticity, Glutamate, Depression

227. Inflammation-Induced Depressive Symptoms: Persisting Sex Differences in Late Life

Joshua Cho[1], Richard Olmstead[1], and Michael Irwin[2]

[1]David Geffen School of Medicine at UCLA, [2]University of California Los Angeles

Background: In younger adults, the female preponderance in depression prevalence is well established, and female sex has been shown to increase vulnerability to inflammation-induced depression. However, such female preponderance decreases in post-menopausal period, and it is unknown whether female sex increases vulnerability to inflammation-induced depression in late life. This study examined whether older females (vs. older males) showed greater increases in depressive symptoms in response to an inflammatory challenge.
Methods: In a randomized double-blind placebo-controlled design, volunteers aged 60-80 (N=87; 41 females) received either a single infusion of low-dose endotoxin (derived from Escherichia coli; 0.8 ng/kg of body weight) or placebo (same volume of 0.9% saline). Depressive symptoms were repeatedly assessed over 6 hours using the Montgomery-Asberg Depression Rating Scale (MADRS).
Results: Endotoxin (vs. placebo) robustly increased depressive symptoms (X^2=17.24, df=3, p<0.001). When stratified by sex, the effect of endotoxin on depressive symptoms was significant in females (X^2=10.73, df=3, p=0.01) but not in males (X^2=6.97, df=3, p=0.07).
Conclusions: While older females presented with significant increases in depressive symptoms in response to an experimental inflammatory challenge, older males failed to mount a significant depressive response. To our knowledge, this is the first study to demonstrate sex differences in inflammation-induced depression among older adults. Although hormonal and social milieu considerably changes in late life, female sex still appears to be an important vulnerability factor for inflammation-induced depressive symptoms. This persisting sex difference in depressive symptom response to an inflammatory challenge across the lifespan provides further insight into biological mechanisms of the excessive female burden of depression.
Supported By: R01AG051944; K23AG049085
Keywords: Inflammation, Depression, Depressive Symptoms, Sex Differences, Late-life

SYMPOSIUM
Advancing Diagnostic Biological Markers for PTSD: Findings From DOD Systems Biology

3:00 p.m. - 5:00 p.m.
Chair: Charles Marmar
Co-Chair: Marti Jett

228. Cross-Sectional and Longitudinal Studies of Cellular Aging and Related Biomarkers in Combat PTSD

Gwyneth Wu[1], Jee In Kang[2], Ruoting Yang[3], Josine Verhoeven[4], Rasha Hammanieh[5], Rachel Yehuda[6], Victor Reus[1], Janine Flory[6], Duna Abu-Amara[7], Marti Jett[5], Charles Marmar[7], Owen M. Wolkowitz[1], and Synthia Mellon[1]

[1]University of California, San Francisco, [2]Yonsei University College of Medicine, [3]Advanced Biomedical Computing Center, Frederick National Laboratory for Cancer Research, [4]VU University Medical Center, [5]U.S. Army Center for Environmental Health Research, [6]James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, [7]New York University School of Medicine

Background: PTSD is associated with aspects of accelerated biological aging. We studied cross-sectionally and longitudinally two distinct indices of biological aging in PTSD, telomere shortening and epigenetic aging, as well as serum BDNF.
Methods: We analyzed telomere length, epigenetic aging, and BDNF in association with PTSD diagnosis in male

combat-exposed veterans (n=213) and in a subset of these veterans (n=57) around 3 years later. For cross-sectional data analyses, participants were categorized as PTSD vs. non-PTSD, based upon DSM and CAPS scores. Of those veterans who were followed longitudinally, 16 were categorized as "persistent PTSD", 14 improved to non-PTSD, and 27 remained "non-PTSD" at both time points.

Results: Cross-sectional analysis at T=0 showed that subjects with PTSD had shorter telomere lengths (p=.024) than those without PTSD, among veterans exposed to high trauma as assessed by the DRRI. Acceleration of epigenetic aging, assessed by DNA methylation and Horvath's method, was shown in the whole sample (epigenetic age minus chronologic age = 4.51 years) and was attenuated in PTSD compared to non-PTSD (p = 0.005). Longitudinally, subjects with persistent PTSD had significantly higher serum BDNF than non-PTSD across the two time points (p = .008). Higher BDNF at T=0 was associated with greater symptom severity at follow-up (p=.043).

Conclusions: Our data suggest that combat trauma is associated with accelerated epigenetic aging. High trauma-exposed veterans with PTSD have shortened telomeres. Elevated serum BDNF levels, which may be compensatory, are associated with attenuated acceleration of epigenetic aging in PTSD and with poorer longitudinal outcome.

Supported By: Department of Defense; U.S. Army:
W81XWH-09-2-0044
W81XWH-14-1-0043
W81XWH-10-1-0021
W911NF-16-1-0355

Keywords: PTSD - Posttraumatic Stress Disorder, Combat, Cellular Aging, BDNF, Longitudinal Cohort

229. A Cohort Study of OIF/OEF Veterans: A Blood Epigenomic Assessment

Rasha Hammamieh[1], Aarti Gautam[1], Nabarun Chakraborty[2], Seid Muhie[2], Ruoting Yang[3], Duncan Donohue[2], Bernie Daigle[4], Yuanyang Zhang[4], Duna Abu Amara[5], Janine Flory[6], Rachel Yehuda[6], Linda Petzhold[4], Frank Doyle[4], Charles Marmar[5], and Marti Jett[1]

[1]US Army Center for Environmental Health Research, [2]Geneva Foundation, [3]Advanced Biomedical Computing Center, Frederick National Laboratory for Cancer Research, [4]University of California, [5]NYU School of Medicine, [6]Icahn School of Medicine at Mount Sinai, James J. Peters VAMC

Background: Management of post-traumatic stress disorder (PTSD) is complicated by the overlapping symptoms of its comorbidities. A comprehensive understanding of molecular pathophysiology of PTSD could facilitate unbiased biomarker-driven next-generation intervention strategies. In this study, epigenomic profiles were characterized as to the implications for behavior, immune response, nervous system development, and relevant PTSD comorbidities such as cardiac health and diabetes.

Methods: 83 PTSD-positive male veterans of US Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) were matched to 83 controls by age and ethnicity. PTSD diagnosis was determined by a clinician-administered PTSD scale (CAPS) >40, while the control group demonstrated a CAPS <10. Methylation status of DNA extracted from whole blood was assayed using microarrays.

Results: We identified DNA probes that were statistically differentially methylated (FDR < 0.1), representing approximately 3,600 unique genes. Interestingly, a significant number of genes facilitating telomere maintenance and insulin reception were hyper-methylated at both promoter and gene body sites; therefore, the DNA methylation status in these genes could be prevailing. Nearly 85% of the differentially methylated probes were hyper-methylated in PTSD patients. The majority of these probes encode the candidate proteins responsible for transcription regulation and enzymatic actions. Genes involved in memory consolidation, emotion/aggressive behavior, and perturbed circadian rhythm were preferentially hyper-methylated. The biological validation study used an independent test set comprised of 31 PTSD+ /31 PTSD- veterans screened using the same protocol.

Conclusions: PTSD perturbed the cellular and humoral immune system. Genes involved in several PTSD comorbidities, such as cardiomyopathy and poor insulin management, were also altered.

Supported By: USAMRMC Military Operational Medicine Research Program (MOMRP); Defense Health Agency (DHA); Congressional Special Interests (CSI); MOMRP 190040

Keywords: PTSD - Posttraumatic Stress Disorder, Epigenomics, Blood Epigenomics, Biomarkers

230. Distinct Profiles of Extracellular Vesicles-Encapsulated RNA in Veterans With Post-Traumatic Stress Disorder

Kai Wang[1], Min Young Lee[1], David Baxter[1], Kelsey Scherler[1], Taek-Kyun Kim[1], Duna Abu-Amara[2], Janine D. Flory[3], Rachel Yehuda[3], Charles Marmar[2], Marti Jett[4], Inyoul Lee[1], and Leroy Hood [1], PTSD Systems Biology Consortium

[1]Institute for Systems Biology, [2]NYU School of Medicine, [3]James J. Peters Veterans Administration Medical Center Bronx/Icahn School of Medicine at Mount Sinai, [4]Integrative Systems Biology Program, U.S. Army Center for Environmental Health Research

Background: Dysregulation of circulating microRNAs in body fluids has been reported in psychiatric disorders such as schizophrenia, bipolar, and post-traumatic stress disorder (PTSD). Recent studies showed that extracellular vesicles (EV) in body fluids may involve in cell-cell communication and can provide more informative biomarker.

Methods: We performed a comprehensive profiling of small RNAs in whole plasma, EV and EV-depleted (EVD) plasma samples collected from combat veterans with PTSD and matched controls by next-generation sequencing. We also characterize the EV-encapsulated large RNA with microarray.

Results: In total, 520 microRNAs were quantified from 24 male veterans with (n=12) and without (n=12) PTSD. The

overall microRNA profiles in whole plasma, EV and EVD plasma were different. The concentration changes of miR-203a-3p (p-value 0.0485) in EV and miR-339-5p (p-value 0.0148) in EVD plasma between PTSD and controls were confirmed in an independent cohort (10 with and 10 without PTSD veterans) using qPCR. The target genes of these two microRNAs were involved in signaling pathways and comorbid conditions associated with PTSD (e.g., neurotransmitter systems such as dopaminergic and serotonergic signaling, inflammatory response, and cardiovascular diseases). Besides microRNAs, we also observed the changes of a few protein coding transcripts in EV; some of these transcripts including NCAM1 (lower in PTSD, p-value 0.0381) and GRIN2C (higher in PTSD, p-value 0.0278) are highly abundant in the central nervous system.

Conclusions: Our findings suggest that PTSD may impact the distribution of RNAs inside and outside of vesicles. Further studies are needed to evaluate the functionality and utility of these RNAs for PTSD.

Supported By: DOD (W81XWH-16-1-0301 and W911NF-17-2-0086)

Keywords: Post-Traumatic Stress Disorder, microRNA, Next-Generation Sequencing, Extracellular Vesicles, Plasma

231. Validation of a Multi-Omic Biomarker Panel and Analysis of Disease Progression Trajectories in a Novel Longitudinal PTSD Cohort

Rohit Rao[1], Kelsey Dean[1], Burook Misganaw[1], Pramod Somvanshi[1], and Francis Doyle III[1]

[1]Harvard University

Background: Signals associated with PTSD development might emerge across multiple levels of physiological regulation. Diagnostic classifiers synthesizing signals from several single-layer molecular signatures into a multi-omic panel can improve diagnostic performance compared to any individual molecular signature. Moreover, studying the longitudinal trajectories of such a multi-omic panel might lead to improved characterization of disease progression at the molecular level, and potentially enable identification of pre-symptomatic individuals.

Methods: Diverse molecular, physiological and clinical features were obtained from three cohorts of US army personnel. Single and multi-omic classifiers were initially identified in a cohort of 83 PTSD positive cases and 83 PTSD negative matched controls, and subsequently refined and validated in a cohort of 29 PTSD cases and 40 controls. A novel longitudinal cohort of 1800 active duty soldiers is used for external validation. Temporal profiles of the signatures constituting the multi-omic panel will be analyzed to characterize differences between individuals presenting post-deployment PTSD symptoms and negative controls.

Results: We previously found that the multi-omic panel results in a small improvement in diagnostic performance in comparison to individual single-omic panels in the initial training and validation cohorts (AUC=0.80, 77% accuracy, 81% sensitivity, 73% specificity). Preliminary external validation in the longitudinal cohort suggests that single-omic metabolic panels constituting the multi-omic panel are significantly associated with PTSD status.

Conclusions: The improved diagnostic performance of the multi-omic panel suggests that the single-omic panels contain complementary biological signals. Further analysis of the multi-omic panel in a longitudinal cohort is expected to reveal novel insights into PTSD progression over time.

Supported By: W911NF-17-2-0086, U.S. Army Research Office

Keywords: PTSD - Posttraumatic Stress Disorder, Biomarkers, Longitudinal Cohort, Multi-omic Analysis

SYMPOSIUM
Hippocampal Hyperactivity in Psychosis
3:00 p.m. - 5:00 p.m.
Chair: Stephan Heckers

232. Peripubertal Stress and Interneuron Loss-Induced Hippocampal Hyperactivity as Risk Factors in the Pathophysiology of Schizophrenia

Anthony Grace[1], Felipe Gomes[1], and Xiyu Zhu[1]

[1]University of Pittsburgh

Background: Schizophrenia brains show parvalbumin GABAergic interneuron loss in the hippocampus which likely drives hippocampal hyperactivity, leading to an over-responsive dopamine system. We demonstrate that this loss is driven by stress during the critical period.

Methods: Normal rats were exposed to 10 days footshock and 3 sessions of restraint stress at PD 31-40 or 65-74 and tested 1-2 weeks or 5-6 weeks after. Separate rats were exposed to valproic acid (VPA) for 15 days starting 5 days before the stress.

Results: Adolescent stress increased VTA DA neuron activity 1-2 weeks (control: n=8, 0.87±0.19 active DA neurons/track (c/t); stress: n=7, 1.5±0.15 c/t; p=0.012) and 5-6 weeks (naïve: n=6, 0.98±0.11 c/t; stress : n=6 rats, 1.58±0.07 c/t; p=0.0009) and increased ventral hippocampal activity (naïve: n=26 neurons/7 rats, 0.62±0.09 c/t; stress: n=48 neurons/10 rats, 0.80±0.08 c/t) post stress. In contrast, adult stress decreased VTA activity (naïve: n=8 rats, 1.02±0.07 c/t; stress: n=10, 0.69±0.06 c/t; p=0.003). VPA treatment in adults caused stress to increase VTA activity (stress+VPA: n=11 rats, 1.46±0.08 c/t;$F_{1,34}$ =27.49, $p < 0.0001$).

Conclusions: These data demonstrate that the timing of environmental stress is critical in determining the pathophysiological consequences. Thus, depression and schizophrenia may share a common genetic predisposition leading to increased stress susceptibility at different developmental stages, with the pathophysiology dependent on the timing of the stressor.

Supported By: NIH MH57440

Keywords: Ventral Hippocampus, Dopamine, Critical Period, Parvalbumin Interneurons, Adolescent Stress

233. Anterior Hippocampal Hyperactivity Limits fMRI Activation During Scene Processing in Early Psychosis

Maureen McHugo[1], Pratik Talati[2], Simon Vandekar[3], Kristan Armstrong[1], and Stephan Heckers[1]

[1]Vanderbilt University Medical Center, [2]Massachusetts General Hospital, [3]University of Pennsylvania School of Medicine

Background: Extant data provide strong evidence for hippocampal hyperactivity in schizophrenia. We have found that volume deficits in early psychosis patients are more prominent in the anterior hippocampus. The origin of functional abnormalities along the hippocampal long axis is unclear. Models of hippocampal function have highlighted a role for the anterior hippocampus in scene processing and construction. Here we test the hypothesis that anterior hippocampal hyperactivity impairs the recruitment of this region during a cognitive task.
Methods: We analyzed fMRI data from 112 individuals (48 early psychosis patients; 64 healthy controls) using a block design 1-back task with scene, face, and scrambled image conditions. We measured BOLD activation in response to scenes and faces compared to scrambled images in each individual. Cerebral blood volume data was collected to measure baseline hippocampal activation from a subset of individuals in the fMRI sample (17 patients; 28 healthy controls).
Results: Relative to healthy controls, we observed decreased activation of the anterior hippocampus in early psychosis patients during scene processing (cluster-wise $pFWE<0.014$) and increased cerebral blood volume in the anterior hippocampus ($t(19.7)=2.77$, $p=0.006$). Increased cerebral blood volume in early psychosis patients was associated with less task-related activation during scene processing in the anterior hippocampus ($r=-0.46$, $p=0.03$).
Conclusions: We find evidence for anterior hippocampal hyperactivity in early psychosis patients that limits their ability to effectively recruit the hippocampus during scene processing. Our findings provide novel support for the anterior hippocampus as a target in the treatment of cognitive deficits and clinical features of psychosis.
Supported By: NIMH R01-MH70560; Charlotte and Donald Test Fund
Keywords: First Episode Psychosis, Hippocampus, Brain Imaging, fMRI, Schizophrenia

234. Hippocampal Glutamate and Resting State Functional Connectivity as Biomarkers of Treatment Response to Antipsychotic Medication

Adrienne Lahti[1], Nina Kraguljac[1], Meredith Reid[2], and David White[1]

[1]University of Alabama at Birmingham, [2]Auburn University

Background: We previously identified the hippocampus as being an important part of a network involved in antipsychotic drug (APD) action. Because APDs have limited clinical effectiveness, it is pivotal to better characterize the functional circuitry and neurochemistry underlying the substantial heterogeneity in treatment response.
Methods: We used MR Spectroscopy (MRS) and resting state fMRI to investigate the effect of APD on hippocampal glutamate + glutamine (Glx) and hippocampal functional connectivity (FC) in 34 unmedicated patients with schizophrenia scanned before and after 6 weeks of APD treatment. Matched healthy controls (HC) were scanned 6 weeks apart. Treatment response was defined based on changes in BPRS scores; patients were divided in good (GR) and poor (PR) treatment responders using a median split.
Results: For Glx levels, there was a significant group (GR, PR, HC) x time interaction. Post hoc contrasts demonstrated the effect was driven by significantly elevated Glx in GR compared to HC at baseline ($p= .01$), and a significant reduction in Glx in GR from baseline to week 6 ($p= .02$). Significant patterns of hippocampal positive FC to the default mode network and negative FC to task positive network were evident in HC and in GR at baseline. Compared to GR and HC, PR had a significant reduction in hippocampal FC to task positive network ($PFDR<0.05$).
Conclusions: We identified two potential biomarkers of treatment response: before treatment, high Glx level identified a group of subsequent GR and reduced hippocampal FC to task positive network identified a group of subsequent PR.
Supported By: R01MH 081014 and R01MH102951
Keywords: Schizophrenia, Hippocampus, Glutamate, Resting State Functional Connectivity, Antipsychotic Drug

235. Hippocampal Hyperactivity in Schizophrenia, Relationship to Cognitive Deficits, and Potential as a Target for Therapeutic Development

Jason Tregellas[1], Josette Harris[1], and Robert Freedman[1]

[1]University of Colorado School of Medicine

Background: This session will describe a series of studies investigating hippocampal hyperactivity in schizophrenia, the relationship of this activity to cognitive deficits, and potential avenues for therapeutic development.
Methods: Neuronal response was examined using fMRI in schizophrenia patients and healthy comparison subjects in a series of tasks, including during a smooth pursuit eye movement task ($N = 28$), a passive listening task ($N = 35$), an attention task with auditory distraction ($N = 39$) and at rest ($N = 56$). The relationship between resting-state hippocampal activity and MATRICS Consensus Cognitive Battery scores (MCCB) also was evaluated. Finally, we examined the effect of the nicotinic agonist DMXB-A, compared to placebo, on hippocampal activity during the eye movement task ($N = 16$).
Results: Relative to healthy comparison subjects, individuals with schizophrenia exhibited hippocampal hyperactivity during the smooth pursuit eye movement task, the passive listening task and the passive listening condition of the attention task (all $p < 0.05$, corrected). Resting hippocampal activity was

greater than that of comparison subjects and was inversely correlated with MCCB composite score. Hippocampal hyperactivity during the smooth pursuit eye movement task was reduced by DMXB-A, compared to placebo ($p < 0.004$).
Conclusions: Hyperactivity of the hippocampus was observed in schizophrenia across multiple low-effort tasks and during rest. Hippocampal hyperactivity may also be associated with cognitive symptoms in the illness. In addition to recent studies of the ability of nicotinic agonists to target hippocampal activity, current and future directions for targeting hippocampal hyperactivity in psychosis will be discussed.
Supported By: NIH Grants P50MH086383, R01MH102224, VA Merit CX000459, and NARSAD Awards
Keywords: Schizophrenia, Hippocampus, Hyperactivity, fMRI

SYMPOSIUM
The Role of Gene Expression Control in Genetic Risk for Schizophrenia
3:00 p.m. - 5:00 p.m.
Chair: Alessandro Bertolino
Co-Chair: Andreas Meyer-Lindenberg

236. Molecular Dissection of Schizophrenia GWAS Significant Loci

Daniel Weinberger[1], Andrew Jaffe[1], Leo Collado-Torres[1], JooHeon Shin[1], Thomas Hyde[1], and Joel Kleinman[1], BrainSeq Consortium

[1]Lieber Institute for Brain Development

Background: GWAS have identified many genetic variants associated with risk for schizophrenia but the underlying molecular mechanisms are largely unknown. Here we investigate genomic regions associated with schizophrenia in prefrontal cortex and in hippocampus.
Methods: We performed deep RNAseq on 900 samples across both the DLPFC and the hippocampus for 551 individuals (286 affected by schizophrenia disorder: SCZD) and tested for association between the genotypes at GWAS variants and nearly expression (eQTL analysis). These datasets represent Phase I and II of the BrainSeq consortium and are available at http://eqtl.brainseq.org/.
Results: We identified 48 and 245 differentially expressed genes by diagnosis (FDR<5%) in HIPPO and DLPFC, respectively, with minimal overlap between the two regions. We found that 9,692 schizophrenia GWAS risk SNPs and proxy SNPs are eQTLs in at least one of the regions, but again with considerable regional selectivity. We also identify potential molecular correlates of in vivo evidence of altered prefrontal-hippocampal functional connectivity in schizophrenia. While risk associated genotype for rs10791098 was associated with the expression of the entire SNX19 gene (p=0.0014), a deeper analysis revealed that risk allele "A" was positively associated with the expression of the junction between exons 8 and 10 (n=658; Junc8.10 1.63E-35) but not with the junction between exons 8 and 9 (p=0.538). In hippocampus the overall pattern of molecular associations with transcript features differed.
Conclusions: Our data underscore the complexity and regional heterogeneity of molecular correlates of schizophrenia and highlight the incompleteness of understanding the molecular pathology associated with schizophrenia based on only DLPFC or HIPPO.
Supported By: Lieber Institute for Brain Development, BrainSeq Consortium
Keywords: Schizophrenia, RNA Sequencing, Post Mortem Brain, GWAS

237. Large-Scale Gene-Trait Association Study Identifies Novel Genes Across Multiple Traits

Wen Zhang[1], Georgios Voloudakis[1], Veera Rajagopal[1], Eric Schadt[1], Johan Björkegren[1], John Fullard[1], Gabriel Hoffman[1], and **Panos Roussos**[1]

[1]Icahn School of Medicine at Mount Sinai

Background: Novel machine learning approaches can generate models for "imputation" (prediction) of gene expression by using solely genetic data as input. These models can be integrated with GWAS to identify changes at the imputed gene expression with much greater power than examining single nucleotide variants. Here, we developed a method that integrates epigenomic information to better estimate variants' effects on gene expression level.
Methods: We generated predictive models of gene expression and epigenome regulation in >100 datasets by using a weighted elastic net model that integrates epigenome and other functional data. We applied these models to >100 GWAS to identify genes that are dysregulated in each trait.
Results: Compared to previous methods, our model improves the accuracy of gene expression prediction in independent datasets. Integration of gene expression predictors with GWAS summary results identified novel trait-associated genes. These genes are enriched for: (1) biological pathways that are relevant to the etiopathogenesis of the trait, and (2) genes that have been associated with disease-specific Mendelian syndromes, clinical signs and mouse models.
Conclusions: Integrating epigenomic information into prediction of transcriptome can improve the performance of imputation and when applied in GWAS data reveals novel tissue-specific trait-associated genes.
Supported By: U01MH116442; BX004189; R01MH109677; R01MH109897; R01MH110921; R01AG050986; BX002395
Keywords: Gene Expression, Epigenome, Machine Learning, GWAS

238. Transcriptome-Wide Isoform-Level Dysregulation in Schizophrenia, Autism, and Bipolar Disorder

Michael Gandal[1], Dalila Pinto[2], Lilia Iakoucheva[3], Chunyu Liu[4], and Dan Geschwind[1], PsychENCODE Consortium

[1]Semel Institute for Neuroscience & Human Behavior at UCLA, [2]Icahn School of Medicine at Mount Sinai,

[3]University of California San Diego, [4]SUNY Upstate Medical University, [5]NIMH

Background: Understanding of the pathophysiology of psychiatric disorders, including schizophrenia (SCZ), autism spectrum disorder (ASD), and bipolar disorder (BD), lags behind most other fields of medicine. Recent work demonstrates that the transcriptome represents a quantitative phenotype that provides biological context for understanding the molecular pathways disrupted in major psychiatric disorders.
Methods: Here we integrate genotype and RNA sequencing (RNA-Seq) in cortical brain samples from a large cohort of 1695 unique subjects with SCZ, BD, ASD, and controls. Analysis was performed across multiple levels of transcriptomic organization, including gene expression, local splicing, transcript isoform expression, and coexpression networks for both protein-coding and non-coding genes.
Results: Over 25% of the transcriptome exhibits differential splicing or expression, with isoform-level changes capturing the largest disease effects, cell-type specificity, and genetic enrichments. Coexpression networks isolate disease-specific neuronal alterations, as well as microglial, astrocyte, and interferon response modules defining novel neural-immune mechanisms. We prioritize disease loci likely mediated by cis-effects on brain expression via transcriptome-wide association analysis.
Conclusions: By integrating RNA-sequencing and genetic data in a large-scale cohort, we refine the shared and distinct molecular pathology of ASD, BD, and SCZ, and provide a quantitative, genome-wide resource for mechanistic insight and therapeutic development.
Supported By: This work is funded by the U.S. National Institute of Mental Health (NIMH) (grants P50-MH106438, D.H.G.; R01-MH094714, D.H.G.; U01-MH103339, D.H.G.; R01-MH110927, D.H.G.; R01-MH100027, D.H.G.; R01-MH110920, C.L.; U01-MH103340, C.L.; MH109885, LMI; MH104766, LMI; MH105524, LMI; MH108528, LMI; R21-MH105881, D.P.; R01-MH110555, D.P.; R01-MH109715, D.P.)
Keywords: Transcriptome, Network-Analysis, TWAS, Functional Genomics

239. Systems-Level Correlates of the Co-Expression of Schizophrenia Risk Genes

Giulio Pergola[1], Pasquale Di Carlo[1], Antonio Rampino[1], Daniel Weinberger[2], and Alessandro Bertolino[1]

[1]University of Bari Aldo Moro, [2]Lieber Institute for Brain Development, School of Medicine, Johns Hopkins University School of Medicine

Background: Since many of the SCZ risk variants are non-coding and may control gene expression, it is plausible that the regulatory elements of gene expression represent a mechanism of risk. However, genetic regulatory elements linking risk genes with altered regulation of gene expression at multiple risk loci are still missing.
Methods: In healthy subjects (n=147) we identified a gene co-expression module enriched for miR-137 targets ($p<.001$) and identified its co-expression eQTLs (co-eQTLs). We computed polygenic scores obtained either combining co-eQTLs of this module or SCZ risk variants within target genes of miR-137 and compared their effects on neurobiological phenotypes of SCZ in four partially overlapping cohorts (n=483). In a second study, we investigated specifically the co-expression of SCZ risk genes. Across multiple independent RNA sequencing datasets (n=915) we identified one gene co-expression module enriched for SCZ risk genes ($p<.001$) and assessed the effects of co-eQTLs on short-term response to olanzapine in patients with SCZ (n=167).
Results: mir-137-related risk for SCZ was associated with working memory, while co-expression scores were associated with emotion recognition (all corrected $p<.05$). In our second study, bioinformatic analyses predicted that SCZ risk genes were co-regulated by miR-101, miR-374, and miR-28. The co-eQTLs of the SCZ risk module were associated with the inter-individual variation between patients in terms of positive symptoms decrease (all $p<.05$).
Conclusions: These findings support the idea that the co-expression of SCZ risk genes may be associated with miRNAs. The inter-individual variability in gene co-expression is also associated with variability in neuroimaging and clinical phenotypes characteristic of SCZ.
Supported By: Fondazione CON IL SUD, Ministero della Salute, IMAGEMEND, Lieber Institute for Brain Development, Hoffmann-La Roche Ltd.
Keywords: WGCNA, Polygenic Score, miRNAs, fMRI, Olanzapine

SYMPOSIUM
Neurodevelopmental Mechanisms of Resilience and Vulnerability to Childhood Trauma
3:00 p.m. - 5:00 p.m.
Chair: Ryan Herringa

240. A Developmental Perspective on Brain Network Architecture, Nodal Abnormalities and Susceptibility or Resilience to Maltreatment

Martin Teicher[1], Kyoko Ohashi[1], Jianjun Zhu[2], Carl Anderson[1], Elizabeth Bolger[1], and Alaptagin Khan[1]

[1]McLean Hospital, Harvard Medical School, [2]South China Normal University

Background: Childhood maltreatment is an important risk factor for psychopathology. However, some maltreated individuals appear remarkably resilient even though they have the same basic array of imaging abnormalities as maltreated individuals with psychopathology. We seek to identify compensatory brain alterations enabling resilient individuals to maintain mental well-being despite alterations in stress-susceptible structures.
Methods: Ninety-node networks were constructed from diffusion tensor imaging and tractography in physically

healthy unmedicated 18–25-year-olds (n=342, n=192 maltreated) and analyzed using graph theory. Amygdala activation to angry / fearful emotional faces was evaluated in a subsample (n=202).
Results: Maltreated individuals with or without psychopathology had sparse global networks with increased small-worldness and vulnerability to disruption (p=.005). Resilient maltreated individuals had reduced nodal efficiency (ability of a node to propagate information throughout the network) in the right amygdala (p<.02) and eight other regions. Brain network architecture in maltreated individuals showed a progressive increase in vulnerability up until 21-22 years of age. Sensitive period analyses indicated that amygdala activation to emotional faces versus shapes was predicted by physical maltreatment between 3-6 years (p<.002) and peer emotional abuse at 13 and 15 years (p=.003).
Conclusions: Psychopathology in maltreated individuals appears to arise from the combination of functional abnormalities in stress susceptible regions and a vulnerable network architecture that cannot effectively compensate for these abnormalities. Lessening the influence of specific nodes enables the network to effectively compensate providing a neurobiological substrate for resilience. Network vulnerability increases into early adulthood resulting in the progressive onset of symptoms in maltreated individuals with preexisting nodal abnormalities.
Supported By: R01 HD079484; R03 MH113077; RO1 DA-017846; R01 MH091391; ANS Research Foundation
Keywords: Maltreatment, Depression, Anxiety, Brain Networks, Resilience

241. Sensitive Periods of Stress and Adolescent Amygdala–Ventromedial Prefrontal Cortex Connectivity: A Longitudinal Investigation

Tiffany Ho[1], Kathryn Humphreys[2], Lucy King[1], Natalie Colich[3], Jaclyn Schwartz[1], Kyoko Ohashi[4], Martin Teicher[4], and Ian Gotlib[1]

[1]Stanford University, [2]Vanderbilt University, [3]University of Washington, [4]McLean Hospital

Background: Converging evidence from human and nonhuman animal studies indicate that early life stress (ELS) is associated with altered connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC), a stress-sensitive circuit that continues to develop throughout adolescence. It is unclear, however, whether there are specific ages during which ELS may have maximal impact on amygdala–vmPFC connectivity in adolescence.
Methods: We obtained information about timing and severity of ELS and performed diffusion-weighted MRI and resting-state fMRI with a community sample of adolescents at two timepoints (baseline: n=109, age 12.07±0.81 years; follow-up: n=89, age 14.04±0.92 years). Random forest regression with conditional inference trees identified ages at which stress severity was most predictive of structural and functional amygdala–vmPFC connectivity at each timepoint.
Results: Severity of stressors occurring at ages 4 and 6 were the most important predictors of structural amygdala–vmPFC connectivity at baseline and follow-up, respectively (all ps<0.02). Severity of stressors occurring at ages 5 and 7 were the most important predictors of functional amygdala–vmPFC connectivity at baseline and follow-up, respectively (all ps<0.03).
Conclusions: We used a longitudinal and multimodal approach to characterize the effects of timing of ELS on neurodevelopment. Sensitive periods for effects of ELS on amygdala–vmPFC connectivity spanned ages 4–7 but shifted from early to mid-adolescence, suggesting that duration of time since stress exposure may be a better predictor of connectivity than age of stress exposure. These findings have important implications for understanding how foundational early stressors may affect adolescent vulnerability to stress through neurodevelopmental processes.
Supported By: R37MH101495; K01MH117442
Keywords: Adolescents, Diffusion MRI, Resting-State fMRI, Early Life Stress, Amygdala

242. Longitudinal Cortical Markers of Persistence and Remission in Pediatric PTSD

Sara Heyn[1] and **Ryan Herringa**[2]

[1]University of Wisconsin - Madison, [2]University of Wisconsin School of Medicine & Public Health

Background: Pediatric PTSD is a complex psychiatric disorder that has previously been associated with atypical brain structure. However, the developmental course of these abnormalities and their role in illness course in youth remains unexplored.
Methods: We conducted a longitudinal magnetic resonance imaging (MRI) study of youth with PTSD at baseline (n=28) compared to typically developing non-traumatized youth (TD, n=27) (average age 14 years at baseline). All subjects underwent clinical assessments and MRI at both baseline and one-year follow-up. At follow-up, youth with PTSD were classified into two diagnostic groups, those with persistent (n=18) and remitted (n=10) PTSD. Cortical thickness (CT) and cortical surface area (CSA) estimates were extracted using cortical parcellation and submitted to mixed-effects models with experiment-wide FDR correction (pFDR<.05).
Results: At baseline, PTSD remitters and nonremitters did not differ on PTSD or anxiety symptom severity, while nonremitters exhibited greater depression severity (p<.05). A group main effect revealed sustained decreases in subparietal sulcus CSA in both remitters and nonremitters compared to TD youth. Persistent PTSD pathology was marked by aberrant longitudinal decreases in superior temporal gyrus, supramarginal gyrus, and superior parietal gyrus CSA. Conversely, remitters exhibited longitudinal increases in frontal pole CSA and ventromedial prefrontal cortex CT compared to both nonremitters and TD.
Conclusions: These neurodevelopmental correlates of illness course in pediatric PTSD provide new insights into the disease

pathology process and implicate prefrontal structural changes as part of an active recovery process. Further work is needed to elucidate whether these novel cortical markers serve as biomarkers and potential targets for protocol-based interventions.
Supported By: NIMH K08 MH100267, NARSAD Young Investigator Grant, AACAP Junior Investigator Award, University of Wisconsin ICTR Translational Pilot Grant Award UL1TR000427, University of Wisconsin Institute of Clinical and Translational TL1 Training Award TL1TR000429
Keywords: Pediatric PTSD, Cortical Trajectories, Structural MRI

243. Altered Fear Extinction Neural Circuitry in Trauma-Exposed Children

Hilary Marusak[1], Craig Peters[1], Allesandra Iadipaolo[1], Farrah Elrahal[1], and Christine Rabinak[1]

[1]Wayne State University

Background: Nearly 50% of individuals are exposed to childhood trauma and as a result these individuals are at increased risk for psychopathology, particularly anxiety disorders. However, the underlying neurobehavioral mechanisms through which childhood trauma confers heightened vulnerability to psychopathology are poorly understood. Given that anxiety disorders are characterized by a failure to appropriately inhibit or extinguish fear, the present study tests the effects of trauma on fear extinction and underlying neural circuitry in children.
Methods: 34 children (6-11 yrs) completed a novel two-day virtual reality fear extinction task. 50% of youth endorsed previous histories of interpersonal violence or medical-related trauma. On day one, participants underwent fear conditioning and extinction. Twenty-four hours later, participants completed a test of extinction recall during functional magnetic resonance imaging. Behavioral (approach/avoidance), physiological (skin conductance), and subjective (fear/contingency ratings) measures of conditioned fear were collected during each session. Posttraumatic stress symptoms (PTSS) were also measured.
Results: There was no effect of trauma on behavioral, physiological, or subjective measures of conditioned fear. However, relative to controls, trauma-exposed children demonstrated higher neural response during extinction recall in the dorsal anterior cingulate cortex (pFWE=0.002), a region associated with the return of fear. Youth with more PTSS showed more avoidant (i.e., side-to-side) movement during fear and extinction learning, reported higher fear during extinction learning, and demonstrated higher neural response during extinction recall in the insula (ps<0.05) - patterns associated with fear renewal.
Conclusions: Alterations in fear extinction neural circuitry may be a core mechanism through which childhood trauma confers heightened vulnerability to psychopathology.
Supported By: American Cancer Society
Keywords: Fear Extinction, Childhood Trauma, BOLD fMRI, Fear Conditioning, Children

SYMPOSIUM
Psychomotor Dysfunction in Major Depression: A Multimethod Symposium on This Understudied Aspect of Major Depression
3:00 p.m. - 5:00 p.m.
Chair: Stewart Shankman

244. Early Childhood Social Communication Motor Deficits in Youth at Clinical High-Risk for Psychosis: Associations With Functioning and Risk

Vijay Mittal[1] and Juston Osborn[1]

[1]Northwestern University

Background: Socio-communicative motor behaviors (e.g., gesture, imitation, pantomime) are an outward manifestation of the dynamic integration of several fundamental processes (e.g., motor function, social perception) that are essential for social development. Although childhood premorbid motor abnormalities are common in children that ultimately develop psychosis in adulthood, little is known about the early childhood socio-communicative motor behaviors in individuals at risk for psychotic disorders.
Methods: The present study utilized retrospective parent reports to examine early childhood socio-communicative motor deficits overall, as well as deficits in three distinct domains, complex movement (repetitive or complicated movements), gesture use (pointing, symbolic), and motor imitation (pantomime, imitation in group play) in the early childhood period (ages 4-5) of adolescent and young adult participants at clinical high-risk (CHR) for psychosis (n = 44) and matched healthy controls (n = 38). Associations between childhood socio-communicative motor behaviors and current functioning (social, academic/work) and symptoms (positive/negative) were examined.
Results: Compared to healthy controls, CHR individuals had greater deficits in total, $t(80) = 2.21$ $p < .05$, $d = .49$, and gesture, $t(80) = 2.03$, $p < .05$, $d = .45$, specific childhood socio-communicative motor behaviors. Early childhood deficits were associated with poor current adolescent/young-adult functioning and greater current negative symptom severity.
Conclusions: These findings suggest that early social developmental abnormalities may cascade and impact later adolescent and young adult function. Similar methodological approaches, focusing on early childhood, may also shed light on pathophysiology of non-psychotic affective disorders, as well as other forms of psychopathology that include a significant neurodevelopmental component.
Supported By: NIMH R01MH094650,
Keywords: Premorbid Adjustment, Developmental Psychopathology, Motor Skills, Prodrome, Clinical High Risk for Psychosis

245. White Matter Contributions to Motor Behavior Across Diagnoses

Sebastian Walther[1], Petra Viher[1], Tobias Bracht[1], and Katharina Stegmayer[1]

[1]University Hospital of Psychiatry, University of Bern

Background: Motor dysfunction is a central feature of psychotic and mood disorders. Abnormal motor behavior has been linked to alterations in the cerebral motor system, particularly cortical motor areas and basal ganglia. Here, we test the associations between white matter ultrastructure and motor retardation in two studies on catatonia and bipolar depression.
Methods: Study 1 included 13 patients with catatonia (SzCat), 33 schizophrenia patients without catatonia (Sz), and 46 healthy controls (HC). White matter alterations were tested with tract based spatial statistics (TBSS) of the diffusion tensor images. Catatonia was defined using the Bush Francis Catatonia Rating Scale.

Study 2 included 19 patients with bipolar depression (BD) and 19 matched controls (HC). Motor activity was quantified using wrist actigraphy for 24 hours. Bilateral corticospinal tract (CST) and interhemispheric connections between bilateral M1 and supplementary motor area (SMA) were reconstructed using diffusion tensor tractography.

We tested group differences (study 1) of fractional anisotropy (FA) or interactions of FA with activity levels (study 2).
Results: SzCat had higher FA values within the CST, internal capsule and other motor areas compared to Sz and HC ($p<.05$ FWE).

BD had higher FA within the left CST. Also, we noted a group x activity interaction on FA in the left CST ($F=5.5$ $p=.025$), with a positive correlation between FA and activity in BD ($r=.53$, $p=014$).
Conclusions: Reduced motor activity in both cohorts was linked to structural alterations within motor white matter tracts. Studying motor tract white matter could contribute to understanding motor retardation in depression.
Supported By: SNF grant Nr. 152619
Keywords: Diffusion Tensor Imaging (DTI), Catatonia, Depression, Actigraphy, White Matter Tractography

246. Synchrony and Asynchrony in Cerebellar-Basal Ganglia Functional Circuits: Implications for Behavior and Psychopathology

Jessica Bernard[1], Hanna Hausman[1], and T. Bryan Jackson[1]

[1]Texas A&M University

Background: While cortical networks have been well studied, our understanding of subcortical networks and subcortical network interactions, is limited. These networks however are of particular importance for our understanding of aging and psychopathology. Here, our goal was to delineate striatal-cerebellar functional connectivity patterns, differences in these patterns in young (YA) and older adults (OA), and their behavioral relevance.
Methods: fcMRI data was collected from 30 YA and 30 OA. We performed a targeted fcMRI analysis of the cerebellum and basal ganglia, and investigated whether age was related to differences in connectivity, and connectivity-behavior (balance and general cognitive function). For all statistics, we used permutation testing. Our results were corrected using an analysis-level FDR of $p<.005$ which takes into account the number or ROIs included in the network and corrects accordingly.
Results: YA striatal-cerebellar connectivity patterns supported semi-discrete circuits that may differentially subserve motor and cognitive performance. However, there was an age-related shift from synchrony to asynchrony in connectivity. Furthermore, connectivity strength was associated with behavior. Greater connectivity between Crus I and the inferior ventral striatum was correlated with general cognitive function, while connectivity between Crus I and superior ventral striatum was associated with balance confidence.
Conclusions: This represents the first investigation to map striatal-cerebellar connectivity in healthy humans, demonstrating a topographic organization in this subcortical network that is behaviorally relevant. The striatal-cerebellar circuit may provide a key scaffold for cortical control of motor behavior. Deficits in this circuit may contribute to the psychomotor disturbance seen in depression, and across psychopathology more broadly.
Supported By: None
Keywords: Resting State Functional Connectivity, Cerebellum, Basal Ganglia

247. BiAffect: Passive Monitoring of Psychomotor Activity in Mood Disorders Using Mobile Keystroke Kinematics

Alex Leow[1], Jonathan Stange[2], John Zulueta[2], Olusola Ajilore[2], Faraz Hussain[2], Andrea Piscitello[2], Kelly Ryan[3], Jennifer Duffecy[2], Scott Langenecker[4], Peter Nelson[2], and Melvin McInnis[3]

[1]University of Illinois at Chicago College of Medicine, [2]University of Illinois at Chicago, [3]University of Michigan, [4]University of Utah

Background: Abnormal psychomotor activity is a salient feature of mood disorders such as bipolar disorder, typified by psychomotor retardation during bipolar depression and psychomotor agitation during mixed and manic episodes. Passively evaluating changes in psychomotor functioning can prove to be a valuable monitoring tool to track symptom course. A pilot study was conducted to establish the feasibility of tracking typing metadata from smartphone keyboard usage to identify changes in psychomotor activity in people with bipolar disorder, and a full-scale study is currently underway.
Methods: The pilot study provided 19 participants with bipolar disorder the custom BiAffect keyboard on Android smartphones to track their keystroke entry metadata such as speed, accuracy, residence time, interkey delays, and corresponding accelerometer displacement—the lattermost two of which were used to quantify psychomotor activity. The main arm of the study is now proceeding on the iOS platform—http://www.biaffect.com

Results: We found that higher accelerometer displacements were positively correlated with both depression (P=.002) and mania (P=.003) scores, possibly because the subjects in the pilot sample displayed more mildly agitated, irritable, or mixed features forms of depression that are more closely associated with psychomotor agitation rather than retardation. Average interkey delay (P=.02) was only positively correlated with depression scores.
Conclusions: The pilot study demonstrated that passive, unobtrusive keystroke sensing alone can serve as an early warning alarm for deviations from normal mood and psychomotor functioning. With further data from the larger main study cohort, more sophisticated modeling can help distinguish deviations associated with manic episodes from those associated with depressive ones.
Supported By: New Venture Fund funded by the Robert Wood Johnson Foundation
Keywords: Bipolar Disorder, Mobile Health Application, Digital Phenotyping, Psychomotor Activity, Passive Sensing

SYMPOSIUM
Complementary Genetic- and Phenotype-First Approaches to Understanding Risk for Developmental Psychiatric Disorders

3:00 p.m. - 5:00 p.m.
Chair: Carrie Bearden
Co-Chair: David Glahn

248. Brain-Behavior Phenotypes in 22q11.2 Deletion Syndrome, Idiopathic Psychosis and a Mouse Model

Raquel Gur[1], Sunny Tang[1], Monica Calkins[1], David Roalf[1], Eric Schmitt[1], Douglas Coulter[1], and Ruben Gur[1]

[1]University of Pennsylvania

Background: The 22q11DS, associated with 25% risk for psychosis, can be a model for idiopathic psychosis. Prospective studies are needed to examine brain-behavior features and developmental course leading to psychosis. Probing brain circuitry in a mouse model can elucidate underlying deficits.
Methods: We examined psychotic features, neurocognitive and neuroimaging parameters in large samples of 22q11DS, idiopathic psychosis (PS) and typically developing (TD) youths. We assessed subthreshold psychosis; neurocognition, including social processing; and, in subsamples, multimodal neuroimaging. In df(h22q11)/+ mice and WT social function was measured on multiple tasks and virally transfected, neuron-specific DREADDs were used to induce or salvage deficits detected.
Results: Psychosis, in 22q11DS and idiopathic, is similar: negative symptoms preceding positive symptoms. Social processing predicts psychosis in both samples. MRI showed lower GM volume in cortical and subcortical regions, including hippocampus, the latter associated with psychotic symptoms. DTI showed aberrant WM microstructure across patient groups with specific deficits associated with psychosis features. A GWAS on hippocampal volumes in 22q11DS identified two globally significant loci, SEMA5B and ASTN2, with roles in neuronal migration. 22qdf(h22q11)/+ mice showed specific deficits in social discrimination, associated with hyperactive ventral CA1. Excitatory DREADDs in ventral CA1 recreated social discrimination deficits in WT mice while inhibitory DREADDs rescued social discrimination performance in deleted mice.
Conclusions: Psychotic features are common in 22q11DS with course resembling idiopathic PS and social processing deficits relate to psychosis. Aberrant brain parameters with temporolimbic abnormalities are associated with social deficits. The mouse model strengthens the link between aberrant limbic functioning and psychosis.
Supported By: NIH U01 MH087626 U01MH101719 U01 MH081902 R01MH107235
Keywords: Clinical High Risk For Psychosis, 22q11 Deletion Syndrome, Brain Imaging

249. Parallel Neuroimaging-Genomics of Sex Chromosome Aneuploidy in Humans and Mice

Armin Raznahan[1]

[1]NIMH NIH

Background: Sex chromosome aneuploidies (SCAs) increase risk for multiple neurodevelopmental morbidities. Better understanding this elevated risk requires clarifying (i) which brain systems are sensitive to changes in X- and Y-chromosome dosage, and (ii) which gene-sets are most likely to mediate effects of SCA on brain development.
Methods: We specify brain systems that are anatomically altered by varying X and Y-chromosome dosage through high-resolution structural neuroimaging in humans (n:300, karyotypes: XO, XX, XXX, XY, XXY, XYY, XXYY) and mice (n:90, karyotypes: XO, XX, XY, XXY) with assorted SCAs. We study candidate transcriptomic drivers of SCA phenotypes by (i) modelling gene dosage effects in beadarray measures of gene expression from human SCA lymphoblastoid cell-lines (LCLs), and (ii) merging maps of altered brain anatomy in SCA with publicly-available atlases of brain gene-expression.
Results: Both humans and mice show replicable evidence for regionally-specific SCA effects on brain anatomy, which involve systems that are critical for adaptive social functioning in each species. Our transcriptomic analyses in human SCA LCLs prioritize sex chromosome genes by dosage sensitivity and reveal order-of-magnitude differences amongst SCAs in the degree of autosomal gene dysregulation. In mice and humans, spatial gradients of neuroanatomical change as a function of SCA are preferentially aligned with expression gradients for specific X- and Y-linked genes in health.
Conclusions: Our multimodal cross-species approach provides a set of highly articulated and falsifiable hypotheses regarding specific pairings of gene-sets and brain-regions which may mediate the neurodevelopmental

impairments that can accompany altered X and Y chromosome dosage.
Supported By: NIMH Intramural Research Program
Keywords: Sex Chromosomes, Neuroimaging, Genetics

250. Gene Dosage Effects on Neurobehavioral Phenotypes and Development: Relevance to Idiopathic Neuropsychiatric Disorders

Carrie Bearden[1], Daqiang Sun[2], Amy Lin[3], Christopher Ching[4], Sebastien Jacquemont[5], Clara Moreau[5], and Julio Villalon[6]

[1]University of California Los Angeles, [2]Semel Institute for Neuroscience and Human Behavior; University of California-Los Angeles, [3]UCLA School of Medicine, Semel Institute for Neuroscience and Human Behavior, [4]UCLA; Imaging Genetics Center, USC, [5]University of Montreal, [6]Imaging Genetics Center, Keck School of Medicine, University of Southern California

Background: 22q11.2 and 16p11.2 genomic regions are dense with highly conserved brain-expressed genes. While the 22q11.2 deletion and 16p11.2 duplication confer greatly elevated risk for schizophrenia, the reciprocal 22q11.2 duplication and 16p11 deletion have lower risk of schizophrenia than the general population. However, both reciprocal copy number variants (CNVs) are associated with Intellectual Disability and Autism Spectrum Disorder (ASD). This 'reverse-genetics' approach can thus elucidate gene dosage effects that may differentiate risk versus protective factors for neuropsychiatric illness.
Methods: In a large, richly phenotyped cohort of 22q11.2 CNV carriers (107 deletion and 38 duplication carriers, 83 typically developing controls) we modeled effects of gene dosage on regional neuroanatomic variation, development, and neurobehavioral traits. Next, we investigated overlap of structural neuroanatomic patterns between 22q-deletion and idiopathic psychosis, as well as convergence between reciprocal 22q11.2 and 16p11.2 CNVs (n=78 deletion, 71 duplication).
Results: Cortical thickness in frontal, inferior parietal and insular cortex shows a significant group x age interaction across 22q11.2 CNVs (all $q<.05$), with earlier age-related thinning in 22q-duplication. Notably, 22q-deletion with psychosis also show significant fronto-temporal cortical thinning, convergent with idiopathic schizophrenia (n=4000). Finally, reciprocal CNVs at 22q11.2 and 16p11.2 show overlapping alterations of the insula (Cohen's d=.48) and inferior frontal gyrus (Cohen's d=.77).
Conclusions: Results indicate differential effects of 22q11.2 CNVs on cortical trajectories. Overlap between 22q11.2 and 16p11.2 suggests common gene dosage effects on social-cognitive brain circuitry across 'neuropsychiatric' CNVs. Neuroanatomic convergence between idiopathic psychosis and 22q-psychosis suggests highly penetrant CNV's can inform our understanding of broader psychiatric disease risk.

Supported By: NIMH R01MH085953; NIH/NIBIB U54EB020403; Simons Foundation Explorer Award
Keywords: Neurodevelopmental Trajectories, Copy Number Variant, Structural Brain Imaging, Psychosis, Autism Spectrum Disorder

251. Measuring and Estimating the Effects of Rare Variants, Genome-Wide, on Cognition

Sebastien Jacquemont[1], Catherine Schramm[1], Antoine Main[2], Aurélie Labbe[2], Tomas Paus[3], Zdenka Pausova[4], Thomas Bourgeron[5], Gunter Schumann[6], Patricia Conrod[1], Sherif Karama[7], Ian Deary[8], Celia Greenwood[9], and Guillaume Huguet[1]

[1]University of Montreal, [2]HEC Business School, [3]Rotman Research Institute, [4]The Hospital for Sick Children, University of Toronto, [5]Institut Pasteur, [6]King's College, London, [7]McGill University, [8]University of Edinburgh, [9]Lady Davis Research Institute, McGill University

Background: With the implementation of genomic analyses in medical diagnostics, variants contributing significantly to disease are identified in over 10% of children with Neurodevelopmental disorders, but the vast majority of these variants are ultra-rare and remain undocumented. The aim of this work is to measure and predict the effects of rare variants on cognition.
Methods: We studied unselected populations and individuals with neurodevelopmental disorders (n>24000). Cognition was measured by IQ or g-factor. Structural and single nucleotide variants were called using genotyping and sequencing data. Genomic scores capturing the nature and function of genes affected by genomic variants were included as variables in linear and nonlinear models to explain the effects of rare variants on cognition. Model validation was performed using intraclass correlation that compared IQ estimated by the model with empirical data.
Results: Among all annotations, haploinsufficiency scores best explain the association of any deletions with PIQ with a decrease of 2.7 points per unit of the probability of being "loss-of-function intolerant" in both unselected and disease cohorts ($P < 10e-10$). Results are consistent across cohorts, unaffected by sensitivity analyses and also apply to single nucleotide variants. There is >0.75 concordance between the effect size on IQ-loss estimated by our model and IQ-loss calculated in previous studies of 15 recurrent deletions.
Conclusions: Models trained on variants in the general population can reliably estimate the effect size of pathogenic deletions and suggest an omnigenic model for cognition. This is a new approach to study undocumented variants too rare to perform individual association studies.
Supported By: CIHR, CFREF, Brain Canada
Keywords: Ultra-Rare Variants, Cognition, Omnigenic

Oral Abstracts

Thursday, May 16, 2019

RISING STAR SESSION: LIFESPAN & DIAGNOSIS 3:00 p.m. - 5:00 p.m.

O1. Dissociating PTSD and Depression Structural Neuroimaging Profiles in Veterans With Mild Traumatic Brain Injury

Benjamin Wade[1], David Tate[2], Carmen Velez[3], Randall Scheibel[4], Heather Belanger[5], Carlos Jaramillo[6], Blessen Eapen[7], Mary Newsome[4], Brian Taylor[8], Sidney Hinds[9], Gerald York[10], Tracy Abildskov[11], Erin Bigler[11], and Elisabeth Wilde[12]

[1]University of California, Los Angeles, [2]University of Utah School of Medicine, [3]University of Missouri St. Louis, [4]Michael E. DeBakey Veterans Affairs Medical Center, [5]James A. Haley Veterans Hospital, [6]C. Kenneth and Dianne Wright Center for Clinical and Translational Research, Virginia Commonwealth University, [7]VA Greater Los Angeles Health Care System, UCLA, [8]Virginia Commonwealth University, [9]Department of Defense/United States Army Medical Research and Materiel Command, [10]Alaska Radiology Associates, [11]Brigham Young University, [12]University of Utah

Background: Post-traumatic stress disorder (PTSD) and major depression (MD) are highly comorbid in Veteran populations with mild traumatic brain injury (mTBI). Disentangling contributions of PTSD and MD aberrant neuroimaging profiles would inform targeted treatments. We investigate whether PTSD and MD profiles are dissociable in structural neuroimaging measures within the large, multi-site cohort of Veterans from the Chronic Effects of Neurotrauma Consortium (CENC).
Methods: Veterans (n=205; age=39.53 years +/- 10.67; 31 Female) with a history of mTBI from four sites were included. The Patient Health Questionnaire-9 (PHQ-9) and PTSD Checklist for DSM-5 (PCL-5) assessed MD and PTSD symptoms. We used FreeSurfer v6.0 and the ENIMGA DTI pipeline to estimate cortical thickness, subcortical volume, and fractional anisotropy (FA) for multiple regions of interest. Bootstrapped mediation analyses assessed whether PTSD symptoms mediated associations between MD and imaging measures and vice versa. Sub-dimensions of the PCL recovered via exploratory factor analysis were also evaluated as mediators.
Results: The total PCL score significantly mediated the negative association between the PHQ and right hippocampal volume ($p<0.05$). Ruminative PCL symptoms significantly mediated negative associations between the PHQ and the right hippocampus and amygdala (both $p<0.05$). Symptoms of negativity bias captured by the PCL significantly mediated the positive association between the PHQ and inferior fronto-occipital fasciculus (IFO) FA ($p<0.05$).
Conclusions: Our findings corroborate that both PTSD and MD influence brain structure in Veterans with mTBI in ways that may be dissociable in clinically meaningful ways; however, the influence of PTSD is more dominant particularly in limbic structures.
Supported By: NARSAD Young Investigator Grant; DoD; VA
Keywords: PTSD - Posttraumatic Stress Disorder, Major Depressive Disorder (MDD), Mild Traumatic Brain Injury, Multimodal Imaging, Factor Analysis

O2. A Mindfulness Interoception Task Engages Distributed Brain Networks That are Dysregulated in Posttraumatic Stress Disorder (PTSD)

Anthony King[1], Chandra Sripada[1], Mike Angstadt[1], Maria Muzik[1], and Israel Liberzon[2]

[1]University of Michigan, [2]Texas A&M Health Science Center

Background: Mindfulness, involving present-moment attention to bodily sensations, has been incorporated into psychotherapies for psychiatric disorders, and is associated with acute and enduring alterations in cross-network connectivity between DMN and attention networks. PTSD has also been associated with DMN-attention network dysregulation.
Methods: Male military veterans with PTSD (N = 32) deployed to Iraq or Afghanistan and healthy age-and-gender-matched community healthy controls (N = 20) underwent fMRI to assess resting-state functional connectivity (rsFC). Connectomes were estimated during unconstrained resting state and during a mindful interoception task; joint independent components analysis (jICA) examined shared and unique aspects of mindfulness- and PTSD-associated connectivity patterns.
Results: Compared to unconstrained rest, mindfulness showed decreased connectivity within DMN, and increased connectivity (decreased anti-correlation) between anterior DMN and DAN, and FPCN and DAN ($p = 7.0 \times 10\text{-}6$). PTSD patients had significantly decreased expression of this same connectivity component during the mindfulness condition compared to healthy volunteers ($p=.009$), and level of change in this component from rest

to mindfulness was correlated with PTSD avoidant symptoms (p=.007).
Conclusions: In this multivariate, whole-brain connectomic analysis, we demonstrate overlap between brain networks engaged during a mindfulness task and brain networks exhibiting baseline abnormalities in PTSD. In particular, both participants in a mindful state and PTSD participants at rest exhibited increased connectivity between DMN, DAN, and FPCN networks, suggestive of increased interoceptive awareness and effortful regulation of attention. It is possible the therapeutic benefits of mindfulness in PTSD are produced by re-engagement of the same core neural circuits that are dysregulated in the disorder.
Supported By: NIMH K23 MH112852-01 to AK
Keywords: PTSD - Posttraumatic Stress Disorder, Mindfulness Intervention, Connectomics, Avoidance

O3. Genetic Variation in the Oxytocin System Impacts Infants' Prefrontal Brain Asymmetry Responses to Emotional Faces

Kathleen Krol[1], Nauder Namaky[1], and Tobias Grossmann[1]

[1]University of Virginia

Background: Experiencing and viewing emotional states has been linked to systematic changes in frontal brain asymmetry responses. In infants and adults, greater left frontal asymmetry indexes approach tendencies, whereas greater right frontal asymmetry reflects withdrawal tendencies. However, little is known about what factors contribute to individual variability in emotional brain processes, especially during infancy. Previous research has identified a single-nucleotide polymorphism on the CD38 gene (rs3796863) linked to autism spectrum disorder, differences in oxytocin release, and attention to emotional faces in young infants. We therefore examined whether CD38 impacts prefrontal brain asymmetry responses to emotional faces.
Methods: 77 11-month-old infants viewed angry and happy faces with direct and averted gaze while functional near-infrared spectroscopy (fNIRS) was recorded. Frontal asymmetry scores were calculated by assessing oxygenated hemoglobin from the dorsolateral prefrontal cortex (dlPFC). CC genotype infants, with a presumably higher risk for ASD and reduced levels of oxytocin, were compared to CA/AA genotype infants.
Results: Our analysis revealed that prefrontal brain asymmetry patterns evoked by emotional direct gaze faces significantly differed as a function of CD38 genotype (p=0.034). Specifically, while CA/AA genotype infants displayed the expected discrimination between emotional faces with greater left lateralization to direct gaze happy faces (indexing approach) and greater right lateralization to direct gaze angry faces (indexing withdrawal), CC genotype infants' prefrontal brain asymmetry responses did not discriminate between emotional faces.
Conclusions: Our findings suggest that already in infancy, variability in prefrontal brain function during emotion processing is impacted by the endogenous oxytocin system.
Supported By: Max Planck Society
Keywords: Emotion Perception, Infancy, fNIRS, Oxytocin, Brain Asymmetry

O4. Regulation of Fear Expression by Activity-Dependent BDNF in Direct Hippocampal-To-Prelimbic Projections

Henry Hallock[1], Henry Quillian[1], Yishan Mai[1], Gregory Hamersky[1], Huei-Ying Chen[1], Brady Maher[1], and Keri Martinowich[1]

[1]The Lieber Institute for Brain Development

Background: Fear dysregulation is prevalent in several neuropsychiatric disorders. Although some molecules, including brain-derived neurotrophic factor (BDNF), have been identified as causally impacting fear expression, how they differentially impact defined neuronal populations to produce fear-related behavior remains unknown.
Methods: We used retrograde tracers to tag hippocampal neurons with projections to the prelimbic cortex in wild-type (w/t) mice and mice with impaired activity-dependent BDNF signaling (-e4 mice). Single molecule fluorescence in situ and immunohistochemistry was used to assess differential gene expression in these cells while chemogenetic stimulation was used to manipulate function.
Results: More projectors co-expressed cFos in w/t mice that received a shock during conditioning vs. mice that received no shock ($t(8) = 2.82$, $p = 0.01$). −e4 mice froze more following conditioning compared to w/t mice ($t(7) = 2.89$, $p = 0.01$). More neurons expressing both SLC17A7 and Ntrk2 RNA co-expressed fear-related Fos in the prelimbic cortex in −e4 mice; the opposite phenotype was observed in the infralimbic cortex ($F(1,47) = 6.45$, $p = 0.01$, brain region x genotype interaction). Projector excitation in w/t mice decreased freezing ($t(26) = 2.92$, $p < 0.01$), while projector excitation in −e4 mice increased freezing ($t(8) = 2.36$, $p = 0.03$). BDNF over-expression in −e4 projectors reduced freezing ($t(4) = 2.48$, $p = 0.04$) and also reversed the molecular phenotype observed in the prelimbic, but not infralimbic, cortex ($F(1,44) = 4.47$, $p = 0.04$).
Conclusions: Our results suggest that BDNF signaling in prelimbic-projecting hippocampal neurons modulates activity in excitatory prelimbic neurons to regulate fear expression in mice.
Supported By: NIMH R01 MH1055929
Keywords: BDNF, Prelimbic Cortex, Fear Expression, Hippocampal Neuroplasticity

O5. Classification of Schizophrenia Using Machine Learning With Multimodal Markers

Linda Antonucci[1], Giulio Pergola[2], Dominic Dwyer[1], Silvia Torretta[2], Raffaella Romano[2], Barbara Gelao[2], Nora Penzel[1], Antonio Rampino[2], Rita Masellis[2], Grazia Caforio[2], Giuseppe Blasi[2], Nikolaos Koutsouleris[1], and Alessandro Bertolino[2]

[1]Ludwig Maximilian University, [2]University of Bari Aldo Moro

Background: Schizophrenia risk is associated with genetic variation and with early life environmental factors. Moreover, cognitive abnormalities are key features of this disorder. Our aim was to use multimodal machine learning to assess the performance of an ensemble of genetic, environmental and cognitive variables on schizophrenia classification.

Methods: 337 healthy controls (HC) and 103 schizophrenia patients (SCZ) underwent a full neuropsychological evaluation, a broad environmental assessment and a genetic risk estimation with polygenic risk scores computation from the Psychiatric Genomics Consortium (PGC2) study. Scores from these three data modalities entered a Support Vector Machine algorithm aimed at classifying HC vs. SCZ. Specifically, we applied decision-based data fusion strategies to integrate the individual predictions of each modality in a nested cross-validation framework.

Results: Results revealed that cognitive features classified SCZ with the highest Balanced Accuracy (BAC, 88.7%) and that the most selected cognitive indices were intelligence quotient and attention. Environmental features classified SCZ with a 65.1% BAC, and the most predictive indices were parental socio-economic status and presence of developmental anomalies. Genetic features discriminated HC from SCZ only at 55.5% BAC. Late fusion combining decision scores from individual modalities classified SCZ with a 77.5% BAC.

Conclusions: Our results suggest that an ensemble of cognitive, environmental and genetic features can classify SCZ with high accuracy and offer insights on cognitive and environmental factors that can be targeted in early identification programs. However, the near chance-level classification ability of the genetic modality alone calls for the implementation of more complex models of interaction between multiple risk factors.

Supported By: "Ricerca Finalizzata" grant (number: PE-2011-02347951), Italy

Keywords: Schizophrenia, Personalized Medicine, Environmental Risk Factors, Cognitive Performance, Polygenic Risk Score

O6. It Still Hurts – How Childhood Maltreatment Hampers Social Distance and Affective Touch in Adulthood

Ayline Maier[1], Caroline Gieling[1], Luca Heinen-Ludwig[1], Johannes Schulz[1], Vlad Stefan[1], Onur Güntürkün[2], Benjamin Becker[3], Rene Hurlemann[4], and **Dirk Scheele**[1]

[1]University of Bonn, [2]Ruhr-University of Bochum, [3]University of Electronic Science and Technology of China, [4]University of Bonn Medical Center

Background: Childhood maltreatment (CM) is a major risk factor for psychopathology, with a particularly strong impact on mental disorders associated with relational problems. A critical unanswered question is how CM may affect social bonding later in life. We hypothesized that CM alters social interactions by changing the preferred interpersonal distance and the processing of affective touch.

Methods: 92 adult, non-medicated subjects (64 females) with low, medium and high degrees of CM were first tested with a social distance paradigm and subsequently underwent a social touch functional magnetic resonance imaging task during which they rated the perceived comfort of slow (comfortable, C-tactile (CT) optimal; 5cm/s) and fast touch (less comfortable, non-CT-optimal; 20cm/s).

Results: Participants with high CM loads preferred a larger social distance and experienced fast touch as less comforting compared to subjects with low CM severity. On the neural level, these findings were paralleled by heightened responses to fast touch in the right somatosensory and insular cortex in high CM subjects. Furthermore, high CM subjects exhibited decreased activation to slow touch in the right hippocampus. This response pattern was found to be independent of CM-associated region-specific reductions in grey matter volume.

Conclusions: Our findings suggest that higher CM loads are associated with a state of hypervigilance characterized by a preference for larger social distance and discomfort of fast touch manifested in a sensory cortical hyper-reactivity and a limbic CT-optimal hypo-activation. This dysregulation may explain why individuals with severe CM often suffer from difficulties in establishing and maintaining close social bonds in adulthood.

Keywords: Childhood Maltreatment, Social Touch, BOLD fMRI, Hypervigilance, Social Distance

Friday, May 17, 2019

ORAL SESSION: DEVELOPMENT, EARLY PSYCHOPATHOLOGY, AND SUBSTANCE USE 12:30 p.m. - 2:15 p.m.

O7. Deep Transcranial Magnetic Stimulation Over the Medial Prefrontal and Anterior Cingulate Cortices Alters Brain Connectivity and Reduces Relapse to Alcohol Use

Maayan Harel[1], Noam Barnea-Ygael[1], Hadar Shalev[1], Itay Besser[1], Moti Salti[1], Robin Kampe[2], Markus Heilig[2], and **Abraham Zangen**[1]

[1]Ben Gurion University, [2]Linköping University

Background: Alcohol Use Disorder (AUD) is a highly prevalent disorder with limited treatment options, partially due to limited understanding of its basic neuropathology. Nevertheless, abnormal neuronal activity in the medial prefrontal and anterior cingulate cortices (mPFC and ACC, respectively) have been suggested to play central roles in alcohol craving, reduced inhibitory control and relapse to alcohol use in AUD. We attempt to reduce craving levels and relapse rates in short-term abstinent AUD subjects using deep transcranial magnetic stimulation (dTMS) over the mPFC and ACC following daily provocations of alcohol craving.
Methods: In this double-blind, sham-controlled, randomized clinical trial we evaluate clinical and neurobiological effects induced by high-frequency (10Hz) dTMS over 3 weeks of treatment and 12 weeks of follow-up. Clinical response is determined using self-report levels of craving and alcohol consumption validated by urine measures, while fMRI is employed to identify alterations in brain connectivity.
Results: Interim results comparing the real (n=16) and sham (n=14) treatment groups during follow up indicate significantly reduced craving levels and relapse rates (measured based on percentage of binge alcohol drinking days) in the real group relative to the sham group. In addition, real treatment prevented an increase in rest connectivity between the ACC and the medial frontal cortex during the 3 weeks of treatment. Such increased connectivity was suggested to correlate with cue induced craving and relapse rates.
Conclusions: dTMS treatment appears to reduce craving levels and relapse rates in AUD, and to modify resting state connectivity in relevant brain areas.
Supported By: The study is supported by Horizon 2020 program research grant SyBil-AA (668863)
Keywords: Deep TMS, Alcohol Use Disorder, fMRI, Functional Connectivity, Anterior Cingulate

O8. Computational Phenotyping in Borderline Personality Using a Role-Based Social Hierarchy Probe

Iris Vilares[1], Tobias Nolte[2], Andreas Hula[3], Zhuoya Cui[4], Peter Fonagy[5], Lusha Zhu[6], Pearl Chiu[7], Brooks King-Casas[7], Terry Lohrenz[7], Peter Dayan[8], and Read Montague[9]

[1]University of Minnesota, [2]University College of London; Anna Freud National Centre for Children and Families, [3]Austrian Institute of Technology, [4]Virginia Tech Graduate Program in Translational Biology, Medicine, and Health, [5]University College London, [6]Peking University, [7]Virginia Tech Carilion Research Institute, [8]Max Planck Institute Tübingen, [9]University College of London; Virginia Tech Carilion Research Institute

Background: Dysfunction in social interactions is a hallmark of several psychiatric disorders. There has thus been a substantial recent interest in characterizing aberrant and normal social decision-making using games from experimental economics. However, these studies have so far covered only a small range of social interactions. One important omission has been social dominance. A maladaptive reaction to social dominance may be particularly relevant for neuropsychiatric disorders such as borderline personality disorder (BPD) in which there is trouble sustaining social relations. Here, we examined how people with BPD behave in social interactions involving differences in social dominance.
Methods: Participants (169 controls and 313 BPDs) played a multi-round Social Hierarchy game where money could be used to increase (or maintain) social status. We then fit computational models to the recorded behavior.
Results: We found no difference between patients with BPD and Controls in the amount spent to become or stay dominant, the challenge rate, or the number of rounds in the dominant position ($p>0.05$). However, and contrary to expectations, we found that BPDs in the dominant position offered higher initial transfers to the other player compared to controls ($p=0.03$). In the computational model, this was associated with a higher positive inequity aversion parameter. Furthermore, BPD patients challenged more when given an unfair transfer ($p=0.02$).
Conclusions: Our results suggest that BPD patients and Controls value social dominance similarly but that BPD patients may be more inequity averse. We offer specific computational parameters that can be used to quantitatively characterize and phenotype each individual.
Supported By: Wellcome Trust Principal Research Fellowship (to PRM); PD was funded by the Max Planck Society
Keywords: Computational Psychiatry, Borderline Personality Disorder, Neuroeconomics

O9. Delineating and Validating Major Dimensions of Psychopathology in the Adolescent Brain Cognitive Development (ABCD) Study

Giorgia Michelini[1], Deanna Barch[2], and Roman Kotov[1]

[1]Stony Brook University, [2]Washington University

Background: Major dimensions of psychopathology have been identified in children and adults, but the studies disagree on their number. We aimed to delineate the hierarchy of childhood and adult psychopathology and validate it against clinically-relevant risk factors and outcomes.

Methods: Participants were 4,524 9- and 10-year-old children and their parents from the Adolescent Brain Cognitive Development (ABCD) study. Exploratory factor analyses evaluated items from the parent-reported Child Behavior Checklist and Adult Self-Report. We compared the ability of models with different numbers of factors to account for association between childhood and parent psychopathology, and predict children's service utilization and social, educational and cognitive functioning.
Results: Five factors emerged in children: internalizing, somatoform, detachment, neurodevelopmental, and externalizing. Adult factors were similar, but externalizing behaviors separated into disinhibited and antagonistic factors. We also considered models with fewer factors, through unidimensional general psychopathology ('p') factor model. Intergenerational analyses revealed substantial familiality between childhood and parent p-factors ($r=0.60$, $p<0.001$), and smaller but significant associations between lower-level convergent dimensions when controlling for p-factors (mean $r=0.14$, $p<0.05$). A model with childhood p-factor alone explained mental health services utilization (R-squared=0.13, $p<0.001$), but the 5-factor model provided incremental validity to explain social, educational and cognitive functioning (R-squared=0.03-0.20, $p<0.001$).
Conclusions: In this first investigation into the hierarchical structure of psychopathology in the ABCD study, we delineate major dimensions of psychopathology that account for a range of clinically-relevant validators, paving the way for future research in this sample. These findings support a hierarchical approach to nosology and hold important implications for classification of psychopathology.
Supported By: NIMH, NIDA
Keywords: Psychopathology, Symptom Dimensions, Functional Outcome, Familiality

O10. How Dopamine Receptor Binding Affects Human Brain Networks in Real Time: Preliminary Evidence From Simultaneous PET-fMRI With a Drug Challenge

Peter Manza[1], Dardo Tomasi[1], Yuan Kai[1], Ehsan Shokri-Kojori[1], Wiers Corinde[1], Macfarland Minoo[1], Jamie Burns[1], Danielle Kroll[1], Dana Feldman[1], Christopher Kure Liu[1], Gene-Jack Wang[1], and Nora Volkow[1]

[1]National Institute on Alcohol Abuse & Alcoholism, National Institutes of Health

Background: The therapeutic effects of drugs such as methylphenidate (MPH), a stimulant medication used for treatment of attention-deficit hyperactivity disorder (ADHD), result from increases in dopaminergic/noradrenergic signaling and their downstream effects on functional brain networks. However, imaging methods used to probe these processes in humans, including PET and fMRI, each have distinct limitations in the type of information they can provide. Simultaneous PET-fMRI has the potential to overcome the limitations of each method and give novel insights underlying MPH's therapeutic efficacy.
Methods: Five healthy adults completed three sessions of simultaneous PET-fMRI with [11-C]Raclopride to assess Dopamine D2/3 receptor availability in the following conditions: 1) oral MPH (60 mg) and IV placebo, 2) oral placebo and IV MPH (0.25 mg/kg) and 3) oral placebo and IV placebo, in a counterbalanced, double-blind design. We correlated MPH-induced dynamic changes in striatal receptor availability ("dopamine release") with dynamic changes in striatal functional connectivity.
Results: MPH increased subjective ratings of "feeling high" and decreased striatal receptor availability (indicating dopamine release) and these effects were greater for IV vs. oral MPH, replicating prior work. Dynamic changes in striatal dopamine release were associated with changes in striatal functional connectivity depending on baseline connectivity strength: regions with high connectivity at baseline showed further increases in connectivity with increases in striatal dopamine release, and vice versa (Caudate:$R2(48)=.23, p<.01$; Putamen:$R2(48)=.24, p<.01$).
Conclusions: Striatal dopamine release altered brain network organization such that it enhanced the differences in connectivity between resting networks. These effects may have relevance for the therapeutic efficacy of stimulant drugs in neuropsychiatric conditions.
Supported By: National Institute on Alcohol Abuse and Alcoholism (Y1AA-3009)
Keywords: Catecholamines, Resting State Functional Connectivity, Positron Emission Tomography, Stimulants, Attention Deficit Hyperactivity Disorder

O11. What Do We Know About the Power of Our Developmental Structural Neuroimaging Studies?

David Kennedy[1], Steven Hodge[1], and J.B. Poline[2]

[1]U. Massachusetts Medical School, [2]Montreal Neurological Institute and Hospital

Background: Understanding the details of brain development is critically important to understand the developmental processes that underlie neurodevelopmental disabilities. Numerous large-scale neuroimaging studies have been and will be performed. In this study, we used the neuroimaging data from the Pediatric Imaging, Neurocognition and Genetics (PING) cohort to set a baseline estimation of effect sizes in order to set expectations for future studies.
Methods: We based this analysis on the FreeSurfer-based structural data available from the PING portal: total N =1239 (644 males/595 females), aged 3-20 years. We model the volume of each structure as a function of: Age, Gender, site, SES, genetic ancestry factors, and Intracranial Volume (ICV). We create an ensemble of models using each permutation of the model factors. We used total hippocampal volume as an example and report the observed model results for sex effect across the unique model combinations of these factors.
Results: We see a dichotomy between the models that do and do not include ICV, which greatly reduces the magnitude of the sex effect from 650 to 220ml (medians). All sex effects are significant, though the models that include ICV show an increase in R-squared from 0.21 to 0.40 (medians), indicating a better fit to the data.

Conclusions: These results confirm that statistical model selection is key to any interpretation of results in the literature and that model selection results should be a key part of scientific reports. We recommend that specific tools are built for this while avoiding p-hacking.
Supported By: NIH-NIBIB P41 EB019936
Keywords: Neurodevelopment, Neuroanatomy, Biostatistics, Power, Structural Neuroimaging

O12. Neurofunctional Processing Changes With Increasing Abstinence in Methamphetamine Addiction: A Cue-Reactivity fMRI Study

Shubao Chen[1], Shucai Huang[2], Cheng Yang[3], Weifu Cai[3], Hongxian Chen[3], Wei Hao[3], Tieqiao Liu[3], Patrick Worhunsky[4], Xuyi Wang[3], and Marc Potenza[4]

[1]The Second Xiangya Hospital, Central South University; Yale School of Medicine, [2]The Fourth People's Hospital of Wuhu, [3]The Second Xiangya Hospital, Central South University; Hunan Key Laboratory of Psychiatry and Mental Health, Chinese National Clinical Research Center on Mental Disorders (Xiangya), Chinese National Technology Institute on Mental Disorders, Mental Health Institute of the Second Xiangya Hospital, Central South University, [4]Yale School of Medicine

Background: Although MA-induced neurofunctional changes have been investigated, few studies have focused on comparing neural responses to sexual and drug cues with respect to shorter- or longer-term abstinence.
Methods: Forty-nine subjects with shorter-term MA abstinence (STMA) (drug abstinence duration less than 3 months), 50 with longer-term MA abstinence (LTMA) (drug abstinence duration more than 16 months) and 47 non-drug-using healthy control subjects (HCs) participated. A functional magnetic resonance imaging (fMRI) cue-reactivity task consisting of three different kinds of cues (neutral, MA, and sexual) was used.
Results: In summary, STMA subjects were younger than HCs ($p=0.006$) and had the highest education ($p<0.001$); HCs had higher education than LTMA subjects ($p=0.027$). Behaviorally, both STMA and LTMA showed higher impulsivity than HCs ($p<0.001$). A group-by-condition interaction and post-hoc contrasts indicated that LTMA subjects showed greater sexual-related positive activity in the left superior frontal cortex (SFC) relative to HCs ($pFWE<0.05$). Within group, in left SFC, STMA showed greater sexual-related positive activity relative to neutral-related negative activity, LTMA showed greater sexual-related positive activity relative to neutral- and MA-related negative activity. The MA- and sexual-related activity in the left SFC was negatively correlated with impulsivity in STMA ($pcorrected<0.05$), but not in LTMA or HC groups.
Conclusions: The findings suggest that duration of abstinence may impact responses to sexual cues in individuals with MA. These findings may have clinical relevance given the use of MA for sexual purposes and the relevance of responses to natural versus drug rewards for addiction recovery.
Supported By: Natural Science Foundation of China (81571307) to Xuyi Wang, Natural Science Foundation of China (81371465) to Tieqiao Liu, Fundamental Research Founds for the Central Universities of Central South University (2016zzts148) to Shubao Chen, National Basic Research Program of China (2015CB553504) to Wei Hao and National Research Program of China (2016YFC0800908-Z02) to Hongxian Chen.
Keywords: Methamphetamine Dependence, fMRI, Drug Abstinence, Cue-Reactivity, Superior Frontal Cortex

O13. DNA Methylation Biomarkers Predict Antenatal and Postpartum Depression and Associate With Postpartum Changes in Resting State Functional Connectivity

Zachary Kaminsky[1], Lauren Osborne[2], Alicia Smith[3], Claudia Buss[4], and Jennifer Payne[2]

[1]The Royal's Institute of Mental Health Research, [2]Johns Hopkins University School of Medicine, [3]Emory University School of Medicine, [4]Charite University Medical Center Berlin

Background: Previous work out of our laboratory has identified DNA methylation variation in the TTC9B and HP1BP3 genes that is prospectively predictive of the development of postpartum depression (PPD) with 80% accuracy when evaluated during pregnancy. The primary objective was to evaluate the efficacy of the PPD epigenetic biomarker models as a function of timing of antenatal blood draws and the presence or absence of a previous psychiatric diagnosis in multiple datasets.
Methods: TTC9B and HP1BP3 DNA methylation was evaluated using sodium bisulfite pyrosequencing in 1st, 2nd, and 3rd trimester from three prospective PPD cohorts (N=53,113, 68).
Results: 1st trimester biomarkers predicted 3rd trimester Edinburgh Postnatal Depression Scale (EPDS) score > 13. A support vector machine model detected cases with an Edinburgh Postnatal Depression Scale (EPDS) score > 13 with an AUC of 0.77 (95% CI: 0.64-0.77) from 3rd trimester blood, which was replicated in a second independent cohort with an AUC of 0.84, (95% CI: 0.72-0.97). TTC9B was associated with changes in resting state functional connectivity between 2 to 6 weeks postpartum in distinct brain regions and interacted with the change in serum estradiol levels from 3rd trimester to postpartum to mediate week 6 EPDS scores (beta= 2.8x10-4 + 1x10-4, $F=3.227$, $df=3/43$, $p=0.0072$).
Conclusions: Our predictive models continue to accurately predict depression in the postpartum period in a prospective, replicable, and accurate manner, suggesting that they have the potential to be developed into a clinical tool enabling the identification of women at future risk to PPD.
Supported By: R01MH104262, R01MH112704
Keywords: Postpartum Depression, TTC9B, HP1BP3, Epigenetics, Biomarkers

RISING STAR SESSION: PRECISION MEDICINE
3:00 p.m. - 5:00 p.m.

O14. Cerebral Blood Perfusion Predicts Response to Antidepressant Treatment in Major Depressive Disorder

Crystal Cooper[1], Cherise Chin Fatt[1], Manish Jha[2], Gregory Fonzo[3], Bruce Grannemann[1], Thomas Carmody[1], Aasia Ali[1], Sina Aslan[1], Jorge Almeida[4], Thilo Deckersbach[5], Maurizio Fava[5], Benji Kurian[1], Patrick McGrath[6], Melvin McInnis[7], Ramin Parsey[8], Myrna Weissman[9], Mary Phillips[10], Hanzhang Lu[11], Amit Etkin[3], and Madhukar Trivedi[1]

[1]University of Texas Southwestern Medical Center, [2]Mount Sinai School of Medicine, [3]Stanford University, [4]Dell Medical School - University of Texas at Austin, [5]Massachusetts General Hospital, [6]New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, [7]University of Michigan, [8]Stony Brook University School of Medicine, [9]College of Physicians and Surgeons Columbia University, [10]University of Pittsburgh, [11]Johns Hopkins University

Background: Major Depressive Disorder (MDD) has been associated with brain-related changes. However, biomarkers have yet to be refined. Cerebral blood perfusion, as measured by Arterial Spin Labeling (ASL), has been used to understand brain function, detect differences in MDD, and could serve as a marker for treatment selection. The current investigation aimed to identify perfusion predictors of treatment response.
Methods: Participants underwent pre-treatment neuroimaging, including ASL, as part of the EMBARC trial, a multisite randomized placebo-controlled trial of antidepressant response in MDD. Participants received either sertraline (n=114) or placebo (n=117). Response was monitored for 8-weeks. To identify brain regions where perfusion levels differentially predicted (moderated) treatment response, a whole-brain, voxel-wise linear mixed effects model was conducted. Composite moderator analysis combined the effect of individual perfusion moderators and identified which contribute to sertraline or placebo as the "preferred" treatment. Remission rates were calculated for participants "accurately" treated based on the composite moderator (lucky) versus "inaccurately" treated (unlucky).
Results: Level of perfusion moderated improvement with sertraline over placebo. Perfusion in the putamen and anterior insula, inferior temporal gyrus, fusiform, parahippocampus, inferior parietal lobule, and orbital frontal gyrus contributed to sertraline response. Remission rates increased from 37% for all those who received sertraline to 53% for those who were lucky to have received it and sertraline was their perfusion-preferred treatment.
Conclusions: Perfusion patterns in brain regions involved with affect and default mode processing were observed to moderate treatment response favoring sertraline over placebo. Accurately matching patients with defined perfusion patterns could significantly increase remission rates.

Supported By: NIMH
Keywords: Major Depressive Disorder (MDD), Arterial Spin Labeling, Cerebral Blood Flow, Prediction of Treatment Outcome, Biomarkers

O15. Intrinsic Brain Connectivity Moderators of Psychotherapy Response and Changes in PTSD: A Combined Connectomic, Network Level, and Seeded Connectivity Approach

Gregory Fonzo[1], Madeleine Goodkind[2], Desmond Oathes[3], Yevgeniya Zaiko[4], Meredith Harvey[4], Kathy Peng[4], Elizabeth Weiss[4], Allison Thompson[4], Sanno Zack[4], Barbara Rothbaum[5], and Amit Etkin[6]

[1]Dell Medical School, The University of Texas at Austin, [2]New Mexico Veteran's Affairs Healthcare System, [3]University of Pennsylvania, [4]Stanford University School of Medicine, [5]Emory University School of Medicine, [6]Stanford University School of Medicine; Stanford Neurosciences Institute; Veterans Affairs Palo Alto Healthcare System

Background: Trauma-focused psychotherapy is a first-line treatment for post-traumatic stress disorder (PTSD). Treatment mechanisms are poorly understood, and heterogeneity in treatment response is vast. Brain phenotyping is a promising method to assess treatment suitability and identify treatment mechanisms, but an understanding of the neural processes underlying therapeutic benefit and facilitating favorable treatment response is nascent. Here, we assay intrinsic patterns of brain connectivity across multiple units of analysis (whole brain connectome, network-level interactions, and seeded connectivity of PTSD-relevant structures) to determine the intrinsic connectivity features most useful for identifying treatment mechanisms and outcome-predictive effects.
Methods: Individuals with PTSD were randomized to immediate treatment with prolonged exposure therapy (N=36) or a treatment waitlist (N=30). Individuals underwent clinical and resting state functional magnetic resonance imaging assessment prior to randomization and 1 month following cessation of treatment/waitlist. Treatment-moderating connectivity and treatment-related changes were assessed utilizing linear mixed models with multiple brain units of analysis: a 200-parcel whole brain connectome; resting network-level interactions; and seeded subregional connectivity in the amygdala, insula, and hippocampus.
Results: While limbic connectivity showed patterns of treatment-specific change distributed across the brain (FDR p's $<$ 0.05), connectome and network-level metrics did not yield significant treatment effects. In contrast, only a network-level metric (lower baseline visual to default mode network connectivity) moderated the effect of treatment on PTSD symptoms (FDR $p = 0.027$).
Conclusions: Treatment-specific changes in intrinsic brain connectivity are apparent only when assaying seeded connectivity of PTSD-relevant brain structures, whereas treatment-outcome predictive features emerge only from assessing interactions of large-scale resting networks.

Supported By: R01MH091860
Keywords: PTSD - Posttraumatic Stress Disorder, Psychotherapy, Brain Imaging, fMRI, Resting State fMRI, Clinical Trials

O16. Distinct Neural Networks Predict Opioid Versus Cocaine Abstinence in Polysubstance Users

Sarah Lichenstein[1], Dustin Scheinost[1], Marc Potenza[2], Kathleen Carroll[1], and Sarah Yip[1]

[1]Yale University School of Medicine, [2]Yale University

Background: Opioid use disorder (OUD) is a major public health crisis; while effective treatments are available, it has proven difficult to predict treatment outcomes. Using a novel machine learning approach, connectome-based predictive modelling (CPM), we previously identified patterns of neural network connectivity that predict abstinence from cocaine during treatment and replicated these findings in an independent sample. Understanding neural mechanisms of treatment response in OUD may facilitate the development of personalized and/or novel treatment approaches.
Methods: CPM was applied to identify neural networks of within-treatment opioid abstinence (based on biweekly urine screens) among n=53 methadone-maintained polysubstance users entering cocaine treatment. fMRI data was acquired during pre-treatment Stroop task performance. Additionally, we assessed the specificity of both opioid and cocaine abstinence networks to predict different substance use outcomes (opioid versus cocaine abstinence) across different brain states (Stroop versus monetary incentive delay task versus resting-state). Finally, we compared network strength between treatment responders, treatment non-responders, and healthy controls (n=38).
Results: We identified an opioid abstinence network (p=.018), characterized primarily by stronger within-network motor/sensory connectivity, and reduced connectivity between the motor/sensory network and medial frontal, default mode, and frontoparietal networks. Opioid and cocaine networks were anatomically distinct, specific for predicting opioid or cocaine abstinence only (respectively), and robust across multiple brain states. Healthy controls displayed intermediate network strength relative to treatment responders and non-responders.
Conclusions: Distinct neural networks predict opioid versus cocaine abstinence during treatment. If replicated, these results may inform the development of novel opioid-specific treatment approaches to improve the prognosis of individuals with OUD.
Supported By: R01DA015969, P50DA09241, K01DA039299, 5T32DA022975
Keywords: Opioid Use Disorder, Neural Networks, Prediction of Treatment Outcome, Neuroimaging, Polysubstance Use

O17. Mindfulness-Based Cognitive Therapy Modulates Functional Brain Activation During Affective Distraction in Treatment-Resistant Depression: A Randomized Controlled Study

Susanna Fryer[1], Stuart Eisendrath[1], Zindel Segal[2], Brian Roach[3], Judith Ford[1], Daniel Mathalon[1], and Erin Gillung[1]

[1]University of California, San Francisco, [2]University of Toronto, [3]NCIRE/University of California, San Francisco

Background: Mindfulness-based cognitive therapy (MBCT) has a growing evidence base for treating depressive disorders. However, the neural mechanisms underlying MBCT treatment benefits remain unclear. This study investigated treatment-related changes in functional brain response during an affective working memory task from a randomized controlled study of MBCT in patients with treatment-resistant depression (TRD).
Methods: TRD patients (n=62) and healthy controls (HC; n=30) performed an fMRI emotion working memory task before and after TRD patients received 8 weeks of behavioral intervention (either MBCT or Health-Enhancement Program (HEP), a comparator condition). FMRI activation was examined pre- and post-treatment in 30 MBCT and 32 HEP patients in a priori regions of interest defined from meta-analysis of extant fMRI mindfulness studies. Analyses focused on the contrast of negative vs. neutral distraction during working memory maintenance.
Results: Significant Group x Time (p=.007) effects were observed in dorsal anterior cingulate and left inferior parietal regions. Planned follow-up comparisons (Bonferroni-corrected) indicated these interactions were explained by i) dorsal ACC response decreasing post-treatment, in MBCT relative to the HEP group (p=.04, corrected) and ii) inferior parietal response decreasing post-treatment in the HEP relative to MBCT group (p=.03, corrected).
Conclusions: MBCT treatment was associated with less anterior cingulate response. This pattern suggests decreased reliance on regions relevant for cognitive control during affective distraction, consistent with MBCT-induced enhancement of emotional regulation. In contrast, changes localized to inferior parietal cortex were observed only in the HEP group, suggesting that these two treatments target distinct functional neurocircuitry.
Supported By: R01AT004572-02S1
Keywords: Mood Disorders, Cognitive Behavioral Therapy, Working Memory, Brain Imaging, fMRI, Dorsal Anterior Cingulate

O18. Biological Aging in Mental Health: An Integrative Study of Five Biological Age Indicators

Josine Verhoeven[1], **Laura Han**[1], Rick Jansen[1], Yuri Milaneschi[1], and Brenda Penninx[1]

[1]VU University Medical Center

Background: Aging increases the risk of poorer somatic health conditions such as cardiovascular disease, cognitive decline, and mortality. These risks are also commonly observed in individuals with mental health disorders. Current high-throughput technologies have enabled the development of omics-based clocks that accurately track aging (biological aging indicators). Here, we integrate a “traditional” indicator, telomere length (TL), with four “modern” biological aging indicators based on epigenetics, transcriptomics, proteomics, and metabolomics and examine their associations with lifestyle, and physical and mental health.

Methods: Using data of the Netherlands Study of Depression and Anxiety, we estimated TL (N=2936), epigenetic (N=1130), transcriptomic (N=1990), proteomic (N=1589), and metabolomic age (N=2510). Biological clocks were built using cross-validated lasso models and associated with a wide panel of lifestyle (e.g. BMI, smoking, physical activity), physical (somatic diseases), and mental health (e.g. DSM-based major depression, childhood trauma) determinants.
Results: Small but significant intercorrelations were found between most of the biological aging indicators (all $r<0.15$), indicating little conceptual overlap. Advanced levels of these indicators were correlated with BMI (all), metabolic syndrome and male sex (4/5), and smoking (pack years) and current depression (3/5). Higher epigenetic and proteomic ages were consistently associated to all mental health determinants (current depression, depression severity, childhood trauma).
Conclusions: Our findings suggest that different biological aging indicators may track other aspects of the aging process. Moreover, lifestyle and somatic health indicators are consistent determinants of more advanced biological aging. Importantly, our study demonstrates that mental health is also significantly and consistently related to more advanced aging at multiple biological levels.
Supported By: The Netherlands Study of Depression and Anxiety (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (Zon-MW, grant 10-000-1002) and participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe).
Keywords: Biological Aging, Somatic Health Indicators, Mental Health, Telomere Length, Omics

O19. Attenuation of Anti-Suicidal Effects of Ketamine by Opioid Receptor Antagonism

Nolan Williams[1], Boris Heifets[1], Brandon Bentzley[1], Christine Blasey[1], Keith Sudheimer[1], David Lyons[1], and Alan Schatzberg[2]

[1]Stanford University, [2]Stanford University School of Medicine

Background: It is unknown if this opioid mechanism of action is also involved in ketamine's acute anti-suicidality effects. We tested whether pretreatment with naltrexone prior to intravenous ketamine could attenuate ketamine's acute anti-suicidality effects in humans.
Methods: In a double-blind, cross-over study of 14 adults with treatment-resistant depression and chronic suicidality, 12 completed both conditions (randomized order): 50mg naltrexone preceding 0.5mg/kg ketamine (K+N) and placebo preceding 0.5mg/kg ketamine (K+P). Item 3 of the Hamilton Depression Rating Scale (HDRS-17) served as the primary outcome measure for suicidality. The responder criterion was defined a priori as a $\geq$50% reduction on the 17-item Hamilton Depression Rating Scale following the ketamine infusion on the first day in the K+P condition.
Results: In the 12 participants who completed both conditions, there was a significant effect of naltrexone compared to placebo pretreatment (linear mixed model, fixed pretreatment effect, $p=0.008$), with an attenuated reduction in mean HDRS-17 item 3 score in the naltrexone compared to placebo group. In the group of 7 ketamine responders, there was a significant reduction in the mean HDRS-17 item 3 score during the K+P condition from baseline to D1 (Bonferroni, $p<0.001$) but not in the K+N condition (Bonferroni, $p=0.720$). All 7 responders had a score of 0 on item 3 of the HDRS-17 in the K+P condition; whereas, 3 of 7 had a score of 0 in the K+N condition.
Conclusions: Ketamine's acute anti-suicidality effect in humans requires opioid system activation.
Supported By: NARSAD, NIH
Keywords: Depression, Opioid Antagonist, Mu-Opioid System, Mu-Opioid Receptor Agonism, Suicide

ORAL SESSION: MOOD DISORDERS & SUICIDE
3:00 p.m. - 5:00 p.m.

O20. Resting State Whole Brain Network Activity in Depression From Intracranial EEG Signals

Katherine Scangos[1], Ankit N. Khambhati[1], Patrick Daly[1], Alia Shafi[1], Heather Dawes[1], Andrew Krystal[1], and Edward F. Chang[1]

[1]University of California, San Francisco

Background: Major depression (MDD) is associated with altered connectivity across distributed brain networks. In the present study we utilized intracranial electroencephalography (iEEG) to investigate both altered connectivity and differences in activity across these networks that may characterize MDD and serve as a biomarker of disease state.
Methods: Twenty-four hours of iEEG recordings from 41 subjects undergoing pre-surgical mapping for refractive epilepsy were examined. Twenty subjects (49%) had comorbid MDD [Patient Health Questionnaire-9 $\geq$10]. Whole-brain estimates of iEEG activity were generated by applying a Gaussian process regression technique for inferring neural activity across sparsely placed intracranial sensors (SuperEEG). A multiscale community detection method identified clusters of distributed functional sub-networks across the groups. Standard signal processing techniques were applied to identify spectral power features across these clusters. Supervised machine learning identified neural features that distinguished MDD subjects from controls. Finally, the functional network architecture across the two groups was compared.
Results: Stable functional clusters across the population were identified. A set of spectral power features across these clusters classified subjects with and without MDD with 72% accuracy (AUC 0.73, leave-one-out cross validation). Brain regions and functional networks (default mode (DMN), limbic)

were more functionally integrated with other regions and networks in MDD. Higher relative alpha and theta power in the limbic network and DMN and lower gamma power in the DMN drove differences across the networks.
Conclusions: These findings provide a new understanding of network organization in MDD and for the first time link neural activity patterns with altered functional connectivity using direct neural recordings.
Supported By: Brain Initiative
Keywords: Major Depression, ECoG, Biomarkers, Neural Networks

O21. Resting-State Functional Connectivity, Cortical Gaba and Allopregnanolone in Postpartum Depression: A Functional Magnetic Imaging and Spectroscopy Study

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Background: Postpartum depression (PPD) is associated with abnormalities in resting-state functional connectivity (RSFC) but the underlying neurochemistry is unknown. We hypothesized that the neuroactive steroid allopregnanolone (ALLO) is correlated to cortical GABA concentrations and RSFC in PPD as compared to healthy comparison women (HCW). We measured group RSFC with fMRI and pregenual anterior cingulate cortex (ACC) GABA+/Cr concentrations with magnetic resonance spectroscopy (MRS) and quantified peripartum ALLO using liquid chromatography/tandem mass spectrometry.
Methods: A prospective study evaluated 53 peripartum women. Serial HAM-D and blood samples for ALLO were completed across 5 visits. Healthy women (n=28) and women who developed unipolar PPD (n=25) completed a single postpartum fMRI/MRS scan. Edited MRS spectra were acquired using MEscher-GArwood Point-REsolved Spectroscopy Sequence (MEGA-PRESS). We completed both an ICA and a seed-based analysis to examine group differences in RSFC. A Bonferroni correction was applied for multiple comparisons of hypothesized correlations between measures.
Results: Within the default mode network (DMN) an area of the dorsomedial prefrontal cortex (DMPFC) had greater connectivity with the rest of the DMN in PPD (p=0.002) and was correlated to HAM-D (p=0.008). pgACC GABA+/Cr correlated positively with DMPFC RSFC in a region spanning the right anterior/posterior insula and right temporal pole (r=+0.661, p=0.001). Plasma allopregnanolone was higher in PPD (p=0.03) and positively correlated with intra DMPFC connectivity (r=+0.548, p=0.000) but not GABA+/Cr.
Conclusions: These results provide initial evidence that PPD is associated with altered DMN connectivity; cortical GABA+/Cr concentrations are associated with postpartum RSFC and allopregnanolone is associated with postpartum intra-DMPFC connectivity.
Supported By: NIMH 5K23MH097794-01
Keywords: Magnetic Resonance Spectroscopy, Resting State Functional Connectivity, Postpartum Depression, Neuroactive Steroid, GABA

O22. Transcriptional Organization of Gene Networks in Human MDD and Their Correlates in Different Mouse Models of Stress

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Background: Our capacity to better define the contribution of brain-specific molecular alterations associated with MDD passes through the use of well validated mouse models. However, while these models induce some of the behavioral and clinical features of MDD, the extent by which they reproduce its molecular and transcriptional alterations is still a matter of debate.
Methods: Here, combining differential expression and gene coexpression network analyses, we overlapped human profiles in different brain regions with those from three mouse models of stress including chronic variable stress (CVS), prolonged social isolation (SI) and chronic social defeat stress (CSDS) and capitalized on converging pathways to define molecular and physiological mechanisms underlying the expression of stress susceptibility.
Results: Our results show a major rearrangement of transcriptional patterns in MDD, with limited overlap between males and females. Our interspecies analyses suggest that every model reproduces common but also distinct transcriptional alterations relevant to the disease. We identified key regulators of gene networks underlying MDD and confirmed their impact as mediators of stress susceptibility. For example, downregulation of the female-specific hub gene Dusp6 in mouse prefrontal cortex mimicked stress susceptibility in females, but not males, by increasing ERK signaling and pyramidal neuron excitability.
Conclusions: Together our findings reveal the extent by which CVS, SI and CSDS mouse models of stress reproduce the transcriptional alterations associated with MDD and highlight functional pathways driving stress susceptibility in a sex-specific fashion, highlighting the importance of studying sex-specific treatments for this disorder.
Supported By: CIHR, FRQS, NARSAD, ULaval-Sentinelle Nord
Keywords: Major Depressive Disorder (MDD), Transcriptomics, Mouse Models, Stress, Sex Differences

O23. Inhibitory Control and Neuroprogression of Mood Disorders

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Background: Inhibitory control has been implicated in various psychiatric disorders, including mood disorders, and is associated with fronto-striatal and fronto-limbic circuit dysfunction. However, little of this work has examined how such cognitive processes change across the lifespan, and how such developmental changes may interact with mood disorder progression. The current study used a multisite cross-sectional design to evaluate inhibitory control accuracy and interference resolution speed across the youth through adult lifespan.
Methods: Participants were youth and adults, ages 13-86, who completed the Parametric Go/No-Go task (PGNG), which assesses inhibitory control accuracy and interference resolution speed. Psychiatric history was confirmed by structured interviews with masters- or doctoral-level clinicians. Healthy controls (HC, n=319), individuals with a history of major depressive disorder (MDD, n=578), and individuals with bipolar disorder (BP, n=346), were assessed during euthymic or depressed mood states. Multiple linear regressions were run on several performance measures from the PGNG to examine the effects of age, diagnosis, and their interactions.
Results: With increasing age, all participants demonstrated significantly worse percent correct target trials (PCTT). MDD and BP exhibited significantly worse performance than HC on PCTT. BP also demonstrated worse percent correct inhibitory trials (PCIT). Finally, there was a significant interaction between diagnosis and age, such that MDD showed a decrease over age in PCIT.
Conclusions: Mood disorders show deficits in several inhibitory control processes across the lifespan. Depression shows increased dysfunction across the adult lifespan, suggesting a neuroprogression of the disorder. Closer scrutiny of developmental and age effects are suggested.
Supported By: T32-MH067631 (KLB), MH101487 (SAL)
Keywords: Mood Disorders, Inhibitory Control, Lifespan

O24. Components of the Stress Response Differentiate Suicide Ideators and Suicide Attempters

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[1]Columbia University & New York State Psychiatric Institute, [2]University of Pennsylvania

Background: The stress response may provide critical psychobiological information regarding the transition from suicidal thought to action. The Trier Social Stress Test (TSST) paradigm of psychosocial stress can be used to probe functioning of both the HPA axis and the sympathetic adreno-medullary system (SAM) in these at-risk patients.
Methods: A modified TSST was administered to 102 unmedicated patients with current major depressive episode (24 with prior suicide attempt, 44 without past attempt but with current suicidal ideation, and 34 with no suicidal thinking or attempt) as well as 75 healthy volunteers. Salivary cortisol, alpha-amylase and heart rate were collected pre-stress and at five timepoints after. Heart rate, mood and subjective ratings were also collected.
Results: Groups differed in both cortisol response ($F[12,680]=1.78$, $p=.048$) and alpha-amylase levels ($F[3,139]=4.07$, $p=.008$). Past suicide attempters exhibited the largest peak change in cortisol, but overall output for both cortisol and alpha-amylase was largest among the suicide ideators who had never made an attempt.
Conclusions: Components of the stress response may represent critical biological factors differentiating those who act upon their suicidal ideation. Concomitant elevation of the two components of the stress response may confer protection against acting on suicidal thinking.
Supported By: NIMH
Keywords: Psychosocial Stress, Depression And Suicide, HPA Function, Salivary Alpha Amylase

O25. Distinct Symptom-Specific Targets for Circuit-Based Neuromodulation

Shan Siddiqi[1], Stephan Taylor[2], Daniel Cooke[1], Alvaro Pascual-Leone[1], Mark George[3], and Michael Fox[1]

[1]Harvard Medical School/Beth Israel Deaconess Medical Center, [2]University of Michigan, [3]Medical University of South Carolina

Background: Major depression is currently defined by a constellation of different symptoms which are heterogeneous between patients. Different symptom clusters may respond better to different neuromodulation targets. Recent biotyping approaches have not yet translated into clinical advances.
Methods: Stimulation sites were recorded on structural MRI for three patient cohorts who received left prefrontal TMS for treatment of depression (discovery n=30, replication n=81, validation n=12). Each patient's TMS site was mapped to underlying brain circuits using functional connectivity MRI from a large connectome database (n = 1000).
Results: We identified two distinct circuit targets effective for two discrete clusters of depressive symptoms. Dysphoric symptoms, such as sadness and anhedonia, responded best to stimulation of one circuit, while anxiety and somatic symptoms responded best to stimulation of a different circuit. This optimal two-cluster solution was not identified in the sham arm of the replication study (n=87). Connectivity with these circuits was strongly predictive of the rank-transformed ratio of dysphoric to anxiosomatic improvement in the discovery ($r=0.76$, $p<10\text{-}5$), replication ($r=0.55$, $p<10\text{-}7$), and validation ($r=0.67$, $p=0.02$) datasets. There was no such

relationship in the sham arm of the replication (r=-0.02) or validation (r=0.26) datasets.
Conclusions: Using a data-driven approach based on therapeutic response to an anatomically-targeted causal intervention, we identified novel identifying symptom-specific circuits and corresponding therapeutic targets. This approach may prove useful for other disorders and brain stimulation modalities.
Supported By: Sidney R. Baer Fellowship in Clinical Neuroscience
Keywords: Neuromodulation, Brain Imaging, fMRI, Biotypes, Transcranial Magnetic Stimulation (TMS)

O26. Psychosocial and Neural Factors Contributing to Suicide Risk in a Large Transdiagnostic Sample

Robin Aupperle[1], Rayus Kuplicki[1], Danielle DeVille[1], Sahib Khalsa[1], Hung-wen Yeh[2], Timothy McDermott[1], Namik Kirlic[1], Teresa Victor[1], and Martin Paulus[1], Tulsa 1000 Investigators[1]

[1]Laureate Institute for Brain Research, [2]Children's Mercy Hospital, Kansas City

Background: Understanding factors contributing to suicide is important for identifying at-risk individuals and potential treatment targets. Previous research implicates depression, anxiety, trauma history, impulsivity, and medial prefrontal cortex (mPFC) dysfunction as potential contributors to suicidal ideation or behavior. The current study used a large, transdiagnostic cross-sectional sample with in-depth phenotyping to identify psychosocial factors and neural activations associated with suicide risk.
Methods: 500 participants completed an extensive mental health, neuropsychological, and demographic assessment battery as part of the Tulsa 1000 study. Three machine learning algorithms (support vector machine, random forest, k-nearest neighbor) were trained and their predictions combined by stack ensemble in repeated nested cross-validation, to assess prediction accuracy of selected variables on Mini International Neuropsychiatric Inventory suicide risk level. Independent samples t-tests compared matched groups with major depressive disorder who did (N=31) or did not (N=64) report previous suicide attempts, concerning mPFC activity during the Stop Signal response inhibition task (long versus short stop signal delay).
Results: A combination of measures were identified accounting for 27% of variance in suicide risk score (RMSE=0.68; MAE=0.46), with top predictors including depressive and anxiety symptomatology, positive affect and wellbeing, rumination, and guilt. Suicide attempters exhibited less activation (hard-easy) within two mPFC clusters ($p<.005$).
Conclusions: Results support the importance of depression and anxiety symptoms and highlight both negative and positive valence domain factors of importance for suicide risk and treatment. mPFC dysfunction may contribute to response inhibition abnormalities for suicide attempters and could represent a potential neural target for interventions aiming to reduce suicide risk.
Supported By: William K. Warrend Foundation; NIMH K23 MH108707
Keywords: Suicide, Depression, Cognitive Control, Response Inhibition, Functional MRI

O27. Developing a Directly Translational, Non-Subjective Measure of Individual Differences in Negative Affective Bias in Mood and Anxiety Disorders

Jessica Aylward[1], Lucie Daniel-Watanabe[1], and **Oliver Robinson**[1]

[1]UCL

Background: Mood and anxiety disorders are ubiquitous but current treatment options are ineffective for many. Improved treatments are unlikely without better animal-human translational pipelines and non-subjective measures of individual differences in symptoms. Here, we translate a rodent measure of negative affective bias (and computational model) into humans, and explore its relationship with 1) mood/anxiety diagnosis, 2) transient induced-stress, and 3) self-reported symptoms at scale.
Methods: Participants were screened for mood or anxiety disorder symptomatology according to a face-to-face neuropsychiatric interview and completed a 2AFC task involving decisions about rewarded ambiguous and unambiguous outcomes. N=77 (47=asymptomatic/30=symptomatic) completed study 1; N=47 asymptomatic completed study 2; and N=990 (unscreened) online MTurk participants completed study 3. Outcome measures were choice ratios, and parameters recovered from a computational model; the drift diffusion model (DDM) analysed using t-tests and regression (+ Bayesian equivalents).
Results: Symptomatic individuals demonstrated increased negative affective bias ($p=0.003$, $d=0.732$) relative to asymptomatic individuals as well as reduced DDM drift rate ($p=0.008$). No significant effects were observed for the within-subjects stress-induction in study 2 ($p=0.06$, $d=0.28$). Study 3 indicates that negative bias on drift rate might be driven by individual differences in depression symptoms ($\beta=-0.104$).
Conclusions: Humans with pathological diagnosis (but not transient induced-stress) directly mimic rodents undergoing anxiogenic manipulation, and large-scale data suggests that this task hold promise as a non-subjective measure of individual differences depression symptomatology. Our results therefore establish a direct non-subjective translational pipeline from rodents to individual differences in pathological mood and anxiety symptoms in humans.
Supported By: MRC (MR/K024280/1)
Keywords: Anxiety Disorder, Computational Psychiatry, Depression, Translational Neuroscience, Affective Bias

Saturday, May 18, 2019

ORAL SESSION: SCHIZOPHRENIA & COGNITION
12:30 p.m. - 2:30 p.m.

O28. Risk and Resilience to Psychosis Spectrum in the Longitudinal Philadelphia Neurodevelopmental Cohort

Ruben Gur[1], Tyler Moore[1], Monica E. Calkins[1], David Roalf[1], Theodore D. Satterthwaite[2], Kosha Ruparel[1], Adon F.G. Rosen[2], and **Raquel E. Gur**[1]

[1]University of Pennsylvania, [2]University of Pennsylvania, Perelman School of Medicine

Background: The Philadelphia Neurodevelopmental Cohort (PNC), a community sample of ~9,500 youth (8-21 years) ascertained through pediatric services, ~1600 had neuroimaging. Psychosis spectrum (PS) symptoms at intake were associated with neurocognitive deficits and abnormalities in brain structure and function. Follow-up allows examination of associations between intake parameters and outcome.
Methods: We compared psychotic features, neurocognitive and neuroimaging parameters in PS to typically developing (TD) youths; 639 participants were clinically assessed twice, and a subset of 322 were followed a third time. We contrast intake measures of those who entered as PS and remained so at 2 and 4-years follow-up (Persisters), to those who entered as PS but did not meet PS criteria as follow-ups (Resilient).
Results: The Resilient group at intake had better neurocognitive performance in working memory, episodic memory, language and non-verbal reasoning and emotion identification. Furthermore, individuals who entered as TD and PS emerged at follow-up, had poorer performance at intake in the same neurocognitive domains. MRI showed lower gray matter volume at intake in Persisters across cortical regions, while the Resilient group had volumes within the TD range. Emergence of PS was also related to intake volumes across cortical regions and thalamus. All effects were stronger in females than males.
Conclusions: Longitudinal data of youth during the dynamic period of brain maturation and evolution of psychosis are essential to identify measures associated with risk and resilience to psychosis. Longitudinal PNC data indicate that poorer neurocognitive performance and lower brain volumes are associated with both persistence and emergence of PS.
Supported By: R01 MH107235, P50 MH 096891,
Keywords: Attenuated Psychosis Syndrome, Developmental Psychopathology, Volumetric Neuroimaging, Neurocognitive Development, Resilience

O29. Deconstructing Simple and Choice Decision and Movement Time in Psychosis

Joey Trampush[1], Alina Henn[2], Dwight Dickinson[3], Karen Berman[4], and Daniel Weinberger[5]

[1]University of Southern California, [2]Osnabruck University, [3]National Institute of Mental Health, [4]DIRP, NIMH, NIH, [5]School of Medicine, Johns Hopkins University

Background: Reaction Time (RT) is a much-valued predictor and outcome variable in psychological experimentation. Once a perceptual process determines a relevant signal has been presented, two subsequent actions occur: (1) a mental decision to trigger the motor response, termed Decision Time (DT), and (2) a motor process, termed Movement Time (MT). Here, we disentangled the contribution of DT and MT to overall RT, determined the predictive power of DT/MT on general cognitive ability ("g"), and estimated the degree of familiality of DT/MT.
Methods: Controls (N=508) and siblings with (N=297) and without (N=175) schizophrenia completed simple and choice RT tasks on the Multi-Operational Apparatus for Reaction Time (MOART) system and a comprehensive neuropsychological battery. Linear regression and variance components analyses estimated the magnitude of variance in cognitive performance attributable to DT/MT and the degree of familiality.
Results: DT during simple RT accounted for 14% of the variance in g in controls and 17% in probands, whereas MT during choice RT accounted for 3% and DT during choice RT 1%. Simple and choice DT had a practically null genetic correlation within families (h2 < 1%), whereas at simple and choice MT evidenced relatively strong familiality (h2 ~.30).
Conclusions: Simple DT, the most basic mental process under study, was the most robust predictor of cognitive performance across groups, the most impaired RT variable in schizophrenia, and yet had no genetic correlation within families. We speculate simple decision-time performance is a basic state-like factor with substantial influence on cognitive performance rather than a trait-like factor under genetic influence.
Supported By: NIH IRP
Keywords: Reaction Time, Decision Time, Movement Time, Psychosis, Cognition

O30. Multivariate Pattern Analysis Reveals Structural Brain Network Abnormalities in Schizophrenia

Aristeidis Sotiras[1], Guray Erus[2], Monica Truelove-Hill[2], Antonia Kaczkurkin[2], Ganesh B. Chand[2], Chiharu Sako[2], Dominic B. Dwyer[3], Ruben C. Gur[2], Raquel E. Gur[2], Yong Fan[2], Theodore D. Satterthwaite[2], Nikolaos Koutsouleris[3], Daniel H. Wolf[2], and Christos Davatzikos[2]

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Background: Numerous studies have reported abnormalities in gray matter volume in schizophrenia (SCZ). However, past accounts have been limited by small samples and analytics that do not evaluate complex multivariate patterns. We examined brain structure deficits in SCZ by capitalizing on a large international sample, and recent advances in unsupervised multivariate analysis methods.
Methods: We analyzed T1-structural MR images of 671 patients with SCZ from three sites [controls = 364

(age = 29.5±7.0 years; 44.2% female) and SCZ = 307 (age = 30.9±7.3 years; 35.2% female)]. We calculated spatially aligned gray matter tissue density maps (TDMs) for every subject, and derived structural covariance networks (SCNs) by applying non-negative matrix factorization to combined healthy and patient TDMs. We used regression analysis to independently evaluate group differences in SCNs, and the Bonferroni procedure to correct for multiple comparisons.

Results: We identified 34 SCNs that optimally summarize the high dimensional TDMs. Disease status was associated with reduced SCN volume in the insular cortex, temporoparietal junction, inferior frontal gyrus (pbonf $\leq$ 10-6); superior frontal pole (pbonf $\leq$ 10-5); orbitofrontal cortex (pbonf $\leq$ 10-4); inferior frontal pole, superior frontal cortex, left lateral occipital pole, superior temporal gyrus (pbonf $\leq$ 10-3); right lateral and medial occipital cortex (pbonf $\leq$ 10-2); postcentral gyrus, and right dorsolateral prefrontal cortex (pbonf $\leq$ .05).

Conclusions: Our results suggest that higher-order association cortices may provide a pathophysiological substrate for SCZ. Importantly, the data driven decomposition of brain structure into robust SCNs across multiple datasets paves the way for identifying subtle markers of psychosis risk.

Supported By: R01-MH112070 -02

Keywords: Multivariate Analysis, Schizophrenia, Gray Matter Volume

O31. The Impact of Network Topology on Individual Differences in Cognition and Symptomatology

Uzma Nawaz[1], Ivy Lee[1], George Ling[1], Olivia Lutz[1], Neeraj Tandon[1], Synthia Guimond[1], Dost Ongur[2], Shaun Eack[3], Matcheri Keshavan[1], Kathryn Lewandowski[2], Mark Halko[1], and **Roscoe Brady**[1]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, [2]McLean Hospital/Harvard Medical School, [3]School of Social Work, University of Pittsburgh

Background: Resting state fMRI has allowed in vivo identification of the brain's organization into functionally connected networks. This framework has supplemented historical schema of how cognition, behavior, and symptoms are reflected in brain organization. The spatial organization of these networks demonstrates significant inter-individual variation. We sought to determine if this variation is reflected in cognition and psychiatric symptomatology.

Methods: 105 participants (60 schizophrenia; 45 control) underwent a rsfMRI scan, behavioral, and cognitive assessments. A connectomic multivariate pattern analysis examined participant-level individual voxel connectivity that corresponds to cognitive / behavioral domains.

Results: Inter-individual differences in network spatial organization demonstrated significant ($p<.001$) effects on multiple measures of cognition and symptom severity. The impact of network topology on these phenotypes was linked to highly circumscribed (~11mm3) sub-regions of heteromodal association cortices. The topographic organization of networks, within these critical regions, demonstrated large (r ~.5), region-specific effects on behavioral and cognitive measures. In all cases examined, the strongest phenotype-connectivity relationships in the brain were always explained by network topology.

Conclusions: The almost universally accepted practice of group averaging rsfMRI data obfuscates important relationships between network topology and cognitive and behavioral phenotypes. Many previously reported correlations between phenotype and connectivity may be misinterpretations of individual variation in network topology. Recently proposed individual parcellation solutions still obscure interactions between network topology and anatomy critical to phenotypic variation. We argue that individual network topology is a marker of cytoarchitectonic variation. This variation at critical cortical regions cortices is linked to expression of normative cognition and pathological symptomatology.

Supported By: NIH K23MH100623

Keywords: Resting State Functional Connectivity MRI (fcMRI), Brain Networks, Cognition, Schizophrenia

O32. Functional Network Connectivity Impairments and Core Cognitive Deficits in Schizophrenia

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[1]University of Maryland School of Medicine, [2]Keck School of Medicine, University of Southern California, [3]The University of New Mexico

Background: Cognitive impairment contributes to disability in patients with schizophrenia and may be related to altered functional networks that subserve cognitive functions. We evaluated the integrity of major functional networks and assessed their role in supporting two cognitive functions affected in schizophrenia: processing speed (PS) and working memory (WM).

Methods: A total of 261 patients and 327 controls were aggregated from three cohorts and their brain function was evaluated using ENIGMA rsfMRI analysis pipeline. Mega-analysis was used to derive functional connectivity (FC) measures. Canonical correlation analysis was used to study the association between cognitive deficits and FC measures.

Results: Patients showed a consistent pattern of cognitive and FC deficits across three cohorts. Patient-control differences in FC calculated using seed-based and dual regression approaches were consistent (Cohen's d: 0.31±0.09 and 0.29±0.08, $p<10\text{-}4$). FC measures explained 12-17% of the individual variations in PS and WM in the full sample and in patients and controls separately, with the strongest correlations found in salience, auditory, visual, somatosensory and default mode networks. The pattern of association between rsFC derived from multiple networks and PS ($r=0.45$, $p=0.07$)

and WM (r=0.36, p=0.16) was related to effect size of patient-control differences in the functional networks. No association was detected between rsFC and current medication dose or psychosis ratings.

Conclusions: Patients demonstrated significant deficits in several FC networks that may partially underlie some of the core neurocognitive deficits in schizophrenia. The strength of the connectivity-cognition relationships in different functional networks was strongly associated with the network's vulnerability to schizophrenia.

Supported By: NIH grants U54EB020403, U01MH108148, 2R01EB015611, R01MH112180, R01DA027680, R01MH085646, and T32MH067533

Keywords: Resting State Functional Connectivity, Processing Speed, ENIGMA rsfMRI Analysis Pipeline

O33. EEG Alpha Event-Related Desynchronization Deficits Predict Conversion to Psychosis in Individuals With the Psychosis Risk Syndrome

Avinash Ramyead[1], Brian Roach[2], Holly Hamilton[2], Jean Addington[3], Peter Bachman[4], Carrie Bearden[5], Aysenil Belger[6], Kristin Cadenhead[7], Tyrone Cannon[8], Ricardo Carrion[9], Barbara Cornblatt[9], Erica Duncan[10], Jason Johannesen[11], Gregory Light[7], Thomas McGlashan[11], Margaret Niznikiewicz[12], Diana Perkins[6], Larry Seidman[12], Ming Tsuang[7], Elaine Walker[13], Scott Woods[11], and **Daniel Mathalon**[1]

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Background: Electroencephalographic (EEG) alpha event-related desynchronization (ERD) by task stimuli is reduced in schizophrenia; however, whether this abnormality is present in individuals meeting criteria for the psychosis risk syndrome (PRS) and predicts conversion to psychosis remains unclear.

Methods: Source-localized EEG alpha ERD measures evoked by infrequent target and novel distractor stimuli from an auditory oddball task and structural MRI data were examined in healthy controls (HC; n=227) and PRS individuals (n=231), including 52 converters to psychosis (PRS-C) and 179 non-converters followed for 24 months (PRS-NC) as part of the multi-site NAPLS 2 study. Pre-stimulus alpha power localized to neuroanatomical sources was also compared between groups and correlated with co-localized grey matter volume (GMV).

Results: Compared to PRS-NC (p=.043) and HC (p=.023), PRS-C individuals exhibited decreased posterior cingulate cortex (PCC) alpha ERD to both target and novel stimuli, and the greater their ERD deficits, the earlier they converted to psychosis (p=.02). Greater alpha ERD was associated with faster target reaction time across groups (p=.002). Pre-stimulus PCC alpha power was reduced in PRS individuals relative to HC (p<.006), and this reduction was associated with smaller PCC GMV (p<.008).

Conclusions: PCC-localized alpha ERD, a reflection of brain activation, is deficient during top-down and bottom-up processing of oddball task stimuli in the PRS individuals at greatest and most imminent risk for conversion to psychosis. Pre-stimulus PCC alpha power, reflecting the idling brain, was reduced in PRS individuals and was directly coupled with their PCC GMV, suggesting that psychosis risk induces a linkage between PCC GMV and alpha oscillations.

Supported By: NIMH U01MH076989

Keywords: Clinical High Risk For Psychosis, Time-Frequency EEG, Alpha Event-Related Desynchronization, Auditory Oddball, Outcome Prediction

O34. Gray Matter Network Changes With Aging in a Large Group of Never-Treated Patients With Schizophrenia

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Background: The progressive changes of gray matter and white matter in schizophrenia has been reported. The knowing of progressive pattern of gray matter network may expand our understanding of schizophrenia and its physiopathology. In present study, we enrolled a large group of never-treated schizophrenia patients to investigate the pattern of network changes with aging without the confounding of antipsychotics.

Methods: We stratified 152 never-treated schizophrenia patients into 4 subgroups A1-A4 by age (16-24, 25-34, 35-44,>45), and matched controls for each subgroup were selected from 210 healthy subjects. High resolution T1 images of brain were obtained with a 3.0 T MR scanner (GE), and preprocessed by FreeSurfer. The gray matter network matrices were constructed by correlating the cortical thickness of every pair of regions within AAL brain segmentations across individuals. Results were corrected by non-parametric permutation test.

Results: Compared to healthy controls, patient subgroups showed some common network property changes and deteriorations with aging, which was nodal centrality loss at regions mainly within default mode network (DMN), core network (CN). Network deteriorations were found in more regions with nodal centrality progression in left isthmus cingulate gyrus, posterior superior temporal gyrus, right caudal anterior cingulate gyrus in A2-A4, and left precuneus in A3-A4. Some distinct changes of each subgroup were also observed.

Conclusions: The common changes of topological properties within DMN and CN may represent trait-related gray matter network changes in schizophrenia, and more changes in late age subgroup may represent illness progression with more-wide spread brain abnormalities.
Supported By: NSFC
Keywords: Gray Matter Network, Schizophrenia, Never-Treated, Aging

O35. Relationship of Rich Club Organization and MCCB Reasoning Domain in First Episode Schizophrenia

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Background: Rich club organization enhances robustness and efficiency of interregional communication and functional integration in the human connectome. This characteristic of the human connectome seems to be a prerequisite for cognitive functioning. In schizophrenia, most cognitive functions are deficient. Interestingly, reasoning might have a predictive potential for responsivity to antipsychotic treatment. Therefore, we hypothesized that aberrant rich club organization is associated with reasoning and that this association may be indicative of response to treatment. Here, we explored the relationship between rich club organization and reasoning in schizophrenia.
Methods: We included N=83 (female: N=24) patients with early-phase schizophrenia in the acute phase of the illness with a mean age of 21.55 years (SD=4.85). Reasoning was assessed with the MATRICS Consensus Cognitive Battery (MCCB). Anatomical data was used to construct a structural network with 68 cortical regions and to compute the rich club coefficient. This coefficient was normalized and entered as the dependent variable in a multivariable linear regression analysis with MCCB reasoning as the independent variable, and age, gender, and age-by-gender interaction as covariates.
Results: Rich club organization was positively related to MCCB reasoning (beta=0.3, P=0.006). The 95% confidence interval did not include zero for densities between 0.2 and 0.5.
Conclusions: Our results suggest that rich club organization increases with increasing reasoning capacity in schizophrenia. Given that cognitive deficits are a core feature of schizophrenia, rich club abnormalities may represent a potential biomarker for patients with most severe impairments and poor outcome.
Supported By: P50MH080173; R21MH101746; R01MH060004; K23MH100264

Keywords: Rich Club Coefficient, Graph Theory, Reasoning, MATRICS Consensus Cognitive Battery, Schizophrenia

ORAL SESSION: TRAUMA AND DEVELOPMENT
12:30 p.m. - 2:30 p.m.

O36. Cognitive Function Networks Vary With Quality of Life

Sharon Naparstek Zamler[1], Manjari Narayan[2], Charles Marmar[3], and Amit Etkin[2]

[1]Wu Tsai Neurosciences Institute, Stanford University, Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), Veterans Affairs Palo Alto Healthcare System, [2]Stanford University School of Medicine; Wu Tsai Neurosciences Institute; Veterans Affairs Palo Alto Healthcare System, [3]Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress and Traumatic Brain Injury, NYU School of Medicine

Background: Recent approaches use networks of symptoms to understand psychopathology. Different psychiatric disorders were found to share common impairments in neurocognitive domains, specifically in the field of executive functions. Thus, rather than symptom networks, networks of cognitive functions might play a role as an intermediate phenotype for brain-behavior relationships.
Methods: A transdiagnostic sample of 567 individuals were assessed via a computerized cognitive battery, and self-report quality of life questionnaire (WHO-QOL). We constructed cognitive networks using nonparametric covariance models between 28 variables of interest spanning memory, attention and executive function. Using kernel smoothing and spline regression, we quantify nonlinear trajectories of how the network changes dynamically with WHO-QOL scores.
Results: Psychological QOL was strongly affected by 3 variables measuring switching, inhibition and updating. In particular, performance on these 3 variables propagated strongly to all other cognitive measures ($p < .0001$ for all three) and more so for individuals with low psychological quality of life.
Conclusions: This is the first study that applied network analysis to cognitive functions. Such an approach broadens our understanding of the way different measures of cognition influence and interact with one another. Our findings highlight the dynamic nature of the network, depending on subjective measures of QOL. Taken together, the results call for rethinking how cognitive biomarkers are employed to study brain-behavior mechanisms and serves as another step towards the development of personalized medicine.
Supported By: Cohen Veterans Bioscience
Keywords: Executive Function, Cognitive Neuroscience, Quality of Life, Network Analysis

O37. Individual Patterns of Abnormality in Resting-State Functional Connectivity Reveal Two Data-Driven PTSD Subgroups

Adi Maron-Katz[1], Manjari Narayan[2], Sharon Naparstek Zamler[3], Parker Longwell[4], Emmanuel Shpigel[2], Carlo Servando De Los Angeles[2], Jennifer Newman[5], Duna Abu Amara[6], Charles Marmar[6], and Amit Etkin[2]

[1]Veterans Affairs Palo Alto Healthcare System, and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), [2]Stanford University School of Medicine; Stanford Neurosciences Institute; Veterans Affairs Palo Alto Healthcare System, [3]Stanford University School of Medicine, [4]Stanford University, [5]York University Langone School of Medicine, [6]Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress and Traumatic Brain Injury, NYU School of Medicine

Background: A major challenge in understanding and treating PTSD is its clinical heterogeneity, which is likely determined by various neuro-biological abnormalities and reduces the effectiveness of standard group-comparison approaches. Here we propose using tolerance intervals (TIs), a statistical interval within which, with confidence level (α), a specified proportion (p) of a sampled population falls, to detect patterns of abnormality in patients.
Methods: Resting-state fMRI was recorded from 87 unmedicated PTSD cases and 105 warzone-exposed healthy controls (TEHCs). Functional connectivity (FC) profiles were calculated for 133 cortical and subcortical regions with respect to 7 previously-defined functional brain networks. TIs were calculated to model the distribution of each connectivity value within TEHCs and used to identify connections that presented a significant increase in abnormality rates within cases. This process was repeated 500 times while randomly subsampling 90% of the subjects each time, and region-network connections that were consistently selected were used in a downstream case-clustering analysis.
Results: Analysis revealed two subgroups among PTSD cases, each with a distinct pattern of FC abnormalities with respect to TEHCs. Subgroups differed clinically on levels of reexperiencing symptoms ($p<0.05$, FDR corrected) and behaviorally in performance in a choice reaction-time task ($p<0.005$, FDR corrected).
Conclusions: Our results provide a proof-of-concept for the utility of abnormality-based approaches for studying heterogeneity within clinical populations. Such approaches allow detecting subpopulations with distinct neurobiological signatures within a broad diagnostic category so that further mechanistic investigations can be focused on more biologically homogeneous subtypes.
Supported By: Cohen veterans bioscience
Keywords: BOLD fMRI, PTSD - Posttraumatic Stress Disorder, Subtypes, Resting State Functional Connectivity

O38. Relationships of Sleep With Cortical Thickness Among Trauma Exposed Individuals

Jeehye Seo[1], Katelyn Oliver[1], Caroline Daffre[1], and Edward Pace-Schott[1]

[1]Massachusetts General Hospital & Harvard Medical School

Background: Sleep difficulties may contribute to the functional abnormalities of neural circuitry that underlie the development and persistence of posttraumatic stress disorder (PTSD). We examined associations between sleep physiology, hyperarousal symptoms and regional cortical thickness in trauma-exposed individuals.
Methods: Persons exposed to trauma within the past 2 years (N=77) completed hyperarousal measures derived from the Clinician Administered PTSD scale and PTSD Checklist-5, as well as 2 weeks of actigraphy and sleep diaries, an acclimation and baseline night of ambulatory polysomnography (PSG), and a 3T structural MRI scan. Slow wave sleep (SWS)% and REM% were computed from PSG and mean sleep efficiency (SE) from actigraphy. Cortical thickness analyses were performed with FreeSurfer V6. Among all subjects, correlation maps were generated between cortical thickness and hyperarousal and sleep measures. A Monte Carlo simulation with 10,000 repetitions ensured a family-wise error of <0.05.
Results: Hyperarousal was negatively correlated with cortical thickness in the left paracentral/precuneus, SE was positively correlated with cortical thickness in the isthmus-cingulate/precuneus, medial orbitofrontal cortex and right middle temporal gyrus.
Conclusions: Greater hyperarousal - a prominent symptom of PTSD - was associated with lesser thickness in parietal portions of the default mode network (DMN). In contrast, greater sleep quality (SE) was associated with greater thickness in frontal and parietal portions of the DMN. SE is often reduced in PTSD. Thus, better sleep may protect, but hyperarousal may degrade thickness and perhaps function of the DMN in trauma-exposed individuals.
Supported By: R01MH109638
Keywords: Post Traumatic Stress Disorder, Hyperarousal, Sleep, Cortical Thickness

O39. Combat and Sleep Differentially Impact Resting-State Connectivity in OEF/OIF/OND Veterans

Ashley Clausen[1], Rachel Phillips[1], Courtney Haswell[1], VA Mid-Atlantic MIRECC Workgroup[2], and Rajendra Morey[1]

[1]Durham VA/Duke University Medical Centers, [2]Durham VA Medical Center

Background: Alterations in arousal associated with combat have a negative impact on mental and physical health including posttraumatic stress, cardiovascular disorders, and higher mortality. We examined the unique role of combat on measures of arousal, specifically sleep quality and resting-state connectivity in post-9/11 combat Veterans.

Methods: Male Veterans (n=2,013) completed self-reported psychological symptomology, combat and sleep. A subset (n=160) completed functional neuroimaging. Hierarchical regressions and generalized linear models (GLMs) were used to explore relationships between combat, sleep and whole-brain resting-state connectivity, controlling for age, education, and psychological symptomology. Results were considered significant a $p < 0.001$ (regressions) and t-values > 3.2 (GLMs).
Results: Combat predicted poorer sleep. Stronger resting-state connectivity was observed between: 1) left putamen and right thalamus; left calcarine fissure, middle cingulate cortex, and supramarginal gyrus; and left cuneus and supramarginal gyrus for high combat; 2) left putamen and right thalamus; left calcarine fissure, middle cingulate cortex, and supramarginal gyrus; and left cuneus and supramarginal gyrus for low combat; 3) regions within bilateral cerebellum; and right cerebellum and left inferior occipital lobe for healthy sleep; and 4) regions within bilateral cerebellum; and right cerebellum and left inferior occipital lobe for poor sleep.
Conclusions: Results highlight the unique impact of combat on sleep and resting-state connectivity. Veterans with high combat and poor sleep exhibit stronger connectivity in regions associated with vigilance and emotion. Veterans with low combat and healthy sleep display stronger connectivity in regions associated with regulation of autonomic responses, suggesting a differential impact on brain connectivity.
Supported By: The U.S. Department of Veterans Affairs (VA) Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MIRECC) core funds; the US Department of Veterans Affairs (VA) Office of Research and Development (5I01CX000748-01, 5I01CS000120-02); the National Institute for Neurological Disorders and Stroke (R01NS086885-01A1).
Keywords: Resting-State fMRI, War Veterans, Sleep, Arousal

O40. PTSD Augmented Psychotherapy With Ketamine (KPE) - First Results

Or Duek[1], Ifat Levy[1], Li Yutong[1], Charles Gordon[1], Benjamin Kelmendi[1], and Ilan Harpaz-Rotem[1]

[1]Yale University

Background: Augmenting prolonged exposure (PE) with pharmacotherapy has been suggested as a promising solution to address treatment-resistant PTSD and high dropout rates. Ketamine has been shown to have rapid-acting effects on treatment resistant depression following single infusion and with neurogenesis, that may promote new learning. We present first results of ketamine augmentation of intensive 7-day-PE (KPE) for PTSD patients.
Methods: 17 PTSD patients were randomized to Ketamine or Midazolam groups, after undergoing medical and clinical evaluation. The treatment protocol consisted of 7 daily sessions of PE with one-time 40min infusion of 0.5mg/kg ketamine or midazolam following the first exposure session inside an MRI. Before, after and follow-up treatment measurements included behavioral and fMRI data.
Results: PTSD symptoms scores were significantly reduced in both groups at 30-days follow-up [$F(1,13)=7.47$, $p<0.05$]. After 90 days follow-up, ketamine PTSD symptoms were lower than midazolam.

Resting-state MRI before and after infusion indicated connectivity between caudate and parieto-occipital were significantly higher in the ketamine group [$t(13)=5.74$, $p<0.05$].

Ketamine group showed higher global brain connectivity in tempo-occipital clusters at the end of treatment (7 days after first scan). A negative correlation between default mode network connectivity and PCL5 scores at follow up was found [$r=-0.57$, $t(10)=-2.2$, $p=0.051$)].
Conclusions: Augmenting PE with ketamine is a novel treatment. This study shows promising results in behavioral and neural measures, suggesting higher efficacy for KPE in long-term outcomes. The low number of patients requires us to use these results with caution, but evidence supporting changes in brain connectivity and no drop out propel further investigation.
Supported By: NARSAD 23260
Keywords: PTSD - Posttraumatic Stress Disorder, Ketamine, Prolonged Exposure, Clinical Trials

O41. Longitudinal Changes in Genome-Wide DNA Methylation Levels Related to Treatment Outcomes and Recovery From Post-Traumatic Stress Disorder

Christiaan Vinkers[1], Elbert Geuze[2], Sanne van Rooij[3], Mitzy Kennis[4], Remmelt Schur[4], Danny Nispeling[4], Alicia Smith[3], Caroline Nievergelt[5], Monica Uddin[6], Bart Rutten[7], Eric Vermetten[8], and Marco Boks[4]

[1]VU Medical Center, Amsterdam, [2]Military Mental Healthcare, [3]Emory University School of Medicine, [4]University of Utrecht, [5]University of California, San Diego, [6]University of South Florida, [7]Maastricht University Medical Centre, [8]Leiden University Medical Center

Background: Epigenetic mechanisms play a role in the detrimental effects of traumatic stress and the development of Post-Traumatic Stress Disorder (PTSD). However, there has been less attention whether successful treatment of PTSD can alter these epigenetic changes related to PTSD. This study therefore investigated longitudinal changes of blood-based genome-wide DNA methylation levels in relation to treatment outcomes of PTSD.
Methods: Longitudinal changes of blood-based genome-wide DNA methylation levels were analyzed in relation to treatment outcomes of PTSD in soldiers with remission of PTSD (N=21), non-responding PTSD patients (N=23), and a trauma-exposed military control group (N=23). All PTSD patients received trauma-focused psychotherapy. Replication was sought in an independent sample with recovery of deployment-related PTSD symptoms as outcome.
Results: The successful treatment of PTSD was accompanied by changes in DNA methylation at 12 differentially methylated genomic regions (APOB, MUC4, EDN2, ZFP57, GPX6, CFAP45, AFF3, TP73, UBCLP1, RPL13P, and two intergenic regions). Of these regions, previous longitudinal evidence already strongly implicated ZFP57 methylation to PTSD. Changes in ZFP57 methylation following treatment was over and above the effects of reduced PTSD symptoms and were replicated in an independent cohort.

Conclusions: This is the first study to demonstrate longitudinal changes in DNA methylation related to the effects of psychotherapy for PTSD which go beyond the reduction of symptom severity. Therefore, epigenetic mechanisms are involved both in the emergence and successful treatment of stress-related disorders such as PTSD. Psychological and biological systems closely interact, and our results emphasize the need for an integrated view of psychological and biological treatments.
Keywords: PTSD, Epigenetics, Longitudinal Study, Psychotherapy, Treatment Outcomes

O42. Genetic Overlap and Causality Between Cognitive Ability and Posttraumatic Stress Disorder

Renato Polimanti[1], Andrew Ratanatharathorn[2], Adam Maihofer[3], Karmel Choi[4], Murray Stein[3], Rajendra Morey[5], Mark Logue[6], Caroline Nievergelt[3], Dan J. Stein[7], Karestan Koenen[8], and Joel Gelernter[1], PTSD Working Group Psychiatric Genomics Consortium

[1]Yale University School of Medicine, [2]Columbia University, [3]University of California San Diego, [4]Harvard Medical School, [5]Duke University, [6]National Center for PTSD, [7]University of Cape Town, [8]Harvard University

Background: To investigate the genetic overlap and causality between cognitive ability traits and posttraumatic stress disorder (PTSD), we used large-scale genome-wide data from more than one million individuals investigated by the Psychiatric Genomics Consortium, the UK Biobank, 23andMe, and the Social Science Genetic Association Consortium.
Methods: We applied LD score regression to calculate genetic correlations among the traits investigated, polygenic risk score (PRS) analysis to determine the optimal genetic instruments, and multiple Mendelian randomization (MR) methods to estimate causal effects. Sensitivity analyses were conducted to exclude the presence of horizontal pleiotropy and heterogeneity affecting the MR results.
Results: PTSD showed a strong negative genetic correlation with educational attainment (EdAtt; rg=-0.26, p=4.6×10-8) and cognitive performance (rg=-0.16, p=96×10-4). PRS based on genome-wide significant variants associated with "highest math class completed" (MathClass) and EdAtt significantly predict PTSD (p=7.86×10-4 and p=6.16×10-4), but PTSD PRS does not predict MathClass and EdAtt (p>0.05). MR analysis indicated that MathClass and EdAtt have causal effects on PTSD (β=-0.37, p=2.03×10-6 and β=-0.23, p=0.004, respectively) and these associations are not independent from each other. Investigating further the PTSD-EdAtt relationship, we observed that trauma exposure and risk-taking behaviors are independent risk factors for PTSD (β=0.36, p=2.57×10-5 and β=0.76, p=6.75×10-4, respectively), while income completely mediates the causal effect of EdAtt on PSTD (multivariable MR: Income-β= -0.32, p=0.017; EdAtt-β=-0.04, p=0.786).
Conclusions: We report novel findings based on large-scale datasets regarding the relationship between cognitive ability and PTSD, supporting the role of socio-economic status as the key mediator in the causal relationship observed.
Supported By: R01 MH106595; U01 MH109532; VA National Center for PTSD Research
Keywords: PTSD - Posttraumatic Stress Disorder, Cognitive Performance, Mendelian Randomization

O43. Novel Brain-Behaviour Similarity Subgroups Across Neurodevelopmental Disorders

Grace Jacobs[1], Aristotle Voineskos[1], Natalie Forde[1], Erin Dickie[1], Meng-Chuan Lai[2], Peter Szatmari[1], Russell Schachar[3], Jennifer Crosbie[3], Paul Arnold[3], Margot J. Taylor[3], Anna Goldenberg[3], Lauren Erdman[3], Jason P. Lerch[3], Evdokia Anagnostou[4], and Stephanie Ameis[1]

[1]University of Toronto, Centre for Addiction and Mental Health, [2]Autism Research Centre, University of Cambridge; The Hospital for Sick Children; Centre for Addiction and Mental Health; University of Toronto, [3]The Hospital for Sick Children, [4]Holland Bloorview Research Institute

Background: Neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD) are each highly heterogeneous conditions that feature significant overlap in behaviours, genetic risk factors, cognitive and brain alterations. We used Similarity Network Fusion (SNF), a multi-data integrative clustering tool, to identify novel groups across NDDs featuring more homogeneous brain-behaviour profiles than those associated with categorical DSM diagnoses.
Methods: Measures from T1-weighted (cortical thickness, subcortical volume) and diffusion-weighted (fractional anisotropy) magnetic resonance imaging, and behavioural scores, were obtained for 182 children, aged 6-16 years with ASD (n=91), ADHD (n=52) or OCD (n=39) from the Province of Ontario Neurodevelopmental Disorders (POND) Network. Data integration and spectral clustering were done using SNF. General adaptive functioning measures (not involved in cluster determination) were used to evaluate validity of the identified groups.
Results: Four groups with distinct brain-behaviour profiles that cut across clinical diagnoses were identified. Group formation and top contributing measures driving formation were shown to be stable with resampling. General adaptive functioning ($F=21.46$, $p<0.0001$, $\eta 2=0.28$) was significantly different between groups, as well as were top contributing neurobiological features: right insula thickness ($F=47.76$, $p<0.0001$, $\eta 2=0.44$) and right thalamic volume ($F=18.51$, $p<0.0001$, $\eta 2=0.24$).
Conclusions: Our work provides preliminary indication that multi-modal data-integration methods such as SNF can identify clinical subgroups with homogeneous brain-behaviour profiles that cut across conventional DSM categories. Stability across other samples and testing of clinical validity of these groups is needed to determine whether they may have utility for diagnostic and treatment innovation.

Keywords: Brain Magnetic Resonance Imaging (MRI), Neurodevelopmental Disorders, Clustering, Similarity Network Fusion, Children

ORAL SESSION: NOVEL TOOLS AND TECHNIQUES FOR DISEASE PREDICTION, PROGRESSION AND INTERVENTION

3:00 p.m. - 4:45 p.m.

O44. Patterns of Hippocampal Plasticity and Antidepressant Response to Electroconvulsive Therapy

Amber Leaver[1], Megha Vasavada[2], Antoni Kubicki[2], Benjamin Wade[2], Gerhard Hellemann[2], Shantanu Joshi[2], Roger Woods[2], Randall Espinoza[2], and Katherine Narr[2]

[1]Northwestern Feinberg School of Medicine, [2]University of California, Los Angeles

Background: Studies repeatedly link electroconvulsive therapy (ECT) with hippocampal plasticity. However, whether hippocampal plasticity plays a role in ECT-related antidepressant remains unclear. This magnetic resonance imaging (MRI) study targeted functional and structural changes in hippocampal networks to determine relationships, if any, with ECT therapeutic outcomes.
Methods: Patients with depression (n=57, 30 female) underwent arterial spin-labeled (ASL), blood-oxygenation-level-dependent (BOLD), and anatomical MRI before ECT, after two treatments, and after ECT "index" (~4 weeks). In voxelwise analyses restricted to the hippocampus, amygdala, and parahippocampal cortex, linear mixed-effects models identified loci of cerebral blood flow (CBF) and gray-matter volume (GMV) change after index, separately for responders and nonresponders to ECT. These loci were used as seed regions to define hippocampal networks using BOLD-fMRI data from non-depressed controls (n=36, 19 female); networks were subsequently analyzed using graph theory to examine time-by-response interactions in patients.
Results: Separable loci of CBF and GMV change were identified, with nonresponders exhibiting large increases in bilateral anterior hippocampus, and responders showing CBF increases in right mid and left posterior hippocampus (p-corr<0.05). These regions defined spatially distinct brain networks in functional connectivity analyses. Within these networks, nonresponders exhibited acute increases in hippocampal connectivity after two treatments, while connectivity in responders did not change (p<0.05).
Conclusions: Patterns of ECT-related hippocampal plasticity distinguish treatment responders and non-responders. In particular, the location of ECT-related plasticity within the hippocampus differed with antidepressant outcome, and the impact on network connectivity was more pronounced in nonresponders, suggesting these effects are less attributable to antidepressant mechanisms.
Supported By: NIH U01MH110008, NIH R01MH092301, NARSAD Young Investigator Award

Keywords: Electroconvulsive Therapy (ECT), Magnetic Resonance Imaging (MRI), Major Depressive Disorder (MDD)

O45. Blood Biomarkers for Possible Early Detection of Risk for Alzheimer Disease (AD)

Alexander Niculescu[1], Helen Le-Niculescu[1], Kyle Roseberry[1], Sophia Wang[1], Debomoy Lahiri[1], and Andrew Saykin[1]

[1]Indiana University School of Medicine

Background: AD is a clear and present danger to older adults and has a profound socio-economic impact. Early identification of individuals at risk may open the door to preventive approaches. Memory dysfunction is a key feature of AD.
Methods: We propose to identify blood biomarkers that track a relevant related quantitative phenotype, the retention measure of recall in Hopkins Verbal Learning test (HVLT). Previous work by our group has identified blood gene expression biomarkers that track suicidal ideation and predict future suicidality (Le-Niculescu et al. Molecular Psychiatry 2013, 2015, 2017). We endeavored to use a similar approach to identify biomarkers for the memory measure of retention. We then studied how predictive they were of memory retention in an independent test cohort.
Results: We were successful in identifying gene expression biomarkers that were predictive of memory, more so when personalized by gender and diagnosis. We also examined the biological pathways involved, the drugs that modulate these candidate biomarkers, and repurposing of drugs using the biomarker signature. The top biological pathways were related to neuroinflammation signaling and amyloid processing. Over half of the top predictive biomarkers for memory also had prior evidence of involvement in other psychiatric disorders, particularly depression and stress, providing a molecular underpinning for the precursor effects of these disorders in AD.
Conclusions: Our work may lead to improved early diagnosis of risk and preventive treatment for memory disorders in general, and AD in particular, that result in decreased quality and quantity of life, at a huge cost to individuals, families and society.
Supported By: NIH, VA
Keywords: Alzheimer's Disease, Biomarkers, Blood, Gene Expression, Memory

O46. A National Study for Regional Variation of Inpatient ECT Utilization From 4,411 Hospitals Across the United States

Rikinkumar Patel[1], Venkatesh Sreeram[2], Tanu Thakur[3], Ramya Bachu[4], and **Nagy A. Youssef**[5]

[1]Griffin Memorial Hospital, [2]Harlem Hospital Center, [3]State University of New York Upstate, [4]Providence Hospital, [5]Medical College of Georgia at Augusta University

Background: Electroconvulsive therapy (ECT) has unsurpassed effectiveness in treatment-resistant psychiatric disorders especially mood disorders, psychotic disorders, and catatonia. The objective of this study is to examine regional

variation in the utilization of inpatient ECT across the United States (US), and its impact on length of stay and cost.
Methods: Study of the Nationwide Inpatient Sample databases compared patient and hospital characteristics and regional variation of ECT administration across the different regions of the US.
Results: The study included 41,055 inpatients who had ECT from 4411 hospitals. ECT use is significantly higher in the Midwest region. Higher proportion of females (65.2%) than males received ECT across the US. Medicaid beneficiaries had less probability to undergo ECT compared to Medicare (52.2%) or private insurance (32%). ECT was used mainly for mood disorders (84.3%). Marked reduction of inpatient cost ($25,298 to $38,244) and average hospital stay (16-day) occurred when ECT was initiated within the first 5 days of admission compared to later during the hospitalization.
Conclusions: There is a wide variability of utilization of ECT depending on the region, type of hospital, and type of insurance carrier. ECT is underutilized all over the US. Appropriate utilization of this effective treatment can greatly help patients who are not responding to standard therapeutics and reduce overall healthcare cost and length of stay, and most importantly alleviate suffering.
Supported By: Academic Affairs, Medical College of Georgia at Augusta University
Keywords: Electroconvulsive Therapy, Utilization, Depression, Bipolar, Schizophrenia

O47. Voice-Selective Prediction Abnormalities on the Psychosis Continuum

Ana Pinheiro[1], Michael Schwartze[2], and Sonja Kotz[2]

[1]University of Lisbon, [2]Maastricht University

Background: Auditory verbal hallucinations (AVH) are one of the cardinal symptoms of psychosis but are also present in 6-13% of individuals in the general population. An impaired internal forward model has been proposed to underlie the experience of AVH in psychotic patients, but it remains to be clarified whether similar abnormalities are present in nonclinical voice hearers.
Methods: The current study sought to answer the question of how hallucination predisposition in nonclinical and clinical participants modulates sensory feedback to sound production (predictions) of tones and voices using event-related potentials (ERP) of the electroencephalogram. Participants with low (n=15) and high (n=17) hallucination predisposition based on the Launay-Slade Hallucination Scale (LSHS) scores and first-episode psychotic patients (n=15) were tested in an auditory task consisting of self-triggered and externally triggered tones or self-voices.
Results: Groups differed in their comparison of predicted and perceived self-voice feedback only (group x condition interaction – $F(2, 41)=5.125$, $p=.010$, partial eta squared=.200). As expected, control participants showed a suppressed N1 to self-initiated voices. However, nonclinical participants with high hallucination predisposition displayed an enhanced N1 in response to self-initiated compared to externally generated voices. In psychotic patients, self-initiated sensory feedback was processed similarly to externally generated voices, reflected in a lack of N1 suppression.
Conclusions: Together, these findings suggest that altered sensory feedback to voice production is core to AVH. This provides support for the continuum model of psychosis that suggests that psychotic symptoms form a continuum in the general population.
Supported By: Fundação para a Ciência e a Tecnologia
Keywords: Event-Related Potentials, Voice, Sensory Prediction, Psychosis Continuum, Sensory Attenuation

O48. Retinal Function Anomalies in Young Offspring at Genetic Risk of Major Affective and Non-Affective Disorders: Significance for the Illness Pathophysiology

Anne-Marie Gagné[1], Moreau Isabelle[1], Jomphe Valérie[1], Diop Awa[1], and Maziade Michel[1]

[1]Université Laval

Background: Visual defects are well documented in psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder. One of the most replicated alteration in patients is decreased electroretinographic (ERG) responses. We previously showed a diminished rod b-wave amplitude in a small sample of children born to an affected parent (Hébert 2010). The fact that an ERG anomaly found in patients would also be observed in children at high genetic risk (HR) suggests a neurodevelopmental origin. Our aim was to extend our Biol Psychiatry 2010 study with a large offspring sample in order to search for further ERG anomalies that would also be carried by adult patients.
Methods: The ERG of 99 HRs (mean age 16.03; SD 6.14) and 223 healthy controls balanced for sex and age was recorded in light and dark adaptation condition. The a- and b-wave latency and amplitude of cones and rods were analyzed in HRs and controls.
Results: Cone b-wave latency was increased in HRs (ES: -0.31 p= 0.01). Rod b-wave amplitude was decreased (ES: 0.37; p=0.002) and latency was increased (ES: -0.35 p=0.004)
Conclusions: These new results considerably add to the previously reported findings (Biol Psychiatry 2010). Moreover, these young HRs displayed many ERG anomalies reported in adult patients (Hébert 2015, Hébert 2017) suggesting that the patients' retinal anomalies would mark an early neurodevelopmental hit to the CNS in childhood/adolescence.
Keywords: Retina, Offspring, Bipolar Disorder, Schizophrenia, Major Depressive Disorder (MDD)

O49. Ketamine Promotes Fear Extinction and Rescues Dysfunction of Glutamate Release in a Rat Model of PTSD

Paolo Tornese[1], Nathalie Sala[1], Caterina Paoli[1], Jessica Rosa[2], Ashok K. Datusalia[1], Maurizio Popoli[1], and **Laura Musazzi**[1]

[1]University of Milano, [2]University of São Paulo

Background: Stress represents a major risk factor for psychiatric disorders, including Post Traumatic Stress Disorder

(PTSD). Recently we dissected the destabilizing effects of acute stress in prefrontal cortex (PFC), with particular relevance to the glutamate system.
Methods: Male rats were subjected to inescapable acute footshock stress (FS, 40-min, 0.8 mA, 20 min total of actual shock with random intershock length) and sub-anesthetic racemic ketamine (10 mg/kg) was administered as a single i.p. injection at different times before or after FS. Basal and depolarization-evoked release of glutamate/GABA in PFC was measured with the method of purified synaptosomes in superfusion. Dendritic morphology was assessed in Golgi-Cox stained sections.
Results: Acute inescapable stress rapidly enhanced glutamate release/transmission in PFC, an effect sustained for at least 24 h (1w-ANOVA; $p<0,01$, $n=12$). Unexpectedly, significant atrophy of apical dendrites was observed already 24 h after FS, and for at least 14 days. Ketamine blocked the acute stress-induced enhancement of glutamate release when administered 24 or 72 h before, or 6 h after FS (1w-ANOVA; $p<0,01$, $p<0,05$, $n=10$) and prevented dendritic remodeling (1w-ANOVA; $p<0,05$). Ketamine injection 6 h after FS was also found to facilitate contextual fear extinction (1w-ANOVA; $p<0,01$, $p<0,05$, $n=12$).
Conclusions: These results show a rapid effect of ketamine in promoting contextual fear extinction, in line with previous studies suggesting a therapeutic action of the drug in PTSD models. At a mechanistic point of view, our data are consistent with a mechanism of ketamine involving re-establishment of synaptic homeostasis, through restoration of glutamate release, and structural remodeling of dendrites.
Supported By: Ministry of Education University and Research (MIUR) (PRIN 2015 prot. 2015HRE757_002)
Keywords: Ketamine, Post-Traumatic Stress Disorder, Animal Model, Glutamate, Fear Extinction

O50. Efficacy and Safety of an Asenapine Transdermal Patch (Asenapine Transdermal System, HP-3070) in the Treatment of Adults With Schizophrenia: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 6-Week Inpatient Study

Leslie Citrome[1], **David Walling**[2], Courtney Zeni[3], Marina Komaroff[3], and Alexandra Park[3]

[1]New York Medical College, [2]CNS Network, LLC, [3]Noven Pharmaceuticals, Inc.

Background: HP-3070, a once-daily asenapine transdermal patch for schizophrenia, offers favorable pharmacokinetics.
Methods: In this Phase 3, double-blind, inpatient study, adults with schizophrenia, Positive and Negative Syndrome Scale (PANSS) scores $\geq$80, and Clinical Global Impression-Severity of Illness Scale (CGI-S) scores $\geq$4 were randomized (1:1:1) to HP-3070 low-dose, HP-3070 high-dose (equivalent to sublingual asenapine 5mg and 10mg BID, respectively), or placebo. Primary endpoint was Week 6 PANSS score change from baseline (CFB) vs placebo; key secondary endpoint was Week 6 CGI-S score CFB vs placebo. Safety measures included treatment-emergent adverse events (TEAEs) and dermal assessments.
Results: 614 patients received study medication (204 high-dose, 204 low-dose, 206 placebo). Week 6 least squares mean (LSM) (standard error [SE]; 95% CI) estimates of PANSS score treatment comparison (HP-3070-placebo) for CFB were -4.8 (1.634; -8.06, -1.64; $p=0.003$) and -6.6 (1.630; 9.81, 3.40; $p<0.001$) for high-dose and low-dose groups. Week 6 LSM (SE; 95% CI) estimates for CGI-S treatment comparison (HP 3070-placebo) for CFB were 0.4 (0.100; 0.55, 0.16; $p<0.001$) and 0.4 (0.099; 0.64, 0.25; $p<0.001$) for high- and low-dose groups. Most TEAEs were mild or moderate and consistent with sublingual asenapine. Application site TEAEs were higher for HP-3070 (14.2% high-dose, 15.2% low-dose) vs placebo (4.4%), although discontinuations due to application site reactions or skin disorders were $\leq$0.5% across groups.
Conclusions: In this study, HP-3070 was efficacious, safe, and well-tolerated in treating schizophrenia, meeting primary and key secondary endpoints for both doses. As the first transdermal antipsychotic in the US, HP-3070 will offer patients a novel treatment option for schizophrenia.
Supported By: Noven Pharmaceuticals, Inc., a wholly-owned subsidiary of Hisamitsu Pharmaceutical Co.
Keywords: Schizophrenia, Asenapine, Transdermal Patch, Phase 3

ORAL SESSION: GENETIC RISK AND ANIMAL MODELS FOR DISEASE
3:00 p.m. - 5:00 p.m.

O51. Beyond C4: Analysis of the Complement Gene Pathway Shows Enrichment for IQ in Patients With Schizophrenia and Healthy Controls

Jessica Holland[1], Donna Cosgrove[1], Denise Harold[2], Laura Whitton[1], Aiden Corvin[3], Michael Gill[3], David Mothershill[1], Derek Morris[1], and Gary Donohoe[1]

[1]National University of Ireland, [2]Trinity College Dublin, [3]School of Medicine, Trinity College Dublin

Background: In multiple Genome wide Association Studies (GWAS) of Schizophrenia (SZ), the strongest association with SZ has consistently been found at the major histocompatibility complex - a region synonymous with immune function. Variation in cognitive performance, which is strongly predictive of functional outcome in SZ, is explained by several variants at this locus related to the complement system, including complement C4. Here, we analyse the effects of genes related to complement, and whether these are enriched for IQ or SZ risk.
Methods: To test if genetic variants related to immune function are associated with cognition, a gene-set corresponding to 'complement' function was chosen from previous literature. Gene enrichment analysis was performed for this set based on summary statistics from a GWAS of human intelligence ($N=269,867$), and for SZ ($N=150,064$), using MAGMA. After enrichment analysis, a polygenetic risk score (PRS) was computed for 1238 SZ patients and healthy controls. Block

regression analysis was performed testing a relationship between complement PRS and cognition.
Results: Genes in the complement pathway are significantly enriched for the phenotype of IQ. In a gene-wide analysis of the 31 genes form the complement gene-set (but excluding C4), six genes were nominally enriched for IQ, of which Complement factor H (CFH) survived correction. In a sample of patients and healthy participants (N=1238), the complement pathway was similarly associated with variation in cognition, particularly IQ, although this finding did not survive testing correction (p=0.037).
Conclusions: Collectively, these findings suggest an association between the complement system and cognition that extends more broadly than C4.
Supported By: IRC- Irish Research Council
Keywords: Cognition, Schizophrenia, Cognitive Neuroscience, Immunogenetics

O52. Deep Brain Stimulation of the Medial Forebrain Bundle in a Rodent Model of Depression: Exploring Dopaminergic Mechanisms

Mate Dobrossy[1], Stephanie Thiele[1], Philipp T. Meyer[1], and Volker Coenen[1]

[1]University Freiburg Medical Center

Background: Medial forebrain bundle (MFB) DBS for treatment-resistant major depressive disorder can offer some patients a long-lasting control of the disease. In experimental rodent models of depression, such as the Flinders Sensitive Line (FSL), MFB DBS can alleviate depressive-like phenotype, and it offers a platform to investigate DBS's mechanisms of action. The study examined the role of dopaminergic mechanisms in MFB stimulation-mediated behavior changes using raclopride and microPET.
Methods: Male FSL rats with matched phenotype were divided into 4 groups: FSL (no treatment), FSL+ (DBS), RAC (raclopride), and RAC+ (raclopride and DBS). Animals were implanted with bilateral electrodes targeting the MFB and given 11 days access to raclopride in the drinking water with or without concurrent continuous bilateral DBS over the last 10 days. Behavioral testing was conducted post-stimulation. Pre- and post-raclopride treatment a PET scan was performed to determine the percentage of D2 receptor blockage.
Results: PET imaging showed that raclopride administration blocked approximately 36% of the dopamine receptors in the striatum, and behaviorally the D2R antagonist enhanced depressive-like symptoms in the Forced Swim and the Social Interaction tests, as well in the Elevated Plus Maze. MFB stimulation partially reversed the depressive-like phenotype and reduced the level of D2R blockage as indicated by PET following raclopride administration. The raclopride treated MFB DBS animals had increased levels of D1R and D2R mRNA suggestive of stimulation mediated increase in dopamine receptors.
Conclusions: Chronic and continuous MFB DBS could act via the modulation of the midbrain dopaminergic transmission, including impacting on post-synaptic dopamine receptor profile.
Supported By: Brain-Links-BrainTools Cluster of Excellence funded by the German Research Foundation (DFG, grant number EXC 1086).
Keywords: DBS, Animal Model of Depression, Medial Forebrain Bundle, Dopamine

O53. Maternal Immune Activation Induced Structural Brain Alterations in Macaques: A Longitudinal Study

Roza Vlasova[1], Ana-Maria Iosif[2], Jeffrey Bennett[2], Melissa Bauman[2], Martin Styner[1], Cameron Carter[2], and David Amaral[2]

[1]University of North Carolina, [2]University of California Davis

Background: The impact of maternal immune activation (MIA) on neurodevelopment has been widely studied in rodents. However, only two non-human primate (NHP) neuroimaging studies have been reported. Viral MIA caused reduction of grey and white matter while bacterial MIA was associated with enlargement of brain structures at 12 months. In a pilot study, MIA NHP's showed typical early development with behavioral changes after 2 years. Here, we investigated brain structural alterations associated with MIA in a new sample of NHP's using a longitudinal neuroimaging design.
Methods: 28 male offspring of Rhesus macaques (pregnant mothers received PolyICLC or saline injection) were scanned (Siemens Skyra 3T) at 6, 12 and 24 months. T1w-images were automatically segmented into brain regions using unbiased multi-atlases. Volumetric measurements were extracted for amygdala, hippocampus, lateral ventricles, prefrontal, frontal, cingulate, temporolimbic cortices.
Results: The MIA monkeys generally showed typical behavioral development between 6 and 24 months. Both groups displayed parallel trajectories from 6 to 24 months with no significant group by time interactions. The PolyICLC group had smaller volumes in prefrontal (LH: by 414 mm3, p=0.004; RH: by 398 mm3, p=0.006) and frontal (by 407 mm3, p=0.02; RH: by 414 mm3, p=0.01) cortices. After adjusting for ICV, effects remained significant in frontal and prefrontal cortices. No significant group differences were found in other regions.
Conclusions: These findings suggest that the impact on brain structure of MIA is present early in life, prior to the onset of behavioral manifestations, and anatomical changes appear preferentially in the frontal and prefrontal regions of the brain.
Supported By: NIMH Conte Center (5P50MH106438)
Keywords: Maternal Immune Activation, Non-human Primates, Structural Magnetic Resonance Imaging

O54. The Effect of Gut Microbiota on Glutamatergic/GABAergic Gene Expression in Adult Mice

Vivek Philip[1], Dwight Newton[1], Hyunjung Oh[1], Steve Collins[2], Premysl Bercik[2], and Etienne Sibille[1]

[1]Centre for Addiction and Mental Health, [2]McMaster University

Background: Studies using germ-free (GF) mice (born without gut bacteria) have shown that gut microbiota (bacteria) can influence behaviour by modulating neurochemical pathways in

the brain. Our group showed that bacterial colonization of GF mice leads to normalization of anxiety-related behaviour. GABA deficits leading to disrupted excitation-inhibition balance (EIB) has been reported in mood disorders. This study aims to determine the effect of gut microbiota on EIB-relevant gene expression.
Methods: Using qPCR we analyzed the expression of 15 select glutamatergic/GABAergic genes (EIB proxies) from brains of control, GF, and ex-GF mice colonized with control microbiota (n=6/group) in the hippocampus, amygdala, and medial prefrontal cortex (mPFC). Differential gene expression was assessed using one-way ANOVA with post-hoc Bonferroni correction. Gene co-expression network analysis was performed within and across groups and assessed by permutation analysis.
Results: EIB-related genes showed significant changes in all regions of GF mice versus controls ($p<0.03$). Colonization of GF mice with control microbiota reversed the majority (65%) of such changes in all regions. GF co-expression networks were significantly different versus controls ($p<0.006$) and ex-GF ($p<0.009$) for all regions. Ex-GF networks were not different ($p=0.60$) versus controls in the hippocampus but were in the amygdala ($p=0.011$) and mPFC ($p=0.008$).
Conclusions: The absence of gut microbiota disrupts the expression of EIB-relevant genes, which is normalized following colonization with control microbiota. Interestingly, colonization also restored the co-expression network structure in the hippocampus specifically. Studies interrogating a causal link between microbiota-induced changes in behaviour and EIB-relevant genes are warranted.
Supported By: Farncombe Institute Collaboration Grant
Keywords: Microbiome-Gut-Brain Axis, Glutamate/GABA, Excitation/Inhibition Balance, Commensal Gut Bacteria

O55. The Genetic Factors Influencing Externalizing Psychopathology Overlap With Those Influencing Neurocognition and Show Developmental Variation

Josephine Mollon[1], Emma Knowles[2], Samuel Mathais[3], Amanda Rodrigue[1], Marinka Koenis[2], Ruben Gur[4], Juan Manuel Peralta[5], Elise Robinson[6], Raquel Gur[4], John Blangero[7], Laura Almasy[8], and David Glahn[2]

[1]Children's Hospital/Harvard Medical School, [2]Yale University, [3]Yale University School of Medicine, [4]University of Pennsylvania, [5]University of Texas of the Rio Grande Valley, [6]Harvard Medical School, [7]University of Texas Health Science Center, [8]South Texas Diabetes and Obesity Institute, University of Texas Health Science Center at San Antonio & University of Texas of the Rio Grande Valley

Background: The genetic overlap between dimensions of psychopathology and neurocognition remains unclear. Moreover, while genetic factors underlie most psychopathologies, whether these genetic factors show developmental variation remains unexamined.
Methods: Using data from individuals aged 8 to 21 from the Philadelphia Neurodevelopmental Cohort, we conducted bifactor analyses on psychiatric interview data to generate dimensions of psychopathology (general, anxious-misery, externalizing, fear, psychosis). We used an empirical relatedness matrix to establish the heritability of these dimensions in individuals of European American ancestry ($N = 4614$), as well as their genetic correlations with neurocognition. Gene $\times$ Age interaction analyses were conducted to determine whether genetic factors influence developmental changes in psychopathology.
Results: General and externalizing psychopathologies were significantly heritable ($h2=0.28$, $p=0.006$; $h2=0.49$, $p<0.001$). General psychopathology showed significant phenotypic, but not genetic, correlations with neurocognition. Externalizing was genetically correlated with general cognition ($\rho g=-0.42$, $p<0.001$), working memory ($\rho g=-0.54$, $p=0.011$), face memory ($\rho g=-0.41$, $p=0.005$), verbal reasoning ($\rho g=-0.52$, $p<0.001$), nonverbal reasoning ($\rho g=-0.53$, $p=0.002$), verbal knowledge ($\rho g=-0.27$, $p=0.008$), and motor speed ($\rho g=0.59$, $p=0.001$). Gene $\times$ Age analyses revealed a significant increase in genetic variance on general psychopathology between childhood and adulthood ($\gamma=0.54$, $p<0.001$), suggesting an increase in the scale of action of genetic factors with age. A significant decay in genetic correlation on externalizing psychopathology with age ($\lambda=0.18$, $p=0.025$) suggested variation in genetic factors between childhood and adulthood.
Conclusions: Externalizing psychopathology shares genetic influences with neurocognition. Moreover, the genetic factors underlying externalizing psychopathology show developmental variation between childhood and adulthood.
Supported By: R01 MH107248 and MH107235
Keywords: Developmental Psychopathology, Psychiatric Genetics, Neurocognition

O56. Model Systems in Mice to Study Peripheral Inflammation, Resulting in Neuroinflammation

Lawrence Fourgeaud[1], Jan-Sebastian Grigoleit[1], Shannon Campbell[1], Stormy Needham[1], and Anindya Bhattacharya[1]

[1]Janssen Research and Development

Background: The link between peripheral inflammation and neuropsychiatric disorders has gained momentum in the recent past. Although the sequalae of peripheral inflammation leading to clinical symptomology is unclear, it is becoming apparent that microglia and neuroinflammation play a critical role in the pathophysiology of such disorders. To model the consequences of elevated inflammation, we challenged mice peripherally with LPS and polyI:C to study effects on brain neuroinflammation.
Methods: Adult mice received intraperitoneal injections of LPS and polyI:C. Changes in plasma and brain homogenates cytokines/chemokines levels were measured at 1, 4 and 24 hr using Luminex® multiplex technology. Consequences on microglia phenotypes were analyzed 48h ex-vivo using FACS analysis and immunohistochemistry; or in-vivo using 2-photon imaging microscopy. 2-photon imaging was performed on anesthetized Cx3Cr1GFPhet mice between 50-200 μm deep in the sensory cortex through a thin skulled cranial window using a Thorlabs Bergamo® microscope.

Results: Systemic injection of LPS and polyI:C lead to a transient increase in cytokine/chemokine levels in both plasma and brain. This initial inflammatory response resolved over the course of 24h. Since the consequences on microglial activation follows the initial inflammation, we assessed changes in microglia phenotypes 48h post injection. We observed increased microglial density and changes in microglia morphology reflecting microglia activation ex-vivo; this effect was more pronounced for LPS. To monitor changes in microglia phenotype over time in-vivo, we performed 2-photon imaging and confirmed a clear phenotypic change in microglial morphology upon LPS that was tractable in vivo.
Conclusions: Our data unequivocally demonstrates neuroinflammation after peripheral LPS and polyI:C treatment.
Keywords: Neuroinflammation, Microglia, Two-Photon Imaging, Astrocytes

O57. Neanderthal-Derived Genetic Variation is Associated With Dopamine Synthesis in Living Humans

Michael Gregory[1], Daniel Eisenberg[1], J. Shane Kippenhan[1], Philip Kohn[1], and Karen Berman[1]

[1]National Institute of Mental Health

Background: Prior to disappearing from the fossil record, Neanderthals interbred with modern humans, contributing a legacy that survives in our DNA today. Previously, we found that having greater Neanderthal-derived genetic variation biases human brain and skull shapes to resemble Neanderthal remains. Here, we investigated whether Neanderthal-derived variation also impacts the dopaminergic system using PET.
Methods: Illumina SNP-chip data and 18F-fluoroDOPA (FDOPA) PET (16 mCi, 27 dynamic scan-frames, 90 minutes) were acquired on 173 healthy Caucasian adults (36.5+/-12.4 years, 87 males). After imputation, we calculated the polygenic-load of Neanderthal-derived genetic variants ("NeanderScore") for each individual. PET data were aligned to standard space, FDOPA-uptake (Ki) was measured at each voxel using a cerebellar reference region with the Patlak-Gjedde method, and the results were spatially smoothed (10mm FWHM). Voxel-wise linear regression identified relationships between FDOPA-Ki and NeanderScore, controlling for age, sex, and ancestry-related components at $p<0.05$, FWE-corrected for multiple comparisons.
Results: NeanderScore significantly correlated with FDOPA-Ki in the left caudate extending into the ventral striatum, and in the pons. For both regions, FDOPA-Ki decreased as NeanderScore increased.
Conclusions: Though Neanderthal ancestry has been associated with skull and brain shapes, little is known about the neurofunctional implications of this inheritance. Here, we show that Neanderthal-derived DNA is associated with dopaminergic tone of the ventral striatum and the pons. The Neurosynth meta-analytic database implicates the striatal region in reward processing, and the pontine region in pain pathways. The directionality of the findings suggests that those endowed with greater Neanderthal admixture have lower dopaminergic tone in reward- and pain-associated regions.
Supported By: NIMH Intramural Program
Keywords: Evolutionary Genetics, FDOPA, Neanderthal, Reward Processing, Pain Processing

O58. Childhood Urbanization Affects Prefrontal Cortical Responses to Trait Anxiety and Interacts With Polygenic Risk for Depression

Xiao Zhang[1], Hao Yan[2], Hao Yu[2], Xin Zhao[2], Shefali Shah[3], Zheng Dong[2], Guang Yang[3], Xiaoxi Zhang[2], Timothy Muse[3], Jing Li[2], Sisi Jiang[2], Jinmin Liao[2], Yuyanan Zhang[2], Qiang Chen[3], Daniel Weinberger[3], Weihua Yue[2], Dai Zhang[2], and **Hao Yang Tan**[3]

[1]Institute of Mental Health, Peking University; Lieber Institute for Brain Development, [2]Institute of Mental Health, Peking University, [3]Lieber Institute for Brain Development

Background: Global increases in urbanization have brought dramatic economic, environmental and social changes. However, less is understood about how these may influence disease-related brain mechanisms underlying epidemiological observations that urban birth and childhoods increases the risk for neuropsychiatric disorders, including depression.
Methods: In a genetically homogeneous Han Chinese adult population with divergent urban (N=249) and rural (N=241) birth and childhoods, we examined the structural and functional MRI (3T) neural correlates of childhood urbanicity, focusing on behavioral traits responding to social status threats, and polygenic risk for depression.
Results: Subjects with divergent rural and urban childhoods were similar in adult socioeconomic status and were genetically homogeneous. Urban childhoods, however, were associated with higher trait anxiety-depression ($p<0.05$). On structural MRI, urban childhoods were associated with relatively reduced medial prefrontal gray matter volumes ($p<0.05$ whole brain corrected). Functional medial prefrontal engagement under social status threat during working memory correlated with trait anxiety-depression in subjects with urban childhoods, to a significantly greater extent than in their rural counterparts ($p<0.001$ uncorrected, $p<0.05$ small-volume corrected), implicating an exaggerated physiological response to the threat context. Stress-associated medial prefrontal engagement also interacted with polygenic risk for depression, significantly predicting a differential response in individuals with urban but not rural childhoods ($p<0.001$ uncorrected, $p<0.05$ small-volume corrected).
Conclusions: Developmental urbanicity differentially influenced medial prefrontal structure and function, at least in part through mechanisms associated with the neural processing of social status threat, trait anxiety, and genetic risk for depression, which may be factors in the association of urbanicity with adult psychopathology.
Supported By: R01MH101053; National Natural Science Foundation of China 81361120395
Keywords: Working Memory fMRI, Psychosocial Stress, Polygenic Genetic Correlation, Major Depression, Urbanicity

Poster Abstracts

Thursday, May 16, 2019

POSTER SESSION 1
5:00 P.M. - 7:00 P.M.

T1. Why so Serious? Ability to Accurately Identify Happy Faces is Associated With Individual Differences in Lateral-Orbitofrontal Cortex Volume in Older Men

Joseph Kim[1], Vincent Koppelmans[1], Benjamin Tasevac[1], Kathryn Durnford[1], Jacob Germain[1], Scott Langenecker[1], and Sara Weisenbach[1]

[1]University of Utah School of Medicine

Background: Previous studies suggest that impaired interpersonal functioning can be partly characterized by subtle changes in facial emotion processing. Neuroimaging evidence has shown that the lateral-orbitofrontal cortex (L-OFC) plays a particular role in processing happy faces. In the present study, we test the association between L-OFC volume in older men and women and their facial emotion recognition performance.
Methods: Twenty older-adult participants (61-79, mean ± SD: 67.9 ± 4.9; 11 females and 9 males) with a range of depressive symptom severity (mean HAM-D ± SD: 12.7 ± 9.2) performed the Face Emotion Perception Test (FEPT) and also underwent a structural T1 MRI scan. Structural MRI data were processed for volumetric segmentation using the FreeSurfer image analysis suite. Regression analyses were conducted using L-OFC volume as a predictor, d' (sensitivity index with false alarm taken into account) for happy, sad, angry, and fearful faces as outcome variables, respectively, and age and depression symptom severity as covariates.
Results: For adult men, L-OFC volume positively predicted accuracy for happy face recognition on happy face d' ($B = 1.04$, $p < .05$). This association was not significant in women ($B = -.29$, $p > .1$).
Conclusions: In men, L-OFC volume predicts the ability to accurately judge happy faces. These results extend previous functional neuroimaging findings by demonstrating a potential sex difference in brain-behavior relationships in social cognition of older adults across the depression severity spectrum, and further suggest a possible novel neuromodulatory treatment target for patients suffering from social functioning impairments.
Supported By: VA Rehabilitation Research & Development (CDA) awarded to SLW
Keywords: Emotional Facial Processing, Sex Differences, Orbitofrontal Cortex, Structural MRI, Late-Life Depression

T2. Brain Age in Bipolar Disorders - Effects of Lithium Treatment

Tomas Hajek[1], Holly van Gestel[1], Katja Franke[2], Joanne Petite[1], Claire Slaney[1], Julie Garnham[1], Rudolf Uher[1], and Martin Alda[1]

[1]Dalhousie University, [2]Jena University Hospital

Background: Bipolar disorders (BD) increase the risk of dementia and show biological and brain alterations, which resemble accelerated ageing. Lithium may counter some of these processes and lower the risk of dementia. Yet, no study has specifically investigated the effects of Li on brain age.
Methods: We acquired structural MRI scans from 84 BD participants (41 with and 43 without Li treatment) and 37 controls. We used machine learning model trained on an independent sample of 504 controls to estimate the individual brain ages of study participants, and calculated the BrainAGE score by subtracting the chronological from the estimated brain age.
Results: BrainAGE scores were highest in non-Li, intermediate in Li treated BD participants and lowest in controls ($F(2, 117)=9.74$, $p<0.001$). The estimated brain age was significantly higher than chronological age in the non-Li (4.28±6.33 years, matched $t(42)=4.43$, $p<0.001$), but not the Li group (0.48±7.60 years, NS). Li treated participants had lower BrainAGE scores than the non-Li group ($F(1, 80)=8.69$, $p=0.004$), even when we controlled for antipsychotic treatment, which was associated with greater BrainAGE scores ($F(1, 80)=4.84$, $p=0.03$). Prophylactic response to Li was unrelated to BrainAGE scores.
Conclusions: BD participants not treated with Li showed diffuse brain alterations resembling advanced brain aging. In support of the "neuroprotective" effects of Li, similar changes were not observed in Li treated participants, but were more pronounced in those treated with antipsychotics. The association between Li treatment and BrainAGE was independent of long-term treatment response and may thus generalize beyond BD to neurodegenerative disorders.
Supported By: This study was supported by funding from the Canadian Institutes of Health Research (103703, 106469 and 142255), Nova Scotia Health Research Foundation, Dalhousie Clinical Research Scholarship to T. Hajek, Brain & Behavior Research Foundation (formerly NARSAD) 2007 Young Investigator and 2015 Independent Investigator Awards to T. Hajek. The Ministry of Health, Czech Republic (grants number 16-32791A, 16-32696A).
Keywords: Bipolar Disorder, Lithium Response, Antipsychotics, BrainAGE, Machine Learning

T3. Biological Aging in Mental Health: An Integrative Study of Five Biological Age Indicators

To see this Abstract, please see Oral Abstract #O18.

T4. Poster Withdrawn

T5. The Relationship Between Olfaction and Cognitive Function in a Sample of Healthy Middle-Aged Adults

Kirsten Cline[1], Erin McGlade[2], Deborah Yurgelun-Todd[2], and Chandni Sheth[1]

[1]University of Utah, [2]University of Utah; School of Medicine; Mental Illness Research Education Clinical, Centers of Excellence (MIRECC), Salt Lake City Veterans Affairs

Background: Olfactory dysfunction is an early marker for Alzheimer's disease and Parkinson's disease-related cognitive deficits. Furthermore, among older adults, olfaction predicts future cognitive decline associated with mild cognitive impairment. However, the relationship between cognitive function and olfaction in healthy middle-aged adults has heretofore not been investigated.
Methods: Sixty-one healthy middle-aged adults ages 40-60 (52.4% females, average age = 49 years), completed the University of Pennsylvania Smell Identification Test (UPSIT) as a measure of olfactory function and a battery of neurocognitive assessments including the Boston Naming Test (BNT) and Delis-Kaplan Executive Function System (DKEFS) Verbal Letter Fluency Test. Spearman's correlation tests were performed between UPSIT scores and scores on the BNT and DKEFS Verbal Letter Fluency Test with sex and age as covariates.
Results: Correlations showed a significant positive association between UPSIT scores and performance on the BNT (Spearman's rho=0.35, p=0.006). A positive association between the UPSIT scores and the DKEFS Verbal Letter Fluency Test also was observed (Spearman's rho=0.28, p=0.03).
Conclusions: These results suggest that reduced olfaction is associated with reduced performance in selective cognitive domains, namely verbal retrieval. Performance on the BNT is an indicator of lexical retrieval and word-finding ability, while performance on the letter fluency task indicates lexical access ability as well as executive control.

Thus, olfactory function may provide a window into the earliest age-related brain changes that affect neural aspects of age-related cognitive decline.
Supported By: Utah Science Technology and Research (USTAR, Yurgelun-Todd)
Keywords: Cognitive Function, Olfaction, Middle Aged Adults

T6. Social Anhedonia Mediates the Relationship Between Posttraumatic Stress Severity and Reduced Social Network Diversity

Elizabeth Olson[1], Tate Overbey[1], Gwenievere Birster[1], Scott Rauch[1], and Isabelle Rosso[1]

[1]McLean Hospital/Harvard Medical School

Background: Social dysfunction following trauma exposure often includes social detachment and withdrawal. Translational research indicates that stress exposure can result in blunted reward sensitivity, which may contribute to social withdrawal following trauma exposure. In this study, we aimed to identify the mechanistic contribution of social anhedonia to social withdrawal in trauma-exposed individuals.
Methods: Participants were 39 adults: 18 with DSM-IV posttraumatic stress disorder (PTSD) and 21 trauma-exposed non-PTSD controls (10 male, 29 female; age range 19-50 years). Measures included the Revised Social Anhedonia Scale (RSAS), Social Network Index (SNI), and Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Analyses were conducted in SPSS with Hayes' PROCESS macro using bias-corrected bootstrapped 95% confidence intervals.
Results: Higher posttraumatic stress symptom severity was associated with reduced social network diversity, B = -0.037, SE = 0.016, p = 0.028, and with increased social anhedonia, B = 0.277, SE = 0.079, p = 0.001. After controlling for CAPS-5 total scores, greater social anhedonia was significantly associated with reduced social network diversity, B = -0.068, SE = 0.032, p = 0.043. The indirect effect was significant (95% CI: -0.0539 to -0.0021), and after controlling for social anhedonia, CAPS-5 scores were not significantly associated with social network diversity, B = -0.018, SE = 0.018, p = 0.316.
Conclusions: The relationship between increased posttraumatic stress symptom severity and reduced social network diversity was mediated by social anhedonia, supporting the hypothesis that reward processing deficits may drive the relationship between posttraumatic psychopathology and social withdrawal.
Supported By: Eleanor and Miles Shore Fellowship, Harvard Medical School
Keywords: PTSD - Posttraumatic Stress Disorder, Anhedonia, Stress, Social Functioning

T7. Neural Responses to Script-Driven Imagery in Women With PTSD Following a Traumatic Childbirth

Zohar Berman[1], Arielle Kaim[2], Lisa Shin[3], and Sharon Dekel[1]

[1]Massachusetts General Hospital & Harvard Medical School, [2]Boston University, Massachusetts General Hospital, [3]Tufts University, Massachusetts General Hospital & Harvard Medical School

Background: Although childbirth is considered a uniformly happy event, accumulating evidence suggests that as many as one third of women experience their delivery as psychologically traumatic, and some also proceed to develop childbirth-related posttraumatic stress disorder (CB-PTSD). Nevertheless, the neural aberrations which may underlie this condition are completely unknown. In

particular, it is unclear whether the neural substrates of trauma memory recall, a central process in the development and maintenance of PTSD, are altered in women who developed CB-PTSD. Here we use fMRI to investigate neural responses to script-driven imagery, a well-known procedure to target personal recall of trauma, in women who report a highly stressful childbirth, with and without CB-PTSD.

Methods: Sixty postpartum women will be enrolled in this study. BOLD responses to personalized ''scripts'' portraying the childbirth experience will be compared between the groups and associations with obstetric (e.g., mode of delivery) and psychosocial factors will be assessed.

Results: Differences in BOLD responses to trauma memory recall in women with CB-PTSD compared with non-CB-PTSD controls are expected, including increased limbic and diminished prefrontal activations. Furthermore, CB-PTSD-related neural alterations are expected to be associated with the obstetric and psychosocial factors.

Conclusions: Gaining insights into CB-PTSD's neural mechanisms is a critical step in the efforts to enhance our understanding of this overlooked condition and may help to map and distinguish among postpartum psychopathologies to inform better identification and care of women with this condition, to the consequential benefit of both the mother and the child.

Supported By: The Rothschild Postdoctoral Fellowship (Yad Hanadiv Foundation), Harvard University's Mind Brain Behavior Interfaculty Initiative

Keywords: PTSD - Posttraumatic Stress Disorder, Functional MRI, Emotional Memory, Postpartum, Women's Mental Health

T8. The Association of Heightened Threat Processing and Self-Harm Behavior

Matthew Dobbertin[1], Karina Blair[1], Patrick Tyler[1], Laura Thornton[1], Harma Meffert[1], Stuart White[1], Brittany Taylor[1], Emily Leiker[1], Niraj Shah[1], Kimberly Johnson[1], Heba Abdel-Rahim[1], and Kayla Pope[2]

[1]Boys Town National Research Center, [2]Creighton University-UNMC

Background: Self-harm is common in adolescents and represents a risk factor for suicidal behavior. Thus, reliable markers for self-harm would be useful. However, current risk assessment tools based on demographic/ clinical factors have not proven successful. In this study we seek to identify neural markers associated with self-harm in adolescents.

Methods: 83 participants were recruited shortly after their arrival at a residential care facility and had been referred for severe behavioral and mental health problems. Participants were scanned while they performed an affective number Stroop task which allowed examination of threat processing and response control. BOLD responses were related to self-harm incidents in their first 90 days in residential care.

Results: Increased responsiveness to threat stimuli in the anterior insula cortex (aIC) and middle frontal cortex were positively associated with self-harm episodes recording in the first 90 days of residential care as was responsiveness within dorsomedial prefrontal cortex during goal-directed processing. Importantly, these relationships were observed independently of relationships with anxiety/ depression psychopathology.

Conclusions: These data are consistent with suggestions that enhanced feelings of fear, mediated by the aIC and appraised within middle frontal gyrus, are associated with elevated self-harm behavior. In addition, they suggest that individuals at risk for self-harm behaviors may require compensatory recruitment of regions implicated in response control to maintain appropriate behavioral performance. Together these data represent neural markers associated with self-harm in adolescents and could be important in future suicide-prevention work.

Keywords: Self-Harm, Anxiety, BOLD fMRI, Suicide Behavior

T9. Biased Resolution of Approach-Avoidance Conflict Learning in Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is characterized by alterations in both avoidance and approach systems, showing heightened avoidance of trauma reminders as well as impaired reward processing. Although these competing processes are well-known in PTSD, no prior research has investigated the conflict of approach and avoidance behavior in PTSD. The purpose of this study was to investigate approach and avoidance systems in PTSD using an approach-avoidance conflict task.

Methods: 43 Adult women with a current diagnosis of PTSD and 12 age-matched, healthy controls were recruited to perform an approach-avoidance conflict task. Trials were separated into conflict phases (the option most likely to win points was also most likely to show a trauma-related image) and congruent phases (the option most likely to win points was least likely to show a trauma-related image).

Results: Participants with PTSD earned significantly fewer points during the conflict phase compared to controls, consistent with heightened avoidance at the expense of obtaining reward ($t = -3.02$, $p = .0025$). This group difference was not present during the congruent phase. There was also an impact of PTSD avoidance symptoms, such that greater avoidance was linked with less trial-by-trial learning ($t = -2.96$, $p = .0031$).

Conclusions: These results are the first to show a specific impairment in approach-avoidance conflict resolution in participants with PTSD. These data suggest that the

imbalance of these competing systems produces impairments in approach-avoidance conflict resolution in participants with PTSD, which could generalize to a general sacrifice of potential rewards in the presence of potential trauma reminders.
Supported By: R21
Keywords: Approach/Avoidance, PTSD - Posttraumatic Stress Disorder, Reward Learning

T10. Stress-Induced Salience Network Connectivity is Predictive of Post-Traumatic Stress Levels

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Background: There are substantial individual differences in large-scale network responses to stress including Salience (SN), Default Mode (DMN) and Central Executive Networks (CEN). Here, we investigate whether individual differences in stress-induced network connectivity changes (i.e., delta-FC) represent a vulnerability factor, or an acquired factor for posttraumatic stress disorder (PTSD) symptoms, in a longitudinal study among N=241 police recruits.
Methods: Predictive and acquired effects of stress-induced functional connectivity changes (delta-FC) within SN, DMN and CEN as well as with brain regions also outside the networks were related to symptom development. Specifically, we measured acute stress-induced delta-FC at baseline when recruits just entered the academy (Wave1) and after 1.5 years of potential trauma exposure during service at the emergency aids (Wave2). Neural markers were used to predict changes in perceived stress levels (PSS) and post-traumatic stress symptoms (PCL and CAPS).
Results: Results from prediction analyses show that weakened synchronization between the SN and DMN core regions at Wave1 predicted longitudinal increases in perceived stress level (Rs=-.19, $p<.01$; adjusted $p<.025$) but not in post-traumatic stress symptoms. Interestingly, reduction in overall decoupling between the SN and anterior cerebellum was acquired in participants with higher clinician-rated PTSD symptoms, particularly intrusion symptoms at Wave2 (Rs=-.22, $p<.005$; adjusted $p<.025$).
Conclusions: These results suggest that acute stress-induced enhancement of SN synchronization with DMN may function as a marker of stress resilience after trauma exposure. Alterations in SN synchronization with the anterior cerebellum may play a role in acquired psychopathology of PTSD.
Supported By: Netherlands Organization for Scientific Research (NWO); European Research Council (ERC)
Keywords: PTSD - Posttraumatic Stress Disorder, Resting-State Functional Connectivity, Perceived Stress, Default Mode Network, Salience Network

T11. Mechanisms of Difficulty Discriminating Threat and Safety Cues Among Worriers

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Background: Burgeoning empirical literature suggests individuals with high levels of worry display difficulty distinguishing threat and safety cues. These findings are consistent with theoretical model predicting overgeneralized threat monitoring. The current study aims to examine a potential mechanism of this process by employing cardiac deceleration measures to index response to threat and neutral cues among individuals prone to high and low worry under varying cognitive demands.
Methods: Participants (n=52) completed a self-report measure of worry prior to engaging in and emotional S1-S2 task to elicit cardiac responding to threat and safety cues. Participants completed three blocks of the S1-S2 task under: no cognitive load, visual cognitive load, and verbal cognitive load. ECG data was collected during the task in order to calculated change in HR in response to stimulus cues.
Results: Results indicated a significant main effect of Cognitive Load $F(2,102)=15.355$, $p<.001$, $\eta 2=.231$, such that visual load resulted in larger deceleration than no-load ($M\Delta=.015$ $p<.001$) and verbal load ($M\Delta=.011$ $p=.001$). There was a interaction between group and Cue $F(1,51)=3.858$ $p=.055$, $\eta 2=.07$. Post-hoc comparisons indicate the high worriers demonstrated larger deceleration to both stimulus types compared to low worriers (threat: $M\Delta=-.005$ $p=.038$; neutral: $M\Delta=-.009$ $p=.001$).
Conclusions: The current study suggests that the influence of cognitive load on stimulus processing may be domain specific. Visual demands seem to have the largest impact on cardiac deceleration. Additionally, the results add support that individuals with high levels of worry display difficulty discriminating and that this extends to autonomic indicator of orientation
Keywords: Worry, Cardiac Deceleration, S1-S2

T12. Freezing is Associated With Higher Amygdala Metabolism in Female Adolescent Monkeys

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Background: Although freezing to potential threats is an evolutionarily conserved defense mechanism across species, excessive freezing during adolescence is a risk factor for psychiatric disorders like anxiety and depression. Neuroimaging studies on this risk have implicated a network of regions including the central nucleus of the amygdala (Ce). Here, we extend these previous studies, by utilizing the unique

opportunity provided by the California National Primate Research Center to study animals that have been reared in large, outdoor, naturalistic social groups.
Methods: Twenty 2-3-year-old female rhesus monkeys (macaca mulatta) were selected using a stratified sampling approach of 98 potential subjects. Animal were injected with [18F]fludeoxyglucose (FDG) before behavioral testing. After the injection, animals were exposed to a No-Eye Contact (NEC) Human Intruder Paradigm for 30 minutes. Following behavioral testing, animals underwent PET scans using a piPET scanner. Behavioral data was quantified using a novel computer-automated approach. Whole-brain voxelwise analyses between metabolic activity and freezing during NEC paradigm was conducted using FSL's randomise.
Results: Results demonstrated a significant correlation between amount of time spent freezing to the human intruder and metabolism in a cluster that included the dorsal amygdala region, including portions of the Ce ($p<.05$, two-tailed uncorrected).
Conclusions: Our results replicate the Ce-freezing relationship in adolescent animals raised in a naturalistic outdoor environment. Results show that animals spent more time freezing to the human intruder had higher brain metabolism in the Ce, suggesting that higher amygdala reactivity may mediate individual differences in behavioral responses to potential threats, even in animals with diverse upbringings.
Supported By: California National Primate Research Center, P51-OD011107
Keywords: Neuroimaging, Rhesus Monkey, Anxiety, 18FDG PET

T13. Functional Impacts of Acute Stress on Negative Affective Circuit Function in Anxiety and Depression

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Background: Mood and anxiety disorders are associated with both hypothalamic-pituitary-adrenal (HPA) axis dysfunction and altered amygdala function. Although the amygdala is directly involved in and influenced by HPA axis, the extent to which HPA dysregulation may contribute to and/or explain these neuroimaging phenotypes remains unknown. Using an innovated repeated-measures design in which a commonly used MRI stress induction paradigm is interleaved between emotional face probes, we tested the contribution of abnormal stress responding in amygdala reactivity to emotional faces.
Methods: 16 unmedicated individuals experiencing anxiety and depression symptoms completed the same standardized emotional face imaging procedure twice under two conditions (stress induction, control) separated by at least once week. During each respective visit the emotion task was preceded by either a stress induction paradigm or by a neutral control task. Cortisol levels were acquired across the imaging sessions. Mean contrast estimates for the anger versus neutral face contrast were extracted for the bilateral amygdala and entered into linear mixed model regressions.
Results: There was a significant interaction between condition (stress induction, control) and stress response status (stress reactive, stress non-reactive) for amygdala activation (left: $p=0.006$; Right: $p=0.029$). Those who elicited the expected cortisol stress response following the stress induction saw an increase in amygdala activation across conditions (left: $p=0.039$; Right: $p=0.060$). Conversely, those who did not elicit a cortisol response saw a decrease in amygdala activation across conditions (left: $p=0.039$; Right: $p=0.022$).
Conclusions: Our results advance our understanding of how HPA axis dysfunction may be associated with amygdala function in anxious and depressed individuals.
Supported By: F32MH108299; R01MH101496
Keywords: HPA Axis, Cortisol, Amygdala, Brain Imaging, fMRI, Mood/Anxiety

T14. Predicting Cognitive Behavioral Therapy Treatment Outcome Using Neural Markers of Maladaptive Self-Focused Attention

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Background: Maladaptive self-focused attention (SFA) is a bias toward internal thoughts that may predict poor cognitive-behavioral therapy (CBT) response. In this study, we used resting state functional connectivity MRI to test whether maladaptive SFA maps onto hyperconnectivity within the default mode network (DMN), an intrinsic brain network mediating internally-directed mentation, and whether DMN hyperconnectivity predicts worse CBT response.
Methods: 31 participants (20 patients with self-reported maladaptive SFA, 11 demographically matched healthy controls) completed a baseline resting state BOLD MRI scan. Eligibility was determined by scoring greater than +/- 1SD of the Self-Consciousness Scale normative mean, respectively for each group. Patients then completed 12 sessions of CBT. Seed-to-voxel functional connectivity was computed using a right medial prefrontal cortex (mPFC) seed selected from the literature representing a core DMN hub.
Results: The mPFC seed was more strongly connected with a right mPFC cluster for patients than controls (peak voxel: [+10 +34 -12]; $pFDR < .00001$), which is part of the DMN, but not part of the seed. No regions were more strongly connected in controls. One region in the angular gyrus (AG) (peak voxel: [+56 -48 +52]; $pFDR < .05$) that was significantly correlated with the seed was associated with treatment change (defined as percent symptom reduction).

Less mPFC-AG connectivity predicted better treatment outcome. As the AG is part of certain attention networks, less mPFC-AG connectivity may reflect stronger attentional flexibility.
Conclusions: Brain measures of maladaptive SFA may be sensitive predictors of CBT response, which may help identify successful treatment candidates.
Supported By: NIMH K23 109593-03
Keywords: Default Mode Network, Negative Self-Focus, Resting State Functional Connectivity MRI (fcMRI), Treatment Response, Prediction of Treatment Outcome

T15. Repetitive Transcranial Magnetic Stimulation Reveals a Causal Link Between Right dlPFC Activity and Anxiety Expression

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Background: Clinical anxiety is heterogenous, including symptoms from multiple psychological dimensions (e.g. excessive worry, difficulty concentrating, hyperarousal). Mechanistic work exploring these multiple dimensions is needed for a complete understanding of clinical anxiety. Here, we causally examine the role of the right dorsolateral prefrontal cortex (dlPFC) in anxiety using noninvasive neuromodulation. We hypothesize that the right dlPFC down-regulates anxiety.
Methods: 18 healthy subjects (9 female) participated in a double-blind, sham-controlled repetitive transcranial magnetic stimulation (rTMS) study where we measured anxiety before and after right dlPFC stimulation (10 Hz). We induced anxiety by exposing subjects to the threat of unpredictable shocks. We measured anxiety by recording the acoustic startle reflex to 103 dB white noise probes. We assessed target engagement by measuring Sternberg WM performance during the rTMS session. We optimized the site and orientation of stimulation using fMRI (during working memory) and iterative electric-field modelling.
Results: Contrary to prediction, active but not sham stimulation significantly increased the magnitude of the startle response during unpredictable shock threat ($t(17) = 2.67$; $p = 0.016$). However, active stimulation also reduced accuracy on low load trials during the Sternberg WM paradigm ($t(17) = 2.35$; $p = 0.03$), suggesting 10 Hz rTMS may impair rather than engage the right dlPFC target.
Conclusions: Although these results demonstrate a causal link between right dlPFC functioning and induced anxiety, additional evidence is needed to support the regulation hypothesis. Future studies should expand the interval between stimulation and testing and employ other stimulation protocols.
Supported By: ZIAMH002798
Keywords: Anxiety Potentiated Startle, Repetitive Transcranial Magnetic Stimulation, Threat, Dorsolateral Prefrontal Cortex, fMRI

T16. Neural Response to Positive and Negative Monetary and Social Outcomes are Differentially Influenced by Depression and Social Anxiety

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Background: Social anxiety and depressive symptoms are associated with different neural responses to positive and negative feedback. These differences are often investigated in the monetary domain. Yet negative peer feedback commonly provokes affective symptoms. We developed monetary and social outcome tasks to test effects of affective symptoms and reward domain on brain function.
Methods: Late adolescents (N=204; 130 females; 19.92±2.50 years) with a range of depressive and social anxiety symptoms, underwent EEG to measure the reward positivity (RewP), an event-related potential that indexes reward response in medial PFC and striatum. During monetary and social tasks respectively, a pair of doors or faces were presented on each trial. Participants predicted the door or peer they thought would provide positive feedback (win money/peer likes you), or negative feedback (lose money/peer dislikes you).
Results: A 2 (domain: monetary/social) x 2 (prediction valence: positive/negative) x 2 (prediction outcome: correct/incorrect) interaction emerged ($F(1, 203)=29.41$, $p<.001$). Correct win (9.62μV ± 10.08), like (10.30μV ± 11.56), and dislike you (8.62 μV ± 12.18) outcomes elicited RewP's of similar magnitude. Correctly predicting negative outcomes elicited a RewP in the social, but not monetary domain ($F(1, 203)=49.96$, $p<.001$). Affective symptoms moderated this effect. RewP's were blunted by depressive symptoms ($r=-.16$, $p<.05$) and heightened by social anxiety symptoms ($r=.19$, $p<.01$). Relations with anxiety remained after controlling for depressive symptoms and were stronger for females.
Conclusions: The intrinsic reward of correctly predicting negative peer feedback may help maintain social anxiety symptoms, particularly in females. This suggests a biologically based, symptom-specific target for novel therapeutic intervention.
Keywords: EEG, Reward Prediction, Social Reward, Monetary Reward, RewP

T17. Are Emotional Regulation and Extinction Learning the Same in the Brain? A Meta-Analysis of fMRI Studies

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Background: Successful emotion regulation is important for physical and psychological well-being, and a better interpersonal functioning. Emotion regulation strategies can be divided into automatic (such as extinction) and deliberative (such as reappraisal). We intended to explore to which extent the neurobiological correlates of these processes were comparable or not.
Methods: We performed a meta-analysis comparing extinction and reappraisal fMRI studies, including 1074 participants from 31 extinction datasets, and 1869 participants from 62 reappraisal studies. Original brain maps were obtained from 57 studies, increasing the statistical power. We explored both the regions of differential and common activation between extinction and reappraisal.
Results: Regarding Extinction > Reappraisal, differences were found in the bilateral insula, the putamen, the pons, the thalamus, the hippocampus, the cerebellum, the right pallidum, the bilateral postcentral gyrus, the midcingulate and paracingulate cortices, the inferior, middle and superior temporal gyri, and the occipital cortex, among others. In Reappraisal > Extinction, differences were found in the dorsomedial prefrontal cortex, the bilateral ventrolateral and dorsolateral prefrontal cortices, the supplementary motor area, the left precentral gyrus, the bilateral angular and supramarginal gyri, the posterior cingulate cortex, and the precuneus, among others. Common activation in reappraisal and extinction was found in the anterior cingulate cortex (ACC) and the bilateral insula.
Conclusions: Extinction was related to limbic and subcortical activations, while reappraisal was more associated with the activation of the prefronto-parietal network. However, they also shared the activation of the insula (involved in interoceptive and affective processes) and the ACC (involved in conflict processing and monitoring).
Supported By: Carlos III Health Institute; FEDER funds; AGAUR; ESF
Keywords: Emotion Regulation, Extinction Learning, Meta-Analysis

T18. Trait Anxiety Associated With Differences in BOLD Activation During Fear Generalization Task

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Background: Pathological anxiety has been associated with overgeneralization of conditioned fear, wherein safe stimuli are perceived as threatening due to perceptual similarity to a threat. Neuroimaging studies have implicated structures, including the insula, hippocampus, ventromedial prefrontal cortex, and precuneus, to be sensitive to stimulus differentiation.
Methods: Forty undergraduate students were conditioned to a threat (CS+) and safety cue (CS-; Gabor patches -15° and +15° offset from 0°). Participants then completed a 7T-fMRI scan in which they were presented with additional generalization stimuli varying in their degree of similarity to the CS+ and CS-, as well as a self-report measure of trait anxiety (STAI). After preprocessing, effects of STAI on differences in activation between the CS+ and generalization stimuli were examined.
Results: Less BOLD differentiation between the CS+ and generalization stimuli in the insula was consistently associated with higher trait anxiety (p's < .005). A similar effect was observed in the midcingulate cortex for stimuli most similar to the CS+. For some generalization stimuli, more BOLD differentiation from the CS+ in the precuneus and right hippocampus was associated with higher anxiety.
Conclusions: The current findings suggest the insula plays an important role in the experience of anxiety, as those with higher levels of trait anxiety exhibited overgeneralization of insula activation to stimuli that were perceptually similar to the CS+. The midcingulate cortex, precuneus, and hippocampus may also be disrupted during threat discrimination for anxious individuals; however, as associations were only present for some generalization stimuli, these regions may be involved in more finetuned perceptual processing.
Supported By: R01 MH106574
Keywords: Anxiety, Fear Generalization, BOLD fMRI

T19. Associations Between Early-Life Trauma, Anxiety, and Safety Cue Learning Across Development

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Background: Anxiety disorders are characterized by unremitting fear in the absence of threat. Youth exposed to trauma are at increased risk for anxiety, particularly during adolescence. Given cross-species evidence for diminished fear extinction during adolescence, youth with trauma exposure may benefit from novel approaches to fear reduction, such as safety cues, that could augment prefrontal inhibition of the amygdala.
Methods: The present fMRI study examined safety cue learning from ages 6-30 (N=60). The conditioned inhibition paradigm included phases for acquisition and testing, during which the CS+ and CS- were paired (i.e., safety compound), and the CS+ was paired with a novel CS as a control condition. Early-life trauma and anxiety were assessed using the Childhood Trauma Questionnaire and Anxiety Disorders Interview for DSM-5, respectively. A GLM tested the main effects and interactions of early-life trauma, anxiety, and age on activation in hippocampal-frontoamygdala circuitry during safety learning.

Results: Analyses revealed a three-way interaction between early-life trauma, anxiety diagnosis, and age on prefrontal activation to the safety compound ($F(1,48)=5.42$, $p=.024$). Within the control group (but not anxiety group), individuals with lower early-life trauma exposure showed an age-related increase in rostral anterior cingulate cortex (rACC) activation to the safety compound ($p=.011$). By contrast, individuals with higher early-life trauma exposure displayed an age-related decrease in rACC activation to the safety compound ($p=.528$).
Conclusions: These findings suggest that early-life trauma may interfere with a typical developmental pattern of prefrontal engagement during safety learning and provide novel insight into approaches to optimize interventions for youth with trauma exposure and anxiety.
Supported By: DP5
Keywords: Anxiety, Youth, Early Trauma, Safety Cues, Fronto-limbic Connectivity

T20. Anger Expression in Patients With PTSD: Clinical, Cognitive, and Neural Correlates

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Background: Anger and aggression are common and debilitating symptoms of post-traumatic stress disorder (PTSD). Although fMRI studies have identified regions underlying anger experience and expression, how these circuits interact with trauma remains unclear. Here we explored clinical, cognitive, and neural correlates of anger in trauma-exposed veterans with and without PTSD.
Methods: Resting-state fMRI was recorded from 162 trauma-exposed veterans (age 32.9+/-7.7, 143 male), including 97 without mental illness and 65 with PTSD. Participants were grouped by median split on the trait anger measure STAXI-2. Global functional connectivity values were calculated for 133 cortical and subcortical regions and compared between participants with high and low anger scores. Regions with significant global connectivity differences were subsequently analyzed for group differences in pairwise functional connectivity.
Results: PTSD patients had higher anger scores than trauma-exposed controls ($p<0.001$). In both groups, anger correlated positively with trauma history and negatively with quality of life and performance on a go-no-go task ($p<0.001$). Among PTSD patients (but not controls), anger was associated with global connectivity in 13 regions that spanned the somatomotor, saliency, cerebellar, and default-mode networks ($p<0.05$, FDR-corrected). PTSD patients with high anger scores generally showed weaker global connectivity than patients with low anger scores, who resembled controls. Subsequent analysis of pairwise connectivity revealed significant correlations between anger levels and somatomotor connectivity with striatum, amygdala, and default-mode network ($p<0.05$, FDR-corrected).
Conclusions: Trauma-exposed veterans who develop PTSD have higher anger scores than resilient controls, and these differences may be explained by connectivity between somatomotor areas and amygdala, striatum, and default-mode network.
Supported By: Cohen Veterans Bioscience and the Wu Tsai Neurosciences Institute
Keywords: Aggression, Anger-Irritability, PTSD - Post-traumatic Stress Disorder, Resting-State Functional Connectivity, Resilience And Vulnerability

T21. Causal Role of the Dorsal-Lateral Prefrontal Cortex in Approach-Avoidance Conflict

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Background: How we decide when faced with a decision with embedded reward and punishment, termed approach-avoidance conflict (AAC), is motivated by our drive to approach rewarding, and avoid punishing outcomes. Locating a brain region causally driving human AAC behavior would make significant headway in developing novel treatments for affective disorders involving reduced sensitivity to reward, such as post-traumatic stress and anxiety disorder. The current study utilizes disruptive TMS during an AAC task to probe the causal role of the prefrontal cortex in AAC decision-making.
Methods: 22 healthy volunteers (10 female, mean age = 33.5 +/- 8.9) performed an AAC task in which, on a given trial, they decided between approaching a gain of points (reward) and viewing a negatively-valanced image (punishment) or avoiding both. Five 10Hz pulses were delivered at the onset of each trial to the right ventral-lateral prefrontal cortex (vlPFC), right dorsal-lateral prefrontal cortex (dlPFC), and vertex control site at 120% of resting motor threshold.
Results: Under low punishment conditions, subjects approached lower reward incentives more often, and higher reward incentives less often, when dlPFC was inhibited compared to vertex, or vlPFC regions ($T(21)>=2.63$, $p<=.016$).
Conclusions: Our findings suggest a functional role of the dlPFC in reward sensitivity in the context of conflict. Given the clinical significance of blunted reward sensitivity in affective disorders, particularly in the presence of punishment during approach-avoidance conflict, the identification of the dlPFC as a key region driving this sensitivity is a significant step forward in our understanding of the neural features relevant to clinical symptomatology.
Supported By: DP1 MH116506
Funds from the Wu Tsai Neurosciences Institute.
Keywords: Approach/Avoidance, TMS, dlPFC, Affective Disorders, Anxiety

T22. Dissociative Symptoms in Posttraumatic Stress Disorder (PTSD) are Directly Related to the Severity of Obstructive Sleep Apnea (OSA) and Other Sleep Indices of Sympathetic Activation

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Background: PTSD with dissociative symptoms (DSM-5) is known to be associated with greater PTSD symptom severity, greater psychopathology, and more sleep difficulties. To my knowledge there are no reported studies of polysomnographically measured sleep physiological correlates of dissociation in PTSD patients.
Methods: 34 consenting civilian PTSD patients (32 female; mean±SD age: 45.12±12.19 years) underwent ≥1 nights of Level 3 polysomnography (WatchPAT200; Itamar Medical, Israel) and completed a battery of instruments as part of a larger study of psychosomatic factors in PTSD. Participants completed the Dissociative Experiences Scale-II (DES-II) (Bernstein&Putnam,1986), PTSD Checklist for DSM-5(PCL-5), Beck Depression Inventory-II(BDI-II), and the Pittsburgh Sleep Quality Index-PTSD Addendum (PSQI-PTSD).
Results: The mean±SD PCL-5 score was 41.12±19.02 and DES-II score was 21.29±13.89. DES-II scores correlated significantly with PCL-5($r=0.684, p<0.001$); BDI-II($r=0.620, p<0.001$); and PSQI-PTSD($r=0.590, p<0.001$), and a range of sleep physiological indices including: the respiratory disturbance index (RDI)($r=0.597$, $p<0.001$); oxygen desaturation index (ODI)($r=0.455$, $p=0.008$); sleep efficiency ($r=-0.414$, $p=0.017$); sleep duration: ($r=-0.464$, $p=0.006$); rapid eye movement sleep (REM) duration ($r=-0.370$, $p=0.034$); and REM latency ($r=0.421$, $p=0.015$). A stepwise multiple regression analysis using RDI as dependent variable and age, DES-II, PCL-5, BDI-II, and PSQI-PTSD as independent variables revealed DES-II scores ($\beta=0.658$, $t=4.543, p<001$) remained the only predictor of RDI (adjusted R squared=0.412).
Conclusions: Dissociative symptoms in PTSD correlated directly with PTSD symptom severity, depression and sleep disturbances, and sleep physiological indices of sympathetic activation such as OSA and sleep fragmentation. An inverse relation of dissociation with REM duration is further consistent with increased PTSD severity (as high baseline REM is associated with decreased fear conditioning in PTSD) and sympathetic activation.
Keywords: Dissociative Subtype, Dissociation, PTSD - Posttraumatic Stress Disorder, Autonomic Reactivity, Obstructive Sleep Apnea

T23. OCD Treatment Response to Technology- Supported Mindfulness Meditation and Changes in EEG Oscillatory Activity

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Background: Mindfulness-based interventions (MBI) have shown promise in the treatment of mood and anxiety disorders. The goal of this study was to investigate the efficacy of a technology-supported mindfulness meditation (TSM) practice for OCD using a consumer grade EEG-based biofeedback device ("Muse"). Measured clinical outcomes focused on obsessive compulsive symptom reduction and underlying biological mechanisms of changes in EEG oscillatory activity.
Methods: Participants were randomized to an 8-week MBI or waitlist condition. In the MBI condition participants received an EEG headset providing guided daily meditation practices. All participants attended meetings at baseline, week 4 and week 8, involving completion of self-report questionnaires and a brief mindfulness practice using the Muse headset.
Results: There were 55 (N=27 MBI, N=28 Control) participants. A Generalized Linear Model (GLM) statistical approach indicated a significant Time by Condition two-way interaction favouring the MBI condition: $F(1,55) = 6.21$, $p < .05$. A Latent Difference Score modelling approach indicated reduction in Alpha ("Mind Wandering") and Beta frequencies (but not Theta) were temporally associated with improvement in YBOCS (α: $\chi2$ ($4, N = 55$) $= 6.09$; $\chi2/df = 1.52$; AIC $= 52.09$, CFI $= .98$, RMSEA $= .08$; β: $\chi2$ ($5, N = 55$) $= 6.47$; $\chi2/df = 1.29$; AIC $=$ 50.47, CFI $= .98$, RMSEA $= .07$).
Conclusions: The current findings provide preliminary support for the potential clinical benefits of TSM meditative practices for patients experiencing OCD. Improvements in OCD symptoms may be associated with changes in the alpha and beta band waveforms.
Supported By: Frederick W. Thompson Anxiety Disorders Centre
Keywords: Mindfulness, Obsessive Compulsive Disorder (OCD), EEG, Treatment

T24. Abnormal Perceptive Awareness in First-Episode Drug-Naïve Panic Disorder is Associated With Altered Task-Evoked Activity in the Superior Parietal Lobule

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Background: Biased perception plays an important role in the development and maintenance of panic disorder (PD), and high levels of cardiovascular symptoms in PD produce higher levels of heartbeat perception.
Methods: Currently, we investigated brain activity during interoceptive awareness in PD using functional MRI. We recruited 18 subjects with first-episode drug-naïve PD and 21 age- and gender-matched healthy controls (HCs).
Results: We found that the heartbeat perception scores (HPSs) were higher in individuals with PD than in HCs. When comparing greater heartbeats or greater puretones with fixation, PD patients showed higher activity in the bilateral superior parietal lobule (SPL) than HCs. Further, patients with PD exhibited a significant positive correlation between BOLD activity in the left SPL and HPS during the heartbeats vs. fixation condition and a positive correlation between BOLD activity in the right SPL and HPS, although this did not reach significance.
Conclusions: We identified impaired activation in the bilateral SPL during interoception and exteroception. The increased activation during interoceptive stimuli might render PD patients more engaged in processing information associated with their

internal states, which may increase the probability of panic attacks. Our study provides insight regarding PD treatment, whereby inhibition of the SPL can be used to reduce cardiac interoceptive accuracy and relieve cardiac syndromes.
Keywords: Panic Disorder, Perceptive Awareness, Brain Imaging, fMRI, Heartbeat

T25. State-Dependency of the Stimulation-Induced Evoked Response in EEG

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Background: Repetitive transcranial magnetic stimulation (rTMS), a treatment for depression, is ineffective in ~30% of people. Variability in baseline cortical excitability could play a role in this. However, we currently do not have a strong understanding of the effect of state on TMS output. In the present study we investigated the functional significance of TMS-evoked electroencephalography (EEG) outputs by manipulating cortical excitability of the stimulated cortex using working memory (WM) load.
Methods: 21 healthy young-adults received subthreshold single TMS pulses during the WM-maintenance of a low or high "load" letter-number sequence to the left posterior dorsolateral prefrontal cortex (lp-dlPFC) because of its validated significance to WM. Left anterior dlPFC was also targeted and the left motor cortex was a control site.
Results: Stimulating lp-dlPFC resulted in increased local p50 latency recorded over the lp-dlPFC and the p200 peak at the left inferior parietal lobe (IPL) in the high versus the low “load” condition ($t(18)>=-2.4$, $p<=.022$). Local lp-dlPFC theta power was reduced in high load ($t(18)=2.11$, $p=.04$), whereas functionally connected right p-dlPFC and left IPL theta power were significantly elevated ($t(18)>=2.9$, $p<=.01$). These state-dependent changes were specific to the lp-dlPFC stimulation site.
Conclusions: These results provide insight into how TMS-evoked EEG potentials and spectral features relate to the excitability of the cortex, and provide potential EEG outputs for the determination, and optimization, of cortical state relative to rTMS treatment for psychiatric disorders. This is an important first step to understanding how to make TMS a more effective and viable treatment option.
Supported By: DP1 MH116506
Funds From the Wu Tsai Neurosciences Institute
Keywords: Transcranial Magnetic Stimulation (TMS), Electroencephalography (EEG), Depression, Anxiety, Plasticity

T26. Mental Context Reinstatement Balances Retrieval of Fear Versus Safety Memories in the Human Brain

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Background: As Pavlovian extinction serves as a model for anxiety treatment, there is motivation to better understand how extinction memories are encoded, stored, and expressed so as to bolster the strength of clinical treatment. Here, we used multivariate pattern classification (MVPA) of functional MRI in humans to decode a multivariate signature selective to encoding and 24-hour retrieval of extinction memories.
Methods: Patients with PTSD (20) and psychologically healthy controls (20) underwent a two-day fear conditioning, extinction, and fear renewal test during functional MRI. Task-irrelevant images of scenes were interspersed throughout extinction to tag scene-selective extrastriate visual cortex using MVPA. We then used this MVPA classifier to quantify contextual reactivation of the extinction context during a 24-hour fear renewal test. We hypothesized that neural reactivation of the extinction context, 24-hours after extinction, would predict successful retrieval of extinction memories in healthy controls, but not patients with PTSD.
Results: We were able to successfully classify the extinction mental context and identified neural reactivation of the extinction context in healthy controls, but not in PTSD, 24-hours later. The magnitude of context reinstatement in healthy subjects correlated with activity in canonical extinction neurocircuitry, including ventromedial prefrontal cortex, hippocampus, and amygdala.
Conclusions: The findings show that neural context reinstatement helps resolve competition between fear and safety memories in healthy populations, but that people with PTSD fail to retrieve the extinction context at a future test. Quantifying mental context reactivation could be used as an innovative measure to evaluate successful treatment in disorders marked by excessive fear and anxiety.
Supported By: NIMH
Keywords: Fear Conditioning And Extinction, BOLD fMRI, PTSD - Posttraumatic Stress Disorder, Renewal, Pavlovian Conditioning Fear Procedure

T27. Emotional Patterns: Multivariate Pattern Analysis and Test-Retest Reliability of an fMRI Emotional Faces Task

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Background: Functional MRI studies involving emotional face processing are often used to probe neural circuitry related to psychiatric disorders and treatments. However, results from test-retest reliability studies of emotional face processing have been highly variable. Multivariate pattern analysis (MVPA) is a relatively new analytic approach that identifies patterns of activity predictive of specific brain states. MVPA has been associated with high sensitivity and specificity, but test-retest reliability has not been explored.
Methods: Across two studies, 66 healthy adult participants completed an fMRI scan concurrent with an emotional faces task. In study 1 (N=39), MVPA was used to develop a neural

pattern predictive of emotional faces versus shapes. In study 2, we fit this pattern to data from 27 participants who completed the same fMRI protocol on two separate days. We assessed the reliability of this neural pattern at the group level by computing the correlation distance (Pearson's r) of multivariate patterns between time points.
Results: In study 1, the neural pattern had sensitivity of 95.28% and specificity of 93.33% for emotional faces. In study 2, the similarity of pattern fit across time points had a mean Pearson's r of 0.3072.
Conclusions: Findings from study 1 suggest MVPA can effectively predict activation during emotional faces tasks. Study 2 results indicate that multivariate patterns across time points are greater in similarity than that reported by previous research assessing correlations between different paradigms of similar constructs (Kragel et al., 2018). Future work is needed to delineate test-retest reliability of MVPA methods at the individual subject level.
Supported By: NIH Award Number K23MH108707
Keywords: Multivariate Classification, Reliability, Emotional Processing, Face Processing, Anxiety

T28. A "Primate-Approach" to Studying Approach-Avoidance Conflict in Humans

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Background: Approach-avoidance conflict (AAC) arises from decisions where approaching leads to both reward and punishment and avoiding leads to neither. One prominent symptom of affective disorders is exaggerated avoidance, leading to sustained and/or exacerbated symptoms. While the neural characterization of AAC behavior could provide promising biomarkers for clinical intervention, the complexity of existing task designs limits our current understanding. Therefore, we have created and validated a novel task fashioned after primate studies and utilizing innately evocative outcomes.
Methods: The task pins shock punishment against juice reward by varying the ratio of their button-evoked delivery. Four blocks of this task were piloted on 22 healthy volunteers (12 female; Age=29.5 +/- 11.1 years) to obtain information about the response distribution, equivalence and evocativeness of outcomes, and behavioral stability. 256-channel EEG was recorded during the task, and theta band power source estimates were extracted. All p-values were FDR-corrected.
Results: The results found the task: 1) elicited stable behavior (Kendall's W = .79) and 2) utilized evocative outcomes with balanced value ($t(21)=.63$, $p=.53$) across participants. Further, lateral prefrontal and inferior parietal theta power were found to be elevated in conflict blocks compared to no-conflict blocks ($|z|\geq 2.05$, $p\leq .04$), the degree to which negatively predicted avoidance ($|z|\geq 2.11$, $p\leq .035$).
Conclusions: The current task framework elicits stable behavior using evocative and balanced outcomes. Interestingly, theta band power in prefrontal and parietal areas is shown to negatively predict avoidance. This task platform will open up biological research examining the neural patterning underlying AAC behavior in humans, and its correspondence to clinical phenotypes.
Keywords: Prefrontal Cortex, Approach/Avoidance, Affective Disorders, Anxiety, Translational Research

T29. Neural Correlates of Safety Cue Learning in Children With and Without Anxiety Disorders

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Background: Exposure-based therapy for pediatric anxiety is based on principles of fear learning and extinction. Animal studies have shown that presenting threat and safety cues simultaneously (conditioned inhibition) may be a promising approach to augment fear reduction. Here, we investigate the neural correlates of fear and safety cue learning in children with and without anxiety disorders.
Methods: 24 children with anxiety disorders and 23 healthy children performed our novel conditioned inhibition task in the MRI scanner. This task consists of four phases: conditioning, testing, extinction, and reversal. During testing, we presented conditioned threat and safety cues simultaneously (i.e., safety compound). Dependent measures were reaction time (RT), skin conductance response (SCR), and brain activity during conditioning and testing.
Results: During conditioning, all children responded more slowly to threat cues than safety cues, $F(1,31)=6.75$, $p=0.014$, but there was no difference in SCR, $F(1,35)=0.29$, $p=0.593$. fMRI findings showed no group differences, but children with more anxiety symptoms showed less differentiation between threat and safety cues in the dorsolateral prefrontal cortex (cluster-corrected $Z>2.3$, $p<0.05$). During testing, the safety compound did not reduce fear over and above a novel compound and there was no relationship with anxiety, as assessed by RT, SCR, and fMRI.
Conclusions: Anxiety symptoms were associated with poorer differentiation between threat and safety cues in the prefrontal cortex. The results of the present study will provide insights into altered threat and safety cue learning in pediatric anxiety disorders, which could eventually inform exposure-based treatment.
Supported By: Intramural Research Program at the National Institute of Mental Health (NCT00018057)
Keywords: Fear Conditioning, Safety Cues, Anxiety Disorders, fMRI

T30. White Matter Integrity in Individuals At-Risk for PTSD Development: A Longitudinal Investigation

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Background: While most individuals are resilient in the aftermath of trauma, a substantial minority go on to develop post-traumatic stress disorder (PTSD). Previous work indicates white matter integrity may be a useful biomarker in predicting PTSD. Specifically, the integrity of the cingulum bundle, corpus callosum (CC), and uncinate fasciculus (UF) may be related to negative trauma outcomes. Therefore, the current study investigated the predictive utility of white matter integrity in the acute stages of trauma to chronic PTSD symptoms and examined how white matter integrity varies with PTSD symptoms over time.
Methods: Fifty-seven trauma survivors (27 male; Mage=31.67) were recruited from the emergency department at Froedtert Hospital (Milwaukee, WI). Participants completed the PCL-5 to assess severity of PTSD symptoms and underwent diffusion-weighted MRI 2 weeks (T1) and 6 months (T2) post-trauma. Tract integrity measures of the three aforementioned tracts were analyzed using FreeSurfer's TRACULA.
Results: Results show increased integrity of the anterior cingulum and UF at T1 is related to greater reexperiencing (t=2.63, p=0.01) and arousal symptoms at T2 (t=2.36, p=0.02), respectively. In addition, increased integrity of the CC from T1 to T2 was related to decreased total PTSD symptoms (t=-2.61, p=0.01), and more specifically, decreased cognitive (t=-2.37, p=0.02) and arousal symptom severity (t=-2.89, p=0.005). Increased integrity of the posterior cingulum over time was also related to increased arousal symptom severity (t=-2.69, p=0.01).
Conclusions: Results of this study help elucidate the structural brain changes related to PTSD and may provide a potential biomarker for clinicians to help identify those at risk for PTSD development.
Supported By: R01 MH106574
Keywords: PTSD, Diffusion Tensor Imaging (DTI), Trauma, White Matter Integrity

T31. Amygdala and Hippocampal Activation to Conditioned Stimuli During Extinction Following Threat Avoidance

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Background: Models of anxiety suggest that avoidance of a conditioned fear stimulus prevents new safety learning, thereby serving to maintain fear. However, there is little empirical data in humans on the impact of avoidance of conditioned fear stimuli on subsequent fear extinction. Functional magnetic resonance imaging (fMRI) studies in humans have implicated the amygdala and hippocampus in the extinction of fear through classical conditioning paradigms. In the present study we investigated the effect of avoidance of threat on amygdala and hippocampus activity during a subsequent extinction phase using ultra high-resolution (7T) fMRI.
Methods: 29 undergraduate participants completed a classical conditioning task, followed by either avoidance of threat (N=15) or a non-avoidance control (N=14). To investigate the impact of avoidance on subsequent fear extinction, we compared BOLD activation evoked by the conditioned stimulus (CS+) during extinction in the avoidance vs. non-avoidance groups.
Results: There was a significant effect of avoidance of threat, such that participants who were previously able to avoid the shock associated with the CS+ showed reduced activation in the central amygdala and hippocampus (ps<.05) in response to the CS+ during extinction compared to those who did not receive the instruction to avoid the CS+.
Conclusions: These findings suggest that avoidance of threat may be associated with attenuation of activity in the central amygdala and hippocampus during extinction. This may represent preliminary evidence of a mechanism through which avoidance of threat interferes with subsequent extinction learning.
Supported By: Daniel M. Soref Charitable Trust
Keywords: Avoidance, Fear Extinction, BOLD Functional MRI

T32. Characterizing the Cardiovascular Response to Fear Extinction in PTSD

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Background: Posttraumatic stress disorder (PTSD) is a highly impairing condition that negatively impacts cardiovascular functioning. While there is a known association between PTSD and cardiovascular risk, little is known about underlying physiological mechanisms. Fear extinction is a well-established biomarker that is impaired in PTSD, and fear conditioning paradigms are a highly useful way to examine this phenomenon. Thus, the current study used fear conditioning to probe the cardiovascular response to extinction among individuals with PTSD.
Methods: Participants were 51 trauma-exposed adults with significant PTSD symptoms. All participants underwent a fear conditioning paradigm that included an extinction phase, during which heart rate (HR) was collected. We examined HR in response to the danger signal (over 6 seconds of conditioned stimulus presentation) that was previously paired with an aversive unconditioned stimulus.
Results: For HR across 6 seconds, there were significant quadratic effects ($F[1,50] = 18.83$, $p < .001$). Consistent with a typical fear response,.5-2s after stimulus onset, there was a pattern of HR deceleration during early extinction. When comparing early vs. late extinction, there was a significant interaction for the HR response, in that the deceleration diminished over the course of extinction ($F[1,50] = 25.22$, $p < .001$).
Conclusions: This is the first study examining the cardiovascular response and heart rate dynamics to fear extinction in PTSD. Consistent with prior research, HR initially decelerated, and this decreased over the course of extinction. Future studies will determine whether cardiovascular markers of fear

responding are differentially associated with PTSD compared to healthy controls.
Supported By: MH071537 (KJR), MH092576 (TJ), MH098212 (TJ), Brain and Behavior Research Foundation (TJ)
Keywords: PTSD, Startle, Heart Rate, Extinction

T33. Acute Prazosin Administration Does Not Reduce Stressor Reactivity in Healthy Adults

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Background: Norepinephrine plays a critical role in the stress response. Clarifying the psychopharmacological effects of norepinephrine manipulation on stress reactivity in humans has important implications for basic neuroscience and treatment of stress-related psychiatric disorders, such as posttraumatic stress disorder and alcohol use disorders. Preclinical research implicates the alpha-1 norepinephrine receptor in responses to stressors. The No Shock, Predictable Shock, Unpredictable Shock (NPU) task is a human laboratory paradigm that is well positioned to test cross-species neurobiological stress mechanisms and advance experimental therapeutic approaches to clinical trials testing novel treatments for psychiatric disorders. We hypothesized that acute administration of prazosin, an alpha-1 noradrenergic antagonist, would have a larger effect on reducing stress reactivity during unpredictable, compared to predictable, stressors in the NPU task.
Methods: We conducted a double-blind, placebo-controlled, crossover randomized controlled trial in which sixty-four healthy adults (32 female) completed the NPU task at two visits (2 mg prazosin vs. placebo).
Results: A single acute dose of 2 mg prazosin did not reduce stress reactivity in a healthy adult sample. Neither NPU startle potentiation nor self-reported anxiety was reduced by prazosin (vs. placebo) during unpredictable (vs. predictable) stressors.
Conclusions: Further research is needed to determine whether this failure to translate preclinical neuroscience to human laboratory models is due to methodological factors (e.g., acute vs. chronic drug administration, brain penetration, study population) and/or suggests limited clinical utility of alpha-1 noradrenergic antagonists for treating stress-related psychiatric disorders.
Supported By: National Institute of Alcohol Abuse and Alcoholism (F31 AA022845)
Keywords: Prazosin, Startle Response, Posttraumatic Stress Disorder, Alcohol Use Disorder, Stress Reactivity

T34. Effects of Repeated Cortico-Striatal Optogenetic Stimulation on OCD-Like Behaviors in Rats

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Background: Accumulating evidence points to orbitofrontal cortex-ventromedial striatum (OFC-VMS) circuitry hyperactivity in Obsessive-Compulsive Disorder (OCD). Hyper-activating this pathway in inbred mice produces excessive grooming and other perseverative behaviors that outlast the stimulation. We aim to replicate these findings in outbred rats, where there are few reliable models of OCD-related behavior.
Methods: Optical-fibers were implanted into the VMS and opsin delivered into the OFC (AAV5-CaMKIIa-hChR2(H134R)-EYFP, n=4; AAV5-CaMKIIa-EYFP control, n=2) of male Long-Evans rats. After waiting 5-6 weeks for viral expression, rats received repeated optical stimulation (5 min/day, 6 consecutive days, 10 ms, 10 Hz, 5 mW). Self-grooming was evaluated for 5-min periods: before, during, immediately after and one-hour after stimulation. Operant attentional set-shifting, marble burying, and nestlet shredding test sessions were performed before and after the opto-stimulation.
Results: OFC-VMS stimulation did not increase grooming (2-way RM-ANOVA, $F(5,20)=0.87$, $p>0.05$) or nestlet shredding ($F(1,4)=1.25$, $p>0.05$), but increased marble burying ($F(1,4)=19.06$, $p<0.05$). No changes were observed in set-shifting (Reaction_Time: $t=-2.24$, $p>0.05$; Errors: $t=2.07$, $p>0.05$; for regression coefficient, trials=10520). Stimulation did not change locomotor behavior ($F(5,20)=1.38$, $p>0.05$), inconsistent with prior mouse reports.
Conclusions: Using a similar approach to that previously used in mice, we could not reproduce a reported model of compulsive behavior in rats. We saw evidence of limited target engagement (motor changes), even with confirmed anatomic placement. If optogenetic effects on behavior do not reliably transfer even between rodent species, this may have important implications for designing rodent-to-human translational pipelines.
Supported By: São Paulo Research Foundation (FAPESP, 2017/22473-9); OneMind Institute; the MnDRIVE Brain Conditions Initiative; UMN Medical Discovery Team on Addictions
Keywords: Obsessive Compulsive Disorder (OCD), Animal Model, Optogenetics, Grooming, Set-Shifting

T35. Rapid-Eye Movement Sleep and Brain-Derived Neurotrophic Factor as Predictors of Stress Resilience and Vulnerability

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Background: PTSD affects approximately 24 million Americans. Currently, no methods exist to predict individual differences in stress responding prior to stressor exposure. In this project, we examined baseline peripheral BDNF levels and REM changes after mild and intense stress as indices of stress resilience or vulnerability.
Methods: Rats had blood drawn, were surgically implanted with electrodes for sleep recording and a datalogger to record body temperature. Baseline sleep was recorded on day 1. On day 3, rats were placed in a novel chamber (NC) and sleep was recorded. On day 4, received shock training (ST: 20 mild footshocks: 0.8 mA, 0.5 s duration over 30 minutes) and sleep was recorded. Rats were separated into vulnerable (Vul, n=21) or resilient (Res, n=25) groups based on whether or not they

had a 50% or greater reduction in REM in the first 4 hours of sleep post-ST, respectively. Blood plasma was collected and analyzed using a BDNF ELISA.
Results: Analysis of the 1st 4 hours of sleep showed that Res rats had significantly higher baseline peripheral BDNF levels compared to Vul rats. Post-NC and Post-ST REM was significantly lower in Vul rats compared to baseline. Res rats had no significant change in REM post-NC or ST. Post-NC and ST REM was significantly lower in Vul rats compared to Res rats. Body temperature and behavioral freezing were not significantly different between groups.
Conclusions: These data demonstrate that peripheral BDNF and post-mild stress REM may be useful predictors of stress resilience and vulnerability prior to intense stressor exposure.
Supported By: NIH
Keywords: Brain-Derived Neurotrophic Factor, PTSD - Posttraumatic Stress Disorder, REM Sleep, Stress Resilience

T36. Recall but Not Acquisition of Conditioned Safety Requires the Infralimbic Cortex in Rats

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Background: The ability to discriminate between danger and safety is crucial for survival across species. Whereas danger signals predict the onset of a threat, safety signals ensure the non-occurrence of an aversive event, thereby inhibiting fear and stress responses. Patients suffering from PTSD show impaired learning to suppress their fear response in the presence of a safety cue. To elucidate the underlying neurbiology of safety learning, we investigated the effects of temporary IL inactivation with muscimol, a selective GABAA receptor agonist, on the acquisition and recall of conditioned safety utilizing the startle paradigm.
Methods: Following the establishment of a robust safety learning protocol utilizing the Startle paradigm, rats underwent brain cannulation of the IL and were either submitted to our 'Conditioned Safety' or 'Control Conditioning' protocol. Muscimol or vehicle injections were performed either shortly before acquisition or before the recall session.
Results: While random presentations of US and CS did not affect startle response in the recall session, explicit unpairings of US and CS- led to a significant decrease in startle magnitude upon CS- presentation. Temporary inactivation of the IL prior to conditioning did not affect the recall of conditioned safety, whereas IL inactivation prior to the recall session completely blocked the retention of conditioned safety.
Conclusions: Our findings suggest that the IL is essential for the recall of safety memories. Because traumatized persons are often unable to make use of safety cues in order to inhibit fear, this finding could potentially contribute to therapy optimization of anxiety-related psychiatric diseases.
Supported By: DFG, SFB779
Keywords: Safety, Fear Conditioning and Inhibition, Fear and Anxiety, Fear-Potentiated Startle Reflex, PTSD

T37. Effects of Deep Brain Stimulation in Cognitive Flexibility Using an OCD Animal Model

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Background: Deficits in cognitive flexibility are found in several psychiatric disorders, such as Obsessive-Compulsive Disorder (OCD) and depression. These deficits seem to result from disturbances of the corticostriatal circuits. Deep brain stimulation (DBS) targeted to the ventral capsule/ventral striatum seems to influence corticostriatal circuitry, possibly ameliorating inflexibility.
Methods: We used an operant set-shifting paradigm to evaluate behavioral flexibility in Long-Evans rats. We modeled inflexibility with meta-Chlorophenylpiperazine (5-HT2A/C-agonist, mCPP), which in pre-clinical studies induces repetitive/perseverative behaviors. Further, we evaluated the effects of DBS of the dorsal part of the ventral striatum on the flexibility of normal and mCPP-treated animals. Animals received 1) mCPP only (2.0 mg/kg), 2) DBS-only (100-300 μA for 1 h prior to and during the test), 3) a combination drug and DBS intervention. DBS and/or drug were administered on alternate days during daily testing sessions.
Results: mCPP impaired animals' flexibility, increasing reaction time (RT, $t=20.59$, $p<0.01$, for regression coefficient, trials=5892, n=7) and the number of errors ($t=5.13$, $p<0.01$). DBS at 300 μA improved flexibility (reduced RT, $t=-6.13$, $p<0.01$) with unchanged accuracy ($t=-1.47$, $p=0.14$), but in only half the cohort (omnibus RT effect, $t=-1.74$, $p=0.08$, trials=16263, n=8). DBS did not reverse mCPP-induced inflexibility (RT, $t=-1.63$, $p=0.35$; errors, $t=-2.91$, $p=0.02$).
Conclusions: DBS had modest effects on flexibility in this animal model. This may result from individual differences in electrode placement (currently being explored) or from mCPP affecting flexibility through mechanisms outside cortico-striatal circuits. Continued investigation will help to define cortico-striatal circuits' influence and DBS potential benefits on flexibility.
Supported By: This work is supported by the MGH-MIT Grand and Challenges program, the Brain & Behavior Research Foundation, the One Mind Institute, the Harvard Brain Initiative Bipolar Disorder Fund supported by Kent & Liz Dauten, the National Institutes of Health, UMN Medical Discovery Team on Addictions and a private donation from Dr. Michael Jenike.
Keywords: DBS, Cognitive Flexibility, Set-Shifting, Obsessive Compulsive Disorder (OCD)

T38. Genetic Dissection of Catecholaminergic Innervation of the Cognitive Cerebellum

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Background: Studies in humans and non-human primates have identified a region of the dentate nucleus of the cerebellum (DCN), or lateral nucleus in rodents (LCN), which is activated during performance of cognitive tasks. The DCN is implicated in cognitive function in humans with psychiatric illnesses, but virtually nothing is known about its organization. We hypothesized that the locus coeruleus (LC) is the source of catecholamine release in LCN, catecholamines are required for cerebellar enhancement of cognition, and act on LCN glutamatergic output neurons.
Methods: We used advanced viral tracing methods to map catecholaminergic inputs to LCN. We also used fast-scan cyclic voltammetry (FSCV) to record catecholamine release in the LCN while electrically stimulating the LC. We utilized advanced viral techniques in mutant mice to achieve selective knockout of catecholaminergic projections to LCN and tested behavioral consequences of these manipulations.
Results: Mapping indicated catecholamine projections from LC and Purkinje cells to LCN. We did not see labeling in other catecholaminergic nuclei. When the LC is electrically stimulated, catecholamine release in the LCN is observed with FSCV. Tyrosine hydroxylase (Th) lox/lox mice were injected with CAV-Cre (retrograde virus) into LCN coordinates and trained on either an impulsivity or a delayed alternation task. Deletion of Th expression in LCN results in abnormal performance on working memory behaviors, but not motoric ones. When neuronal excitability of glutamatergic LCN output neurons is reduced using DREADDs, working memory is facilitated.
Conclusions: Catecholaminergic innervation of the cognitive cerebellum is important for several cognitive functions, and may represent a novel therapeutic target.
Supported By: 1R01MH116883-01, K08MH104281-04
Keywords: Cerebellum, Cognition, Viral Gene Transfer, Catecholamines, Working Memory

T39. Poster Withdrawn

T40. Alzheimer's Disease DNA (Hydroxy)Methylome in the Brain and Blood: Evidence for OXT Methylation as a Preclinical Marker

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Background: Recent studies point towards an important role for epigenetic mechanisms in the etiology of Alzheimer's Disease (AD). In the present study, we explored the association between AD and epigenetic dysregulation in the brain and at a preclinical stage in the blood.
Methods: Genome-wide levels of DNA methylation and DNA hydroxymethylation were determined in 80 middle temporal gyrus (MTG) tissue samples (45 AD, 35 controls), as well as genome-wide DNA methylation levels in 97 blood samples (55 converters, at least 4.5 years before conversion to AD, 42 controls), using Illumina's HumanMethylation450 BeadChips. Linear regression was used to analyze the normalized probe data with disease status as predictor, adjusting for gender, age, and 5 surrogate variables, followed by the combination of p-values to determine differentially modified regions and a correction for multiple comparisons.
Results: Several statistically significant differentially modified regions were identified in the brain (15) and the blood (12), some close to or within genes previously associated with AD. One AD-associated region close to the transcription start site of OXT (MTG, chr20:3051954-3052484; blood, chr20:3051954-3052346) was found in both the brain (pŠidák = 1.07E-06) and blood (pŠidák = 1.20E-03) samples.
Conclusions: Our data supports the presence of epigenetic dysregulation in AD, also beyond the brain, and both before and after the development of dementia. The nearly identical OXT DMRs found in the blood and brain suggest a systemic epigenetic dysregulation in AD involving OXT. The detection of the OXT DMR at pre-dementia stages indicates its potential as a novel biomarker.
Supported By: ISAO/AN; JPND; NWO; MRC; BMBF; FNR
Keywords: Epigenetics, Alzheimer's Disease, Oxytocin, DNA Methylation, DNA Hydroxymethylation

T41. Impacts of Depression and REM Sleep Behavior Disorder on Cognitive Decline in Parkinson's Disease

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Background: Depression and sleep disorders can impact disease course and quality of life in Parkinson's Disease (PD). They are also known to predict cognitive decline in PD. Here, we assess their effect on progression of cognitive changes in a longitudinal dataset.
Methods: Our sample is drawn from a multi-centric, longitudinal and ongoing study, the Parkinson's Progression Markers Initiative (PPMI). In clinically diagnosed and unmedicated PD individuals (n=404), latent curve growth models were used to assess trajectory of cognitive changes over two-year period in non-demented PD subjects and the extent to which they are influenced by depression and REM sleep behavior disorder.
Results: Cognition gradually declined during the course of PD, evident by the latent variable (estimate of slope= 2.38, $p<0.001$). After controlling for age, gender and APOEe4 status, depression and REM sleep behavior disorder significantly predicted the cognitive decline (p values, 0.002, 0.01 respectively) but not the cognition at baseline. The fit indices confirmed good fit of the overall model to data (CFI=0.95, RMSEA=0.06).

Conclusions: Depression and REM behavior disorder at baseline are potent indicators of future cognitive decline in non-demented PD.
Keywords: Cognitive Impairment, Depression, REM Sleep, Parkinson's Disease, Predicting Factors

T42. Evidence of Structural and Functional Neurodegeneration in Veterans With Mild Traumatic Brain Injury

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Background: Mild Traumatic Brain Injury (mTBI) may predispose individuals to neurodegeneration and the development of dementia. The purpose of this investigation was to identify evidence of neurodegeneration through longitudinal evaluation of structural and functional changes in the visual and central nervous system in veterans with a history of mTBI.
Methods: 69 veterans with mTBI and 70 age-matched control veterans received evaluations at 6 month intervals of visual function, cognition, and Optical Coherence Tomography (OCT) and MRI at 18 months. A linear trend statistical model was used to estimate slopes of change over time in subjects' retinal nerve fiber layer (RNFL) thickness, visual acuity, contrast sensitivity, and tests of cognitive function. Changes in structural MRI (cortical thickness) over 18 months was evaluated in 82 of the subjects.
Results: Compared to controls, Veterans with mTBI showed greater thinning of the retinal nerve fiber layer(RNFL) in the retina ($p=0.004$, Cohen's $d=.56$) and V1 cortex ($p=0.016$, $d=0.54$) along with greater decline in functional measures of vision (visual acuity, $p=0.04$; contrast sensitivity, $p=0.008$) and cognition (Groton Maze Learning Task (GMLT), $p=0.02$, $d=.43$) in mTBI. Greater RNFL tissue loss was associated with worsening performance on the GMLT ($r=-0.28$, $p=0.002$).
Conclusions: We have found longitudinal evidence for neural degeneration over time in Veterans with mTBI, with the greatest change in structural biomarkers (RNFL, V1 cortex), followed by functional abnormalities (visual acuity, cognition).
Supported By: DoD, VA 5I01RX002173-03
Keywords: mTBI, Brain Imaging, Retinal Imaging, Visual System, Cognition

T43. Early Emerging Regulatory Behavior Mediates Association Between Newborn Brain Connectivity and Subsequent Internalizing Symptoms

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Background: A large effort has been made to understand how early emerging infant emotionality and regulatory ability relate to future behavioral outcomes and underlying neurobiology. The current study evaluates associations between newborn amygdala connectivity, infant regulatory ability, and internalizing symptomology at 24-months-of-age.
Methods: High quality resting state functional MRI data were collected in 70 newborn infants (scan age 22.5 ± 9.1 days). Analyses focused on amygdala connections implicated in negative emotionality across the lifespan. Two independent coders (percent agreement $> 85\%$) rated regulatory behavior and emotionality at 6-months-of-age during the still-face episode of the Still-Face Paradigm using a previously established coding scheme. Latency to distress (LTD) was examined as an indicator of infant emotional reactivity and regulatory ability. Internalizing symptomology was assessed using the Child Behavior Check List at 24-months-of-age. Regression analyses were conducted to examine the mediating effect of LTD on the association between newborn amygdala connectivity and emerging internalizing symptomology. All analyses were adjusted for maternal depressive symptomology, gestational age at birth and age at scan.
Results: Stronger newborn Am-MPFC connectivity was associated with greater LTD ($\beta = 75.12 \pm 26.83$, $p < 0.01$), indicating stronger connectivity relates to greater regulatory ability. Greater LTD furthermore mediated the association between stronger connectivity and lower internalizing symptomology at 24-months-of-age ($\beta = -3.71$, 95% CI [-10.06, -0.57]).
Conclusions: Regulatory ability at 6-months-of-age mediates the association between newborn amygdala connectivity and future internalizing symptomology. Understanding the role of early emerging regulatory ability on future internalizing symptomology has implications for identifying its etiology and early risk assessment.
Supported By: Support for this work was provided by the National Institute of Mental Health (grant numbersNIMH R01 MH091351, Supplement to NIMH R01 MH091351,NIMH K99 MH111805); the National Institutes of Health (grant numbers NIH R01 MH-105538,NIH R01 HD-060628, UG3-OD-O23349); the Gates Foundation Grand Challenges Explorations (grant: Early Markers to Predict Cognition and Brain Development); NIH/NIMH (grant numbers R00 MH091238andR01 MH096773).
Keywords: Resting State Functional Connectivity MRI (fcMRI), Neurodevelopmental Trajectories, Internalizing Symptoms, Emotion-Regulation, Newborn Amygdala Connectivity

T44. White Matter Tract Signatures of Emotional Lability and ADHD Traits in Young Children

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Background: 40-50% of children with ADHD present with significant levels of emotional lability, which is associated with poorer outcomes. Characterizing how emotional lability interacts with the diagnostic dimensions of inattention and hyperactivity is therefore critical for effective treatment. As a starting point, we here interrogate the brain basis of this relationship in two white matter tracts crucial for attention and emotion processing: the superior longitudinal fasciculus (SLF) and the uncinate fasciculus (UF).
Methods: Diffusion-weighted images (b-value=0/2000, 45 directions) were acquired in 58 typically developing children aged 4-7 years and preprocessed using motion and signal-dropout correction (FSL/MRTrix). Emotional lability was assessed with the Emotion Regulation Checklist; inattention and hyperactivity were assessed with the SNAP-IV Parent Questionnaire. In a voxel-based analysis, we investigated linear associations between the interaction of emotional lability and ADHD traits, and fractional anisotropy (FA) and mean diffusivity (MD) in the SLF and UF (controlling for main effects, handedness and motion).
Results: Emotional lability, inattention and hyperactivity scores all correlated (r's>.63). The interaction between hyperactivity and emotional lability negatively correlated with FA in bilateral UF, and negatively with MD in left anterior SLF. MD in left anterior SLF also negatively correlated with the interaction between inattention and hyperactivity, and with the interaction between inattention and emotional lability at trend-level.
Conclusions: Our findings suggest that UF and SLF diffusion properties underlie crucial links between emotional lability and ADHD traits in early childhood and demonstrate the utility of behavioral scores to elucidate the brain basis of potential vulnerabilities in young children.
Supported By: Alberta Innovates; NSERC; NSERC CREATE I3T (Canada); CIHR (Canada)
Keywords: Emotion Regulation, ADHD, White Matter, Resilience And Vulnerability, Traits

T45. Emotion Regulation Tendencies Moderate Relationship Between Childhood Trauma and Nucleus Accumbens Activation to Loss

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Background: Traumatic events in early childhood like physical abuse and neglect affect approximately 33% of children, and exposure to traumatic events are linked to difficulties regulating emotional responses in adulthood. To date, little research has examined how childhood trauma exposure and emotion regulation are associated with reward-related responses, such as anticipation of reward gain and loss. Thus, the present study examined the relationship between reward-related brain function, emotion regulation tendencies, and childhood trauma exposure.
Methods: Young adults (N = 213) completed a self-report measure of emotion suppression tendencies and a childhood trauma interview prior to an fMRI monetary incentive delay (MID) task.
Results: Greater childhood trauma was associated with reduced sensitivity to the anticipation of reward loss in the nucleus accumbens [b = -.07, t (209) = -3.01, p = .003] and this effect was moderated by emotion suppression tendencies [b = -.06, t (209) = -3.35, p < .001]. Simple slopes analysis revealed that among individuals low in emotion suppression tendencies (-1 SD), greater childhood trauma was associated with reduced loss sensitivity in the nucleus accumbens, b = .139, t (209) = -3.78, p < .001. This association was not significant among individuals high in emotion suppression tendencies (+1 SD), b = .004, t (209) = 0.16, p = .87. Further, neither childhood trauma exposure, emotion suppression tendencies, nor their interaction were associated with gain sensitivity in the nucleus accumbens.
Conclusions: These findings suggest a nuanced relationship between childhood trauma, emotion regulation, and sensitivity to loss in early adulthood.
Supported By: ROI, T32
Keywords: Emotion Regulation, Nucleus Accumbens, Childhood Trauma, Reward Network, Monetary Loss

T46. The Moderating Role of Age in the Relationship Between Early Life Adversity and Hair Cortisol Concentrations in Adults Admitted to a Psychiatric Emergency Service

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Background: Childhood abuse (CA) exposure increases the risk for psychopathology. Stress hormone secretion has been studied in individuals exposed to CA, mostly using diurnal cortisol profiles. Various factors could account for the discrepant results found so far, such as population's age and clinical characteristics, and type of CA. We aimed to examine the relationship between CA types and the cortisol secretion over the months preceding psychiatric emergency admission in adults.
Methods: 148 adults (76 women) aged 18 to 80 were recruited upon admission to a psychiatric emergency service. Upon admission, hairs were sampled to index the cumulative secretion of cortisol over the last three months and participants filled out the Childhood Experiences of Violence Questionnaire (CEVQ) to assess physical and sexual abuse during childhood.
Results: A multiple linear regression model was run to predict hair cortisol concentrations with the following variables as predictors: age (18-40, above 40), CEVQ score for both the physical and sexual abuse subscales, and interaction between age and each subscale. Sex and psychiatric diagnosis were

entered as covariates. An interaction Age X Physical Abuse was found (F(1,136)=9.92, p=0.002), such that greater physical abuse exposure was associated with higher hair cortisol concentrations in younger adults (B=4.02, p=0.006). This relationship was not significant in older adults.
Conclusions: Physical abuse was associated with hair cortisol concentrations in young adults admitted to a psychiatric emergency service. This highlights the importance of considering individual factors, such as age and CA type, when studying the relationship between CA and stress system dysregulations.
Supported By: Fondation de l'Institut universitaire en santé mentale de Montréal; Fonds de recherche du Québec - Santé
Keywords: Hair Cortisol, Childhood Trauma, Psychiatric Emergency Services, Stress, Adult Psychiatric Population

T47. Associations Between Relational Bullying, Cyberbullying, and Neural Activity to Emotional Faces in Adolescents

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Background: Many adolescents report being victims of in-person bullying and online cyberbullying. Both forms of victimization are associated with heightened risk for internalizing problems, but little research has examined their association with brain activity during emotion processing. We examined associations between relational peer victimization, cyberbullying victimization, and brain activity to threatening (angry and fearful) faces during an emotional face matching task. We hypothesized that both relational victimization and cyberbullying victimization would be associated with altered activity in emotion processing and regulation regions including the amygdala and prefrontal cortex (PFC).
Methods: A community sample of 49 adolescents 12-15 years old underwent fMRI scanning while performing an emotional face matching task and completed self-report measures of peer victimization. Thirty-nine participants (44% female) met quality control criteria.
Results: Relational peer victimization was modestly associated with cyberbullying victimization (r=.30, p=.07). Contrary to expectations, neither form of peer victimization (or their interaction) was associated with amygdala activity to threatening faces. As expected, higher relational peer victimization predicted decreased dorsolateral prefrontal cortex (dlPFC) activity to threatening faces, p-uncorrected<.01, cluster extent=225 voxels, peak coordinates=(-38, 50, 26). Cyberbullying victimization was not associated with PFC activity to threatening faces.
Conclusions: Relational peer victimization, but not cyberbullying victimization, was associated with decreased dlPFC activity during threatening face processing. Given the role of the dlPFC in emotion regulation, this could suggest that experiences of relational victimization are associated with disrupted activity in emotion regulation regions, which could lead to increased risk for the development of internalizing problems in the future.
Supported By: UC Davis; UC Davis Behavioral Health Center of Excellence; National Institute of Food and Agriculture, U.S. Department of Agriculture, Hatch project accession number 1013485.
Keywords: Bullying Victimization, Amygdala, Dorsolateral Prefrontal Cortex, Adolescence, Brain Imaging, fMRI

T48. Childhood Maltreatment Disrupts Brain-Mediated Pathways Between Adolescent Maternal Relationship Quality and Adult Competence and Internalizing Symptoms

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Background: The quality of early caregiving may partially shape brain structure and circuits involved in regulating emotions, including the limbic system and frontal cortex, affecting vulnerability for psychopathology and maladaptation. Given the profound impact of child maltreatment (CM) on psychological and neural development, we tested whether CM alters the pathways linking mother-adolescent relationship, frontal cortex, and adult outcomes.
Methods: We used structural equation modeling to investigate whether CM affected the association between mother-child relationship quality during adolescence, frontal lobe volume in adulthood, and adult internalizing and externalizing symptomatology and competence. Participants included 88 adults (M=30.0 years) who were part of a longitudinal high-risk, low-income sample. Forty-eight participants had a history of CM and 40 did not.
Results: Results showed that relationship quality was positively associated with frontal volume for individuals with no CM (b=.22, p=.01), marginally related for individuals with one CM subtype (b=.11, p=.07), and unrelated for those with multiple CM subtypes (b=-.10, p=n.s.). Greater frontal volume predicted higher levels of adult adaptive functioning (b=.55, p<.001) and fewer adult internalizing symptoms (b=-.40, p=.01), but was unrelated to externalizing symptoms. Frontal volume mediated the effect of maternal relationship quality on adult internalizing and adaptive functioning, but only for individuals without CM.
Conclusions: Secure attachment relationships may play a critical role in tuning the self-regulatory lobe, allowing for more adaptive outcomes. However, this pathway may be altered in individuals with CM. Other methods for tuning the brain's regulatory system may become more influential in predicting individual adaptive functioning in maltreated individuals.
Supported By: 2T32MH015755-39
Keywords: Child Maltreatment, Frontal Cortex, Internalizing Symptoms, Attachment

T49. Acute Transcutaneous Vagus Nerve Stimulation Decreases the Recognition of Sad Facial Expressions in Adolescents With Major Depression

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Background: Transcutaneous vagus nerve stimulation (tVNS) is a promising therapeutic option for major depressive disorder (MDD) in adults. Alternative third-line treatments for MDD in adolescents are scarce. In a pre-clinical experimental trial, we aimed to evaluate the effects of acute tVNS on proxies of depressive symptoms – namely emotion recognition - in adolescents with MDD.
Methods: Adolescents (14-17 years) with MDD (n=33) and non-depressed controls (n=30) participate in the trial. All participants received tVNS and sham-stimulation in a cross-randomized order, while performing different tasks assessing emotion recognition. Simultaneous recordings of electrocardiography and electro dermal activity as well as sampling of saliva for the determination of α-amylase, were used to quantify effects on autonomic nervous system function.
Results: tVNS had no effect on the recognition of gradually or static expressed emotions but altered response inhibition on the emotional Go/NoGo-task. Specifically, tVNS increased the likelihood of omitting a response towards sad target-stimuli in adolescents with MDD, while decreasing errors (independent of the target emotion) in non-depressed controls. Effects of acute tVNS on autonomic nervous system function were found in non-depressed controls only.
Conclusions: Acute tVNS alters the recognition of briefly presented facial expressions of negative valence in adolescents with MDD while generally increasing emotion recognition in controls. tVNS seems to specifically alter early visual processing of stimuli of negative emotional valence in MDD. These findings suggest a potential therapeutic benefit of tVNS in adolescent MDD that requires further evaluation in randomized-controlled trials.
Supported By: Daimler and Benz Foundation & Thrasher Research Fund
Keywords: Adolescent Depression, Vagus Nerve, Emotional Facial Processing

T50. Laminar and Cellular Developmental Trajectories of GABA Transcripts in Cortical Regions of the Visuospatial Working Memory Network in Monkeys

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Background: Visuospatial working memory (vsWM) requires information transfer among cortical regions, including visual and prefrontal cortices, via layer 3 pyramidal neurons whose activity is regulated by GABAergic neurons. In primates, vsWM performance improves through adolescence and certain measures mature earlier in visual cortex (V2) than prefrontal cortex (PFC). GABA neurotransmission undergoes protracted postnatal maturation, with a progressive shift from $\propto$2 (GABRA2)- to $\propto$1 (GABRA1)-subunit containing GABAA receptors, which is important for neural oscillations underlying vsWM. Here we tested whether this shift in pyramidal neurons and in parvalbumin (PV)-containing GABA neurons occurs earlier in V2 than PFC.
Methods: Rhesus monkey V2 and PFC tissue from neonatal, prepubertal, postpubertal and adult age groups was labeled by RNAscope for DAPI (cell nuclei), PV (GABA neuron marker), GABRA1 and GABRA2.
Results: In layer 3, GABRA1 mRNA levels showed adult-like expression earlier in pyramidal cells in V2 than in PFC. However, they did not follow this trajectory in PV cells. For GABRA2 mRNA, trajectories showed adult-like expression earlier in PV cells in V2 than in PFC. However, they did not follow this trajectory in pyramidal cells. The mean GABRA1/GABRA2 mRNA ratio showed adult levels with similar timing in PV cells but with an earlier plateau in pyramidal cells in V2 compared to PFC.
Conclusions: Findings for GABRA1 and GABRA1/GABRA2 mRNA expression trajectories in layer 3 pyramidal neurons and for GABRA2 expression trajectories in layer 3 PV neurons support the hypothesis that V2 achieves adult expression earlier than PFC.
Supported By: R01MH051234 and NIMH MD/PhD R01 Administrative Supplement
Keywords: Parvalbumin Interneurons, Pyramidal Neurons, Developmental Trajectories, Visuospatial Working Memory, GABAA Receptor

T51. Decreased Expression of Class I Major Histocompatibility Complex Molecules in the Subventricular Zone in Autism Spectrum Disorders

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Background: Major histocompatibility complex (MHC) molecules have been implicated in psychiatric neurodevelopmental disorders including autism spectrum disorders (ASD) and schizophrenia (SZ). In the present study we characterized the expression of class I MHC molecules in the human subventricular zone (SVZ) and compared their levels in adolescent and young adults with ASD with respect to controls. Due to the function of the SVZ in cell proliferation, we also examined glial progenitors in these samples
Methods: Postmortem samples were obtained from the NIH NeuroBioBank's brain and tissue repository at the University of Maryland (ASD n = 25; control n = 20). In situ hybridization histochemistry was used to quantify class I MHC-A, B & C transcripts. RNAscope was used to visualize and quantify the expression of markers of oligodendrogensis
Results: Expression of class I MHC-A was identified in the ependymal cell layer of the SVZ and associated blood vessels and found decreased in ASD vs controls. Analysis of RNAscope sections revealed elevated oligodendrocyte progenitors in adjacent white matter including the corpus callosum in ASD compared to controls
Conclusions: The present results report for the first time the anatomical distribution of the mRNA signal of the major class I

MHC loci in the human SVZ and indicate that their expression is downregulated in ASD with respect to control. These results suggest that class I MHC proteins continue to have important neurophysiological roles during adolescent and adult life that may be directly linked to the pathophysiology of ASD

Supported By: P50 MH103222

Keywords: Autism Spectrum Disorder, Post Mortem Brain, MHC, Gliogenesis, RNAscope

T52. Common Functional MRI Markers of Risk for Psychotic, Mood and Anxiety Disorders: A Meta-Analysis

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Background: Many risk factors for psychiatric disorders increase risk for multiple diagnoses and are not specific to one disorder. However, few studies have tested for common alterations in brain function transdiagnostically across risk groups. We conducted a meta-analysis of functional magnetic resonance imaging (fMRI) studies of high-risk individuals.
Methods: A systematic review of studies was performed in PubMed. Inclusion criteria were: task-based fMRI, whole brain analyses, mean subject age < 30 years, and examined a "high-risk" group, as defined by clinical (i.e., subsyndromal symptoms), temperamental (i.e., behavioral inhibition), or familial risk factors. Thirty-six studies were identified (with participants who were at risk for anxiety disorders (n=8), mood disorders (n=7), or psychotic disorders (n=21)), with a total of 1,356 participants. The meta-analysis was conducted in GingerALE using a random-effects model. Studies were combined by calculating the union of each individual study, with a voxel $p < .05$ and a cluster size of 50 voxels.
Results: In the combined sample, transdiagnostic risk was associated with increased activation in the PCC and caudate, and decreased activation in the superior parietal lobule, inferior frontal gyrus, and dorsomedial prefrontal cortex.
Conclusions: Common correlates of risk identified here, i.e., impaired functioning of frontoparietal circuitry and limbic overactivity, are consistent with findings in mood and psychotic disorders and thus may represent candidate transdiagnostic markers of risk for serious mental illness.
Supported By: NIH-NIMH R01MH095904 (DJH) and NIH-NIMH R25MH094612 (MGH/McLean Research Concentration Program)
Keywords: Functional Neuroimaging, At-Risk Youth, Early Risk Detection, Meta-Analysis

T53. Adolescent Development of Prefrontal Inhibitory Timing Assessed Through TMS-EEG

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Background: Adolescence is marked by a protracted maturation GABA-mediated inhibitory circuits during which the temporal characteristics of prefrontal inhibition becomes faster and more precise. We hypothesized that transcranial magnetic stimulation (TMS) evoked potentials (TEP) in human electroencephalography (EEG) would track such temporal shifts.
Methods: We recruited N=13 children (10-12 yrs) and N=14 adolescents (15-17 yrs) for a combined TMS-EEG study. Single- and paired-pulse TMS (sp/ppTMS) was applied to the PFC at short- and long-intracortical inhibition (SICI/LICI) latencies shown to be GABA-A- and GABA-B-mediated, respectively (SICI: 2-7 ms, conditioning pulse=70% resting motor threshold (RMT); LICI: 50-200 ms, conditioning pulse=120% RMT). Test pulses were applied at 120% RMT.
Results: Both children and adolescents demonstrated similar TEPs to prefrontal stimulation; however, TF analysis showed greater theta (4-8 Hz) and high-frequency (>50 Hz) power for adolescents (ps < 0.05). Notably, neither the SICI nor LICI tuning curves followed the expected timing based on prior ppTMS literature targeting the motor cortex. Adolescents showed greater N45 TEP suppression at latencies >4 ms while children showed suppression at latencies <4 ms (p=0.006). In the TF domain, children showed facilitation of theta (2ms, age*SICI: p=0.03) and beta (15-30 Hz) power (50-80 ms; age*LICI: p=0.05).
Conclusions: Inhibitory dysfunction has been shown to be a hallmark of psychosis disorders which tend to onset in late adolescence. This study joins a growing body of work using ppTMS to probe inhibitory circuits in the PFC that suggests the inhibitory profile of PFC circuits is distinct and may serve as a potential biomarker of aberrant PFC development.
Keywords: Adolescence, Inhibition, TMS-EEG

T54. Youth With ASD Symptoms Have Reduced LPP as Learn About Unpredictable Peers During Social Interactions

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Background: Autism Spectrum Disorder (ASD) symptoms encompass difficulties learning about others. Essential for social learning is revaluating others during iterative social interactions. The late positive potential (LPP), an event-related potential associated with evaluating emotionally salient stimuli, is reduced after reevaluation. Yet, little is known about how ASD symptoms relate to LPP as youth learn about peers through social interactions. We examined if learning moderates relations between ASD symptoms and change in LPP over iterative social interactions.
Methods: The LPP was measured via EEG as youth (12.11±2.91 years) interacted with purported peers who provided consistent (100% positive or negative) or inconsistent (50% positive/negative) evaluation in a Virtual-School. Change in LPP (400-1000ms post-evaluation) was calculated by subtracting early (first-48) from late (last-48) interactions. A control group was informed of peer reputations in advance (N=29). A learning group learned peer reputations during social

interactions (N=25). Learning was confirmed via reputation ratings obtained every two-interactions.
Results: Late-vs-early reputation ratings changed more for learning-vs-control groups (p's<0.05). Group moderated relations between change in late-vs-early LPP to inconsistent peer evaluation and ASD symptoms (B's>0.49, p's<0.05). Specifically, in the learning group, reduced late-vs-early LPP to inconsistent social evaluation was associated with more severe ASD symptoms.
Conclusions: Reduced LPP may reflect diminished emotional salience for inconsistent peer evaluations among those with more severe ASD symptoms. ASD-based treatment promoting the emotional salience of unpredictable or inconsistent social interactions may facilitate engagement of the neural mechanisms needed to learn from those interactions.
Supported By: Autism Science Foundation
Keywords: Autism Spectrum Disorder, LPP, ERPs, Learning, Social Cognition

T55. Reward-Action Choice Task (ReACT): The Measurement of Effort Expenditure for Rewards in Adolescents

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Background: Decisions about rewards, and the effort necessary to acquire them, is central to goal-directed behaviour. Adults discount rewards as a function of effort costs, however, less is known about how adolescents make decisions about effort expenditure. The current work details the development of a new task optimized to measure reward-effort decision-making in youth; the Reward-Action Choice Task (ReACT). The ability to estimate the parameters that influence effort-based decision-making, as well as individual differences in intrinsic effort production, is a unique feature of the current task.
Methods: On each trial of ReACT a monetary offer was made. Participants chose to expend minimal effort to obtain the offer, through squeezing a dynamometer, or opted to expend greater effort for a competing offer. Participants relied on intrinsic perception of real-time force production, as this was partially masked on screen. Following this, the force exerted, and resulting winnings, were displayed as feedback. ReACT has undergone two phases of testing in adolescents to date (phase 1: N=27, age =16.1(1.3); phase 2: N=10, age=14.6(1.7)).
Results: Mixed-effects modelling revealed that adolescents made more high effort selections with increasing competing offers (z=3.99, p<.001). Furthermore, intrinsic force production was observed to increase with greater potential winnings (t(8)=5.2, p<.001).
Conclusions: Reward magnitude influenced the likelihood to expend effort in adolescents, in both the decision between two competing offers, and in intrinsic effort expenditure to obtain winnings. Next, ReACT will be administered as an fMRI task, with the aim of elucidating the underlying neural mechanisms of decision-making about effort and rewards in adolescents.
Supported By: NIMH ZIAMH002957-01
Keywords: Effort-Based Decision-Making, Adolescence, Reward Processing, Task Development, Effort Expenditure

T56. DNA Methylation of the Oxytocin Receptor Changes During Infancy and is Impacted by Maternal Behavior

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Background: Oxytocin is a neurohormone that plays a critical regulatory role in mammalian social behavior. Its actions are dependent on its receptor, whose expression is partially controlled by DNA methylation. Heightened methylation of the oxytocin receptor gene (OXTRm) has been found in postmortem brain tissue of individuals with autism spectrum disorder. Given evidence implicating OXTRm in contributing to variability in social function, we examined the role of OXTRm in infant development, with a particular focus on exploring its potential plasticity and sensitivity to the caregiving environment.
Methods: OXTRm was assessed in 101 mother-infant dyads at two timepoints roughly one year apart. Maternal and infant engagement were coded during a free play session at 5 months of age, and infant temperament was assessed at 18 months using the Early Childhood Behavior Questionnaire.
Results: Our analysis shows that infants' OXTRm dynamically changed between 5 and 18 months of life, whereas mothers' OXTRm remained stable. Importantly, infants' change in OXTRm was predicted by maternal engagement, with greater maternal engagement predicting reduced levels of OXTRm (p=0.014). Moreover, lower OXTRm at 18 months was associated with improved behavioral temperament as indexed by reduced levels of discomfort (p=0.005).
Conclusions: Results indicate that maternal engagement may increase oxytocin system efficiency during infancy through reduction of methylation, which is linked to improved behavioral outcomes. This suggests that during infancy, the endogenous oxytocin system changes as a function of social experience, pointing to an epigenetic mechanism by which maternal care may influence infant behavioral development.
Supported By: Max Planck Society
Keywords: Epigenetics, Oxytocin, Maternal Care, Infancy, Infant Temperament

T57. Social Interaction Processing in Adolescents With Non-Suicidal Self-Injury (NSSI) Behavior

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[1]CSAN

Background: Interpersonal stress is a common trigger of nonsuicidal self-injury (NSSI) behavior. Here, we addressed

whether NSSI adolescents have a negative bias in reading social interactions. We developed a task that investigates the neural correlates of social interaction in a simulated online environment in the magnetic resonance imaging (MRI) scanner.
Methods: Thirty NSSI adolescent patients and thirty age-matched controls played the game after clinical assessment. During the game, participants indicated whether they liked or disliked pictures of other fictitious players and similarly their own picture also got judged. In order to identify specific bias in social interaction processing in NSSI, we investigated the perceived quality of the interaction using specific post-scan questions. In addition, we applied a multi-voxel pattern analysis (MVPA) to inspect whether activation during social interaction could discriminate between the groups.
Results: The NSSI group showed a negative bias in reading the social interaction although the overall quality of the social judgment was kept neutral (same amount of "likes" and "dislikes"). NSSI participants felt more rejected more often than controls and when rejected, they felt worse. Using a multivariate approach, we identified brain regions that significantly contributed to the classification between the two groups. In addition, the classification indices in patients correlated with the sensitivity to rejection, measured with post-scan self-report.
Conclusions: NSSI individuals tend to read feedback from others more negatively. MVPA of neural-response during anticipation of social judgment determined a significant classification of NSSI subjects, and classification scores correlated with the subjective effects of social rejection.
Supported By: Other
Keywords: Non-Suicidal Self-Injury, Social Interaction Task, BOLD fMRI, MVPA, Negative Bias

T58. Larger Newborn Left Amygdala Volume Predicts Poorer Working Memory in Toddlerhood

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Background: Larger amygdala volumes in children have been associated with emotion regulation problems. Still, very little research exists on the links between amygdala volume and more cognitive aspects of self-regulation, including executive function (EF), in early childhood. The aim of this study was to investigate associations between newborn left and right amygdala volume and toddlerhood EF (working memory, WM; and inhibitory control, IC).
Methods: A subsample of children FinnBrain Birth Cohort Study that participated in an MRI scan at 2–5 weeks of age and developmental assessment at the age of 30 months was studied (N = 64). Toddler WM was assessed using Spin the Pots task (Hugher & Ensor, 2005) and IC using Snack Delay task (Kochanska, Murray & Harlan, 2000). General cognitive performance was measured using Inter-NDA battery. Only the initial p-values that survived Benjamini-Hochberg correction are reported.
Results: After controlling for child sex, gestational age, age at scan and general cognitive performance, newborn larger left amygdala volume predicted poorer WM in toddlerhood ($T = 3.26$, $p = .008$, $\eta^2 = .11$). The association between amygdala and WM was found to be stronger for girls even after adjustment for intracranial volume ($T = -2.12$, $p = .038$, $\eta^2 = .07$). Amygdala volumes did not predict toddler IC.
Conclusions: These findings are among the first to link newborn brain structure to EF in early childhood. The findings suggest that in addition to emotional outcomes, larger amygdalae after birth may also predict more cognitive aspects of self-regulation, such as poorer WM in young children.
Supported By: Emil Aaltonen Foundation; State Research Grants for Clinical Research, Alfred Kordelin Foundation, Turku University Foundation; Sigrid Juselius Foundations, Finnish Cultural Foundations, Signe and Ane Gyllenberg Foundation, Yrjö Jahnsson Foundation, NARSAD, Academy of Finland, Jane and Aatos Erkko Foundation.
Keywords: Executive Functioning, Amygdala, Early Neurocognitive Development, Brain Magnetic Resonance Imaging (MRI), Self-Regulation

T59. It Still Hurts – How Childhood Maltreatment Hampers Social Distance and Affective Touch in Adulthood

To see this abstract, please see Oral Abstract #O6.

T60. The Longitudinal Study of Anesthesia Effects on White Matter Development

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Background: There is increasing concern about the potential effects of anesthesia exposure on the developing brain. This research in humans is restricted to retrospective studies. To date no studies in rodents or non-human primates have looked at short, clinically relevant exposures corresponding to the dosage a human would typically receive (less than 60 min). We analyzed the effects of relatively brief anesthesia exposures in typically developing rhesus macaques.
Methods: Longitudinal (5 scans/subject) MR diffusion tensor images (DTI) from 32 rhesus macaques (14 females) aged 2 weeks to 36 months were obtained from publicly available UNC-Wisconsin Neurodevelopment Rhesus Database. Low dosage anesthesia exposure was employed for MR imaging or

routine animal care. The anesthesia exposure was normalized to account for varying exposures (isofluorane + ketamine for age < 6-month vs dexdomitor + ketamine for age >= 6 months). DTI data was analyzed using UNC-Utah NA-MIC framework for DTI fiber tract analysis.
Results: Anesthesia exposure negatively affected white matter development (for most of the tracts $p<0.05$, FWE corrected): the higher cumulative anesthesia exposure, the lower fractional anisotropy. Age, but not sex and infant weight, was associated with every white matter tract. No interaction between age and anesthesia exposure was evident.
Conclusions: Even relatively low levels of anesthesia exposure are associated with significant reductions in white matter during early postnatal brain development. Exposure resulted in lower FA values throughout the brain, suggesting that early exposure may delay or even undermine white matter maturation.
Supported By: NIMH (MH901645, MH091645-S1, MH100031) and NICHD (HD003352, HD003110, HD079124)
Keywords: Anesthesia, Macaques, White Matter, Longitudinal Study

T61. Repetitive Transcranial Magnetic Stimulation for Tourette's Syndrome in Children: A Pilot Study

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Background: Tourette's syndrome (TS) often requires treatment but options are limited and carry side effects. Our goal is to determine the safety, tolerability, and possible effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) on tic severity and underlying neurobiology in children with TS. We hypothesize that (1) tic severity will decrease and (2) gamma-aminobutyric acid (GABA) will increase while glutamate will decrease in the supplementary motor area (SMA) with rTMS.
Methods: Open label, uncontrolled, phase IIa clinical trial. Ten children (6-18 years) with TS (Yale Global Tic Severity Scale (YGTSS) score >22) participated. Motor task fMRI generated individualized maps of the SMA. These were uploaded to a TMS neuro-navigation system and synchronized with a TMS robot (Axilum). Treatment consisted of 1800 (1 Hz) stimulations to the SMA bilaterally for 15 weekdays. The primary outcome was change in YGTSS symptom rating. Magnetic resonance spectroscopy (MRS) was completed for GABA (MEGAPRESS) and glutamate (PRESS), with voxels in the SMA and the left and right primary motor areas.
Results: Tic severity decreased with rTMS (57%, $p < 0.001$). GABA increased in the SMA (48%) and dominant motor cortex (23%) but decreased in the non-dominant motor cortex (23%). Glutamate did not change in the SMA (3%) but decreased in the dominant motor cortex (8%, $p = 0.035$), and increased in the non-dominant motor cortex (10%, $p = 0.03$). Procedures were well-tolerated.
Conclusions: Robot-driven, personalized, neuro-navigated rTMS interventions are feasible in children with TS. Ancillary tools may inform mechanisms of action. Future randomized trials are required to demonstrate efficacy.
Supported By: Canadian Institute for Health Research
Keywords: Tourette's Syndrome, Gilles De La Tourette Syndrome, Repetitive Transcranial Magnetic Stimulation, Children And Adolescents, Magnetic Resonance Spectroscopy

T62. Mechanisms of Differential Threat-Related Face Processing Among Youth With Trauma-Related Affective Psychopathology: A Multimodal Eye-Tracking and fMRI Study

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Background: Childhood trauma exposure and affective psychopathology have been associated with emotion identification difficulties. However, a comprehensive study of the behavioral, physiological, and functional neural mechanisms of emotional face processing in youth with trauma-related affective psychopathology (TRAP) is unknown.
Methods: Participants included youth with TRAP (n=22) and typically developing (TD) controls (n=23). Following clinical assessments, youth completed emotional faces paradigms during which fixation duration and count to face regions, pupil diameter, accuracy, and reaction time in separate gender and emotion identification tasks were measured. A separate emotional faces task was completed by all subjects during MRI to measure whole-brain activation and functional connectivity (FC) with the bilateral amygdala during presentation.
Results: TRAP was associated with decreased accuracy in identification of angry and disgust faces as compared to controls. While youth with TRAP overall had fewer facial fixations, fixation count/duration, reaction time, and pupil diameter were found not to be dependent upon gender or emotion type. Average accuracy of anger identification was correlated with amygdala functional connectivity while viewing angry faces. A group by accuracy interaction was identified in amygdala-parahippocampus FC where accuracy was negatively related to FC in TRAP youth, but positively related to FC in TD youth.
Conclusions: Abnormal processing of threat-related emotions in TRAP youth was not associated with behavioral or physiological measures. However, the differential amygdala-parahippocampus FC identified in youth with TRAP may imply abnormal emotional contextualization circuits, potentially related to automatic appraisal (with little conscious processing) of threat-related stimuli.
Supported By: NIMH K08 MH100267, NIH/NCATS UL1TR000427, TL1TR000429
Keywords: Childhood Trauma, Brain Imaging, fMRI, Eye Tracking, Emotional Facial Processing, Child And Adolescent Psychiatry

T63. Neurocognitive Correlates of Resilience in Youth With a History of Traumatic Stress Exposure

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Background: Early-life traumatic stress exposure is associated with psychopathology, yet many individuals are resilient. While substantial research is dedicated to study risk and susceptibility, there is limited understanding of mechanisms that underpin resilience in developing humans. We aimed to characterize the neurocognitive profile associated with resilience in the Philadelphia Neurodevelopmental Cohort (PNC, N=9,498, ages 8-21).
Methods: Participants underwent K-SADS based clinical interview assessment of psychopathology including screening for trauma. Neurocognition was assessed with Penn Computerized Neurocognitive Battery (CNB) measuring the following domains: executive function, episodic memory, complex reasoning and social cognition. We employed linear regression models treating cognitive efficiency as dependent, and trauma exposure, psychopathology, and their interaction as independent variables. Models controlled for sex/gender, age and socioeconomic status (SES).
Results: In youths with high trauma exposure, those with low psychopathology (resilient, N=732) showed superior overall cognitive efficiency compared to those with high psychopathology (N=1595), while no such differences were observed comparing high and low psychopathology in low trauma exposure individuals (exposure X psychopathology interaction t=2.274, p=.023). Follow-up analyses to break down overall cognitive efficiency to specific cognitive domains revealed a similar pattern in complex reasoning efficiency (exposure X psychopathology interaction t=2.168, p=.03), with no significant interactions in other cognitive domains.
Conclusions: Resilient youths who exhibit low psychopathology in the face of high trauma exposure show distinct neurocognitive efficiency pattern characterized by superior complex reasoning, independent of sex, age, and SES. While a cross-sectional design makes causal inference challenging, results may shed light on specific cognitive mechanisms underpinning resilience.
Supported By: This work was supported by NIH grant MH-107235, MH-089983, MH-096891, MH-P50MH06891, the Dowshen Neuroscience fund, and the Lifespan Brain Institute of Children's Hospital of Philadelphia and Penn Medicine, University of Pennsylvania.
Keywords: Stress Resilience, Cognitive Development, Early Trauma, Adolescent Depression, Child And Adolescent Psychiatry

T64. Body-Oriented Therapy Has Positive Effect on Executive Abilities in Preschool Children With ADHD

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Background: It is known that children with ADHD are deficit in executive abilities. We have revealed that body-oriented therapy can impact executive abilities in 6-7 years age children with ADHD (Kiselev & Parshakova, 2018). The goal of this study was to reveal the effect of body-oriented therapy on executive abilities in 4-5 years of age children with ADHD. We compared the efficacy of two methods of treatment (body-oriented therapy for children vs. conventional motor exercises) in a randomized controlled pilot study.
Methods: 16 children with ADHD at the age of 4-5 years were included and randomly assigned to treatment conditions according to a 2×2 cross-over design. The body-oriented therapy included the exercises from yoga and breathing techniques.

To assess the executive functions and attention in children we used 3 subtests from NEPSY (Auditory Attention and Response Set, Visual Attention, Statue). Effects of treatment were analyzed by means of an ANOVA for repeated measurements.
Results: The ANOVA has revealed ($p<.05$) that for all used subtests (Auditory Attention and Response Set, Visual Attention, Statue) the body-oriented therapy was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.48-0.89).
Conclusions: The findings from this pilot study suggest that body-oriented therapy has positive effect on executive abilities in preschool children with ADHD. It influences predominantly the selective and sustained attention, inhibition, monitoring, and self-regulation. However, it is necessary to do further research into the impact of body-oriented therapies on the prevention and treatment of ADHD in children.
Supported By: Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.
Keywords: ADHD, Body-Oriented Therapy, Executive Abilities

T65. Efficacy of Transcranial Near-Infrared Light Treatment in ASD: Interim Analysis of an Open-Label Proof of Concept Study of a Novel Approach

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Background: Autism Spectrum Disorder (ASD) is characterized by variable presentation of difficulties with socialization, communication, and restrictive/repetitive behaviors (RRB), for which no established pharmacological treatment exists. Transcranial Laser Emitting Diode Therapy (TLT) is a noninvasive intervention that leads to cellular plasticity and cytoprotection, was found to be safe and effective in depression treatment. Effects of TLT on ASD symptoms remains to be explored.

Methods: Adult patients with ASD received twice-a-week TLT for 8 weeks in an open-label single group design. Demographic and clinical information was recorded, ASD symptoms were measured at baseline, midpoint, and endpoint by clinician and patient-rated scales (Massachusetts General Hospital (MGH)-Social Emotional Competence Scale-Revised (MGH-SECS-C); Social Responsiveness Scale-Second Edition (SRS-2); Clinical Global Impression (CGI); and Global Assessment of Functioning (GAF). Paired-samples t-test analyses were performed.
Results: Six participants (5 males; 30.2 years, SD = 13.3) completed the study. Four patients (67%) met responder criteria. A statistically significant change was noted in SRS-2 RRB subscales ($p = 0.003$), MGH-SECS-C, and all CGIs and GAF at midpoint and endpoint. A statistically significant change in SRS-2 Social Motivation subscale (Mot; $p = 0.009$) was noted at endpoint. Changes in other scales did not reach statistical significance. One patient developed headaches after initial treatment and spontaneously recovered. No other side effects or serious adverse events occurred. Adherence rate was 98%.
Conclusions: TLT may be a promising treatment for core symptoms of ASD and is a safe, feasible treatment approach. Further research into efficacy in the treatment of core features of ASD is necessary and warranted.
Keywords: Autism Spectrum Disorder, Transcranial Photobiomodulation, Clinical-Trial

T66. Functional Connectivity Between Extrastriate Body Area and Default-Mode Network Predicts Depersonalization Symptoms in Major Depression: Findings From a Multi-Network Comparison

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Background: Depersonalization/Derealisation Disorder (DPD) is a dissociative disorder characterized by feelings of unreality and detachment from the self and surroundings. The greatest likelihood of occurrence of DPD is not as a single disorder but as a comorbidity with mood and anxiety disorders. In the context of major depressive disorder (MDD), DPD is associated with greater depressive severity in terms of treatment resistance, inpatient visits, and longer duration of depressive episodes. In the current investigation, we test four network-based, neural-functional hypotheses of the occurrence of DPD in MDD. These hypotheses are framed in terms of functional relations between 1) extrastriate body area (EBA) and default mode network (DMN); 2) hippocampus and DMN; 3) medial prefrontal cortex and ventral striatum; and 4) posterior and anterior insular cortex.
Methods: We conducted functional magnetic resonance imaging during resting state on 28 female patients diagnosed with MDD. Functional connectivity between seed and target regions as specified by our network-level hypotheses was computed and correlated with scores on the Cambridge Depersonalization Scale. We used a conservative, unbiased bootstrapping procedure to test the significance of neural-behavioral correlations observed under each of the four models tested.
Results: Of the four neural-functional models of DPD tested, only the one proposing that reduced connectivity between the EBA and DMN predicts higher levels of DPD in MDD was confirmed.
Conclusions: Our results indicate that DPD symptoms in MDD patients are related to reduced functional connectivity between brain regions that are proposed to support processing of body-related (EBA) and autobiographical (DMN) information.
Supported By: Warren Foundation; Swedish Research Council; Region Östergötland
Keywords: Depersonalization/Derealization Disorder, Major Depressive Disorder, Extrastriate Body Area, Default Mode Network, Resting State fMRI

T67. Self-Reported Impulsive Behavior and Striatal Dopamine

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Background: Striatal dopamine is thought to serve a central role in impulsive behavior. However, impulsivity is a multidimensional construct (Lynam et al., 2007) and it remains unclear how striatal dopamine (DA) relates to specific dimensions of impulsive behavior.
Methods: We collected two PET indices of striatal dopamine, [11C] Dihydrotetrabenazine (DTBZ) and [11C]Raclopride (RAC), reflecting presynaptic vesicular DA and D2/3 receptor concentration, respectively–and the UPPS-P impulsive behavior scale in 65 healthy adults (mean age = 23.51). Multivariate pattern analysis of striatal voxels with Support Vector Regression was used to quantify the extent to which RAC and DTBZ BP predicted UPP-SP subscales (negative and positive urgency, lack of premeditation, lack of perseverance, and sensation seeking).
Results: Results indicate that both RAC and DTBZ were predictive of total impulsivity and all sub-scales (correlations between leave-one-out prediction and observed scores: r's: .566- .843), suggesting DA is predictive of both general and specific features of impulsivity. RAC and DTBZ were most predictive of UPP-SP lack of perseverance (RAC: $r = .920$; DTBZ: $r = .794$, p's $< .001$) and lack of premeditation (RAC: $r = .853$, DTBZ: $r = .700$; p's $< .001$). Underlying spatial patterns suggested mostly positive associations between PET DA measures and impulsivity, which were uniformly distributed across the striatum.
Conclusions: Results provide evidence for DA playing a critical role in impulsivity, particularly for features associated with a lack of cognitive deliberation. These findings can inform neurobiological models of substance use disorders and the normative development of impulsive behavior.
Supported By: R01 MH080243
Keywords: Addiction, Adolescence, Impulsivity, Dopamine, Striatum

T68. Seed Based Correlation Analysis of Amygdala and Orbitofrontal Regions in Resting State Activity of an Intermittent Explosive Disorder Population

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Background: Intermittent Explosive Disorder (IED) has been studied using task-based functional magnetic resonance imaging. Amygdala and orbitofrontal (OFC) brain regions are altered during emotional processing in IED subjects. However, no research has assessed differences in resting state activity to determine whether intrinsic neural activity in IED is altered.
Methods: Resting state fMRI and structural T1 weighted images were collected on participants diagnosed with IED (n=25) and healthy controls (n=22). The left and right OFC and amygdala were used as seeds to create four connectivity maps for separate group comparisons using the CONN toolbox. Two-tailed group analyses were calculated. Significant results were identified at $p < 0.0125$, correcting for multiple comparisons.
Results: The right amygdala seed showed significantly less connectivity in the left middle (cluster size (k) =191 voxels (382 mm3)) and inferior (k = 135 voxels (270 mm3)) frontal gyrus in the IED group compared to the controls. The left OFC seed showed significantly less connectivity to the precuneus (k = 160 voxels (320 mm3)) in the IED group compared to the controls.
Conclusions: Participants diagnosed with IED showed significantly weaker connectivity in the amygdala to the frontal gyrus as well as in the OFC to the precuneus compared to healthy controls. These results suggest, even at rest, those with IED have weaker connections within areas and networks associated in aggression and emotional control.
Supported By: R21
Keywords: Aggression, Resting State Functional Connectivity, Cognitive Control, rs-fMRI

T69. The Effect of Dopamine Drugs on Reward Discounting: A Systematic Review and Meta-Analysis

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Background: Although numerous studies have suggested that pharmacological alteration of the dopamine system alters reward discounting, these studies have yielded inconsistent findings. Here, we conducted a pre-registered systematic review and meta-analysis to evaluate dopaminergic drug-mediated effects on reward discounting of time delays, probabilities, and physical effort requirements in studies of healthy humans, non-human primates, and rodents.
Methods: We identified potential studies using PubMed. To focus on effects in a normal system, we limited studies to healthy animals excluding effects in human patient groups or animal models of human disorders. This produced a total of 1,343 articles to screen for inclusion/exclusion. Using random-effects with maximum-likelihood estimation, we meta-analyzed placebo-controlled drug effects for (1) DAT, (2) D1-like agonists, (3) D1-like antagonists, (4) D2-like agonists, and (5) D2-like antagonists.
Results: From the literature evaluated thus far (700 of 1,343 articles), we identified 117 effects from 1,517 individual animals. The majority of effects were in rodents (N = 112, with Long-Evans rats comprising 51 effects), while only 4 human effects and 1 non-human primate effect were identified. There were relatively equal numbers of studies using time (N = 43), probability (N = 43), and effort discounting (N = 31) tasks. Meta-analytic effects showed that DAT-binding drugs decreased reward discounting. While D1 and D2 antagonists both increased discounting, agonist drugs for those receptors had no significant effect on discounting behavior.
Conclusions: These findings suggest a nuanced relationship between dopamine and discounting behavior and urge caution when drawing generalizations about dopamine-mediated effects on reward-based decision making.
Keywords: Dopamine, Meta-Analysis, Delay-Discounting, Pharmacology, Decision Making

T70. Could Suicidality in mTBI be Distinct From Depression? A Pilot Study and Theoretical Framework

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Background: Individuals with mild traumatic brain injury (mTBI) are at increased risk for suicidality compared to the general population. mTBI is known to frequently co-occur with psychiatric conditions including post-traumatic stress disorder (PTSD), substance use and depression, though it is unclear if these diagnoses play a role in the increased suicide rate among those with mTBI.
Methods: 22 Veterans were enrolled in the study. Veterans were grouped based on presence or absence of mTBI, with n = 12 for no mTBI group and n = 10 for mTBI group. Presence of mTBI was based on structured TBI interview. A Beck Depression Inventory (BDI), Alcohol Use Disorder Identification Test (AUDIT), and Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) were performed on all participants.
Results: Veterans with mTBI did not differ from veterans without mTBI in frequency of co-occurring psychiatric diagnosis. Veterans with mTBI were more likely to report recent suicidal ideation (SI) per X2 analysis X2=0.391, p=.002, than Veterans without. Among veterans with mTBI, there was no significant difference in BDI score or CAPS-5 score between Veterans who reported recent SI versus those who had not. Veterans with mTBI and suicidal ideation were more likely to report irritability than Veterans with mTBI without SI (X2= 4.5, p =.03).
Conclusions: This suggests that suicidality in individuals with mTBI may be etiologically distinct from a DSM recognized

psychiatric diagnosis. It appears to correlate with symptoms associated with impulsivity.
Keywords: Suicide, mTBI, Depression, PTSD

T71. Obtaining Neurocognitive Assessments From Trauma Survivors: Feasibility and Lessons Learned From the AURORA Study

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Background: Successfully implementing serial neurocognitive assessments (NCAs) in trauma populations is necessary to better understand the development of adverse posttraumatic neuropsychiatric sequelae.

Methods: The AURORA Study enrolls 5,000 trauma survivors at 28 US emergency departments (ED). We examined the performance of a battery of 12 NCAs (assessing working memory, threat, emotion recognition, alertness, and reward learning) administered via smartphone, computer or tablet evaluated in the ED, at 48 hours, weekly during weeks 1-8, and at 3, 6, 9, and 12 months in a cohort of generally low SES trauma patients (N=522).

Results: Follow-up completion rates the 48-hour, 4-week, and 8-week NCAs were 73%, 80%, and 69%, respectively. Most participants (83.4%) used smartphones (45.2% Android, 38.2% iPhone) to complete tasks. Of participants who completed the first at-home assessment (48-hour NCA) via smartphone, most participants continued to use this platform for follow-up activities during weeks 1-4 (N=231/259, 89%). Those who completed via personal computer or tablet, however, were less likely to continue to use the same platform during weeks 1-4 (N=28/48, 58%). Additionally, tests that were more burdensome were less likely to be completed (e.g. Sternberg, 14 minutes, (N=219/260 84%) vs. Verbal Paired Associates, 5 minutes, 249/260 (96%) $P<0.0001$).

Conclusions: Serial NCAs are feasible in low SES posttrauma populations, with most participants completing NCAs via smartphone. NCA test characteristics will be presented with the hope that this data will help researchers to select NCAs for future investigations.

Supported By: This project was supported by NIMH U01MH110925 and the US Army Medical Research and Material Command.

Keywords: Neurocognitive Assessments, Trauma, Smartphones

T72. Resting State Functional Connectivity in Male and Female Collegiate Basketball Players

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Background: Sport participation and its attendant risks have garnered increased scrutiny, as the cognitive and neurobiological consequences of associated brain injuries are not fully understood. Magnetic resonance imaging (MRI) has been shown to be sensitive to subtle brain changes in sub-threshold injuries, and resting state functional connectivity (rs-fMRI) is a promising modality for the study of sex differences in the default mode network (DMN) of athletes.
Methods: Twenty-one Division I basketball players (11 males, 10 females; mean age 20.2±1.5) completed rs-fMRI on a Siemens 3.0T Verio scanner, clinical and neurocognitive measures, including ImPACT (Immediate Post-Concussion Assessment and Cognitive Test), and saliva collection to analyze cortisol levels. Functional connectivity (FC) maps were calculated using the posterior cingulate cortex (PCC) as a seed region for the DMN. Regression analyses for ImPACT scores and cortisol were performed.
Results: Greater DMN connectivity was observed in female players for the frontal lobe and cingulate ($p<0.0001$); cerebellum ($p<0.0001$); and precuneus, angular and parietal ($p<0.002$). Further, we found a positive relationship between ImPACT total symptom score and connectivity with the supplementary motor area, insula, cerebellum and middle frontal region for females. We also found a relationship between salivary cortisol and reduced connectivity between the PCC and right cerebellum in females.
Conclusions: These results provide evidence of sex differences in DMN in collegiate basketball players, as indicated by hyperconnectivity. Further, observed differences in connectivity appear to be mediated in part by cortisol and may thus have biological correlates and clinical implications.
Supported By: PAC-12 Research Initiative
Keywords: Sport-Related Concussion, Resting State Functional Connectivity, Sex Differences, Basketball Player, Cortisol

T73. Common Clinical Presentations of Anti-NMDAr Encephalitis in Adults

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Background: Anti-NMDA receptor (NMDAr) encephalitis is caused by antibodies against NMDAr components. Early symptoms can mimic psychiatric disorders, including schizophrenia, and many patients are initially misdiagnosed. This study focuses on presenting features of anti-NMDAr

encephalitis (anti-NMDArE) in adults likely to be seen by a psychiatrist, to identify patterns of signs and symptoms that may promote early diagnosis.
Methods: PubMed and EMBASE databases were searched systematically for published reports of anti-NMDArE with behavioral or psychiatric symptoms. Frequencies of clinical features from 7 major symptom domains were tabulated, and temporal ranks were assigned based on their relative order of first appearance in each patient. Median ranks were used to sequence clinical features and domains.
Results: 230 unique cases (185 female) age 19+ years met inclusion criteria. After psychiatric/behavioral symptoms, the most common features were seizures (60.4%), disorientation/confusion (42.6%), orofacial dyskinesias (39.1%), mutism or staring (37.4%), other dyskinesias (36.1%), and memory disturbance (34.8%). Median temporal ranks for symptom domains were consistent with the following sequence: behavioral/psychiatric, fever, seizures, catatonic features, cognitive dysfunction, motor dysfunction (including dyskinesias), and autonomic dysfunction.
Conclusions: Every psychiatrist is likely to see patients with anti-NMDArE, and early recognition is crucial. Clinicians should have a high index of suspicion when new psychiatric symptoms arise in the context of a recent viral prodrome, seizures or unexplained fever, or when the quality of the psychiatric symptoms is unusual (e.g., non-verbal auditory hallucinations). Although dyskinesias are somewhat distinctive for this disorder, they often emerge relatively late.
Keywords: NMDA Receptor, Autoimmune Disorder, Encephalitis, Diagnosis, Recent Onset of Psychosis

T74. Developing Methods to Perform Smartphone-Based Studies of Trauma Survivors: Lessons From the AURORA Study

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Background: Nearly 80% of the US population owns a smartphone; this percentage continues to rapidly increase. Smartphones offer tremendous opportunity to identify trauma survivors at high risk of posttraumatic neuropsychiatric sequelae and deliver preventive interventions. Realizing this opportunity requires the development of methods to obtain high quality smartphone data from trauma survivors.
Methods: The AURORA Study enrolls 5,000 trauma survivors at dozens of emergency departments across the US. The Discovery by Mindstrong™ App is installed on participant's smartphone in the emergency department and collects passive and active data (smartphone interface, intermittent flash survey and audio recording) for 12 months.
Results: Eighty percent of Android users recorded 1000 smartphone touches on 75% of days or more, 50% of iOS users recorded 1000 touches on 50% of days or more. Methodologic improvements realized during the first 1,000 iOS/Android users enrolled include moving from unscheduled to quarterly app updates (86% data loss, n=229 vs. 6% data loss, n=356; $p<0.0001$), sharing comprehensive user feedback early in the study with Mindstrong team, and instituting a range of countermeasures. These countermeasures included keyboard improvements and methods to prevent/reduce functional disruptions from smartphone operating system updates.
Conclusions: Smartphone-based passive and active assessments of trauma survivors are feasible. Sharing of methodologic improvements across studies will speed realization of the exciting potential of smartphone-based assessments to improve the lives of trauma survivors.
Supported By: This project was supported by NIMH U01MH110925 and the US Army Medical Research and Material Command. Mindstrong Health.
Keywords: Smartphone, Trauma, Digital Phenotyping

T75. Association of a Specific Metabolomics' Profile and Increased Number of Prior Manic/Hypomanic Episodes in Patients With Bipolar Disorder in Chile

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Background: Omics approaches have facilitated the discovery of biomarkers of psychiatric disorders risk, prognosis and treatment response. However, there is still a need for peripheral blood biomarkers that may distinguish patients with different clinical profiles.
Methods: In this cross-sectional study, we included outpatients and inpatients with bipolar I (BPI) or II (BPII) disorder confirmed by structured interview. Clinical data was obtained by patient interview and medical record review. A targeted metabolomics panel was utilized, including 14 amino acids that were assessed in peripheral blood by mass spectrometry. A hierarchical cluster analysis using the Ward method was performed using the measured metabolites to identify subgroups of patients that shared similar metabolomics profiles. Clinical characteristics between the clusters were compared using t-test / Mann-Whitney test and chi-squared. Statistical significance was set at 0.05.
Results: We incorporated 42 patients in the analyses (64.3% women, 73.8% BP I, history of psychosis 50%, currently euthymic 64.3%, rapid cycling 21.4%). We identified 3 clusters in which their members shared similar metabolites profiles. We found significant differences between clusters 1 and 2 in: age (36.2 ± 11.4 vs 46.8 ± 13.1; $p=0.029$); number of

prior manic/hypomanic episodes (12.9 29.9 vs 23.1 38.9; p=0.039).
Conclusions: Although this study lacks a replication sample, it showed that peripheral blood metabolomics analyses may aid in the differentiation between subgroups of bipolar disorder patients.
Supported By: Fondo de Ayuda a la Investigación, Universidad de los Andes, Santiago, Chile
Keywords: Bipolar Disorder, Metabolomics, Clinical

T76. Deficits in Mental Flexibilty in Depressed Suicide Attempters Across the Lifespan: Initial Data From a Multi-Site Study

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Background: Reduced mental flexibility - assessed via reversal learning tasks and associated with ventral prefrontal dysfunction — has been associated with suicide attempt, primarily in older adults. Its contribution to suicide risk across the adult lifespan is unknown.
Methods: 70 past suicide attempters in a current depressive episode, 75 depressed patients with no suicide attempt history, and 69 healthy volunteers ranging in age from 16 to 80, were recruited in New York, Pittsburgh, and Columbus, Ohio, and compared on a Probabilistic Reversal Learning task designed to isolate errors related to changes in contingency (perseverative errors) and intermittent negative feedback (set maintenance errors). Feedback was probabilistic (80% accurate) for the majority of the task but was turned off in the period immediately after each contingency switch to determine the likelihood of perseverative responding while establishing a new behavioral set.
Results: Past suicide attempters produced more total errors across the task ($F[2,211]=3.26$, $p=.040$). Though reaction times for correct responses were significantly associated with age across all groups ($r = .31$, $p<.001$, with no group by age interaction), error scores were not ($r = -.03$, $p=.70$). Both perseverative errors ($F[2,211]=1.87$, $p=.157$) and set-maintenance errors ($F[2,211]=2.04$, $p=.133$) tended to be greater in past attempters during each phase of the task, but differences did not reach significance across the three groups.
Conclusions: Past suicide attempters exhibited poorer mental flexibility across all conditions of this reversal learning task and across all ages sampled, consistent with a form of ventral prefrontal dysfunction evident across the adult lifespan.
Supported By: American Foundation for Suicide Prevention (AFSP)
Keywords: Major Depression, Suicide Behavior, Reversal Learning, Lifespan

T77. Large Scale Functional Neural Networks Implicated in Bipolar Disorder: A Meta-Analytic Review of Resting-State Functional Connectivity

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Background: Large-scale functional networks have been implicated in a variety of cognitive functions that appear to be affected in mood disorders. Though several meta-analyses have examined resting-state functional connectivity (rsFC) in major depressive disorder (MDD), to our knowledge, none have been conducted in bipolar disorder (BD). The present study aimed to address this gap.
Methods: The present meta-analysis was designed to include studies of whole-brain seed-based rsFC comparing healthy control (HC) subjects to BD individuals. A literature search was conducted in Web of Science and PubMed for articles in press as of 5/1/2018. Analyses were conducted using the Multilevel Kernel Density Analysis (MKDA) MATLAB toolbox.
Results: Nine studies reporting on 441 subjects passed our inclusion criteria. MKDA analyses indicated that BD was associated with abnormal rsFC between seeds in the default mode network (DMN) and a 164 voxel cluster in the right frontal pole also within the DMN. Post-hoc investigation of the studies contributing to this effect suggested that hypoconnectivity may be driving this pattern of abnormal within-DMN rsFC, although the sample size was too small to test for directionality. No meta-analytic abnormalities in rsFC were found in the limbic, ventral attention, or frontoparietal networks, though the relatively low number of available studies for this meta-analysis may have reduced power necessary for detecting such patterns.
Conclusions: Our meta-analytic findings indicate that, similar to MDD, BD may be characterized by abnormal rsFC within the DMN. This study has the potential to inform neurocognitive models of BD.
Supported By: Christina Hough is supported by the National Science Foundation Graduate Research Fellowship Program (NSF Grant Number DGE-1650604). Roselinde Kaiser is supported by Grant Number 1R56MH117131-01.
Keywords: Bipolar Disorder, Resting State Functional Connectivity, Resting State fMRI, Depression, Default Mode Network

T78. Attenuated Default Mode Network Functional Connectivity is Associated With Improvement in Depressive Symptoms Following Mindfulness-Based Cognitive Therapy in a Transdiagnostic Anhedonic Sample

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Background: Mindfulness-Based Cognitive Therapy (MBCT) is an effective intervention for improving depressive symptoms, but the neural mechanisms associated with treatment response are unclear. Mindfulness strategies promoted in MBCT involve psychological processes supported by the Default Mode Network (DMN) such as present-moment awareness and non-judgmental acceptance. Furthermore, DMN hyperconnectivity has been associated with both global depressive symptoms and with anhedonia specifically. Functional magnetic resonance imaging (fMRI) has not yet been reported to assess changes in DMN connectivity following MBCT in a clinically significant mood-impaired sample.
Methods: Eleven adults to date, (age; mean= 35.2 SD= 9.45; range=22 − 49 years old; 10 female), with clinically significant anhedonia completed up to 15 weeks of individualized MBCT. 7 Tesla fMRI and Beck's Depression Inventory-II (BDI) scores were collected pre- and post-treatment. A medial prefrontal cortex (mPFC) seed was used to assess changes in resting-state functional connectivity (RSFC) associated with changes in BDI scores using the CONN toolbox. Results were corrected for multiple comparisons using a false-discovery rate (FDR) adjustment.
Results: BDI scores significantly decreased following MBCT (Pre-treatment M (SD) =20.3 (10.9), Post-treatment M (SD) =6.2 (7.6); p=0.001). Reductions in BDI scores were positively associated with decreases in RSFC between the mPFC and a cluster in the precuneus, after controlling for age and pre-treatment BDI (adjusted R^2 = 0.91; p-FDR corrected = 0.0342).
Conclusions: Attenuated RSFC between regions of the anterior and posterior DMN may partially account for the anti-depressant effects of MBCT. DMN connectivity may provide a mechanistic probe for mindfulness-based clinical interventions.
Supported By: R61 MH110027
Keywords: Mindfulness, BOLD fMRI, Depression, Default Mode Network

T79. Mood Worsening on Hot Days and High Pollen Days in the Old Order Amish With Summer Type SAD

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Background: Summer type Seasonal Affective Disorder (S-SAD) is the less common subtype of seasonal affective disorder (SAD). Although winter SAD is reportedly triggered by shortened day-length and reduced sunlight exposure, evidence regarding triggers of S-SAD is scarce. Previous studies have implicated seasonal changes in heat. Yet another factor present in spring/summer is airborne pollen, reported to be associated with seasonal exacerbation of depression and timing of suicidal behavior. This study explores the relationship of mood worsening with pollen in Old Order Amish (OOA) with S-SAD. OOA have increased exposure to the macro-climate in the summer by not using air conditioning. We hypothesized that those with S-SAD will have significantly higher mood worsening on high pollen days relative to those without S-SAD.
Methods: S-SAD was estimated from 1314 Seasonal Pattern Assessment Questionnaires and related to self-reported associations with mood worsening with weather conditions i.e. cloudy, hot, humid, sunny, dry, grey cloudy, foggy/smoggy and high pollen days using independent-sample t-tests.
Results: A statistically significant difference between S-SAD and no-SAD groups was found for worsening mood on days with high pollen counts(p=.007). Hot(p=.008) and humid days(p=.001) were also related to mood worsening in S-SAD group. No statistically significant difference was found for other weather conditions.
Conclusions: Our results are consistent with previous studies implicating links between thermoregulatory factors and summer depression and studies on aeroallergen exposure and mood, suggesting that exposure to high pollen counts may contribute to SAD with summer pattern. This may have particular importance considering that global warming raised concerns regarding increased exposure to heat and aeroallergens.
Supported By: K18MH093940-01 (PI: Postolache).
Keywords: Seasonal Affective Disorder, Seasonal Pattern Assessment Questionnaire (SPAQ), Seasonality, Old Order Amish

T80. Executive Control and Brain Activity in People With High and Low Levels of Depressive Symptoms

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Background: Attentional deficits in depression may be associated with impaired neuronal networks involved with alerting, orienting, and executive control (Posner& Peterson, 1990). Abnormalities in the corresponding network brain activity detected using event-related potentials may have value in predicting depressive states. The aim of this research was to study brain activity during the Attentional Network Test in participants with higher and lower depressive symptoms score as measured by the Inventory of Depressive Symptomatology (IDS, Rush et al., 1986).
Methods: Fifteen participants who showed IDS score>30 were included in the depression group (mean age=21.47; SD=5.41), and 15 participants with IDS score<20 were

included in the control group (average age=21.60; SD=5.42). Participants performed a modified version of the Attention Network Test (ANT, Fan et al., 2002) with feedback during EEG recording using a Neuron-Spectrum_4 system. The EEG/ERPlab toolbox (Lopez-Calderon& Luck, 2014) was used for preprocessing and measurements of mean amplitude of P300 (250-450 ms) and FRN (Feedback Related Negativity, 200-250 ms) from Fz, Cz, and Pz electrodes.
Results: Behavioral results showed significant differences between groups with higher number of errors for alerting, orienting, and executive control in the depression group ($p<0.05$). Analysis of P300 mean amplitude revealed significant differences between groups in the triggers related to alertness and orienting network ($p<0.05$), and no differences on congruent and incongruent triggers. There is a significant difference between groups in FRN mean amplitude which was more negative in depressed group ($p<0.05$).
Conclusions: Deficits in alerting and orienting neuronal network confirmed an executive deficit in the depression group.
Supported By: Tesearch grant AP05135266 from Ministry of Education and Science of Kazakhstan to AMK.
Keywords: Attention Network Test, Executive Control, EEG, Event Related Potentials, Depression

T81. Gait Disturbances in Major Depression: Is There a Relationship to Normal Pressure Hydrocephalus?

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Background: Increased aldosterone levels cause central mineralocorticoid receptor (MR) overactivity and is associated with therapy refractoriness in patients with major depression. Patients also show increased volume of the cerebral ventricular system, potentially resembling idiopathic normal pressure hydrocephalus (iNPH).
Methods: Ten inpatients with major depression were observed for six weeks, at baseline, week 2 and week 6 thereafter. MR-related biomarkers and clinical outcome were determined (saliva aldosterone and cortisol, HAMD-21, GAF). Furthermore, the gait of the patients was analyzed by measuring gait speed, cadence, step length, its coefficient of variation, with the smartphone, mounted at the patient and the GaitAnalysisPro Application. Furthermore, the idiopathic normal pressure hydrocephalus grading scale (iNPHGS) was administered. A correlative analysis of a pooled dataset was performed.
Results: High aldosterone levels correlated to a lower gait speed ($p=0.031$; $R=-0.45$). A low cortisol-aldosterone-ratio correlated with low gait speed ($p=0.036$; $R=0.44$) and a shorter step length ($p=0.022$; $R=0.485$). Higher scores in iNPHGS ($p=0.026$; $R=-0.453$) correlated with a low coefficient of variation of gait cycle and by trend with higher scores in HAMD-21 ($p=0.062$; $R=0.372$) and significantly with lower scores in GAF ($p=0.021$).
Conclusions: An increase in aldosterone, which appears to be a marker of therapy refractoriness, appears to be related to gait disturbances, which may indicate a resemblance to iNPH.
Supported By: The hormonal analyses were supported by a grant of APVV-0028-10 and VEGA 2/0057/15
Keywords: Depression, Aldosterone, Gait

T82. Neurofunctional Activity During Attentional Control: Identifying Mechanisms of Cognitive Behavioral Therapy Response in Anxious and Depressed Patients

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Background: Cognitive Behavioral Therapy (CBT) is first-line psychotherapy for internalizing psychopathologies (IPs) such as anxiety and depression. IPs are characterized by atypical activation during attentional control. However, mechanisms of change during attentional control have yet to be established.
Methods: During fMRI, 91 patients diagnosed with an anxiety disorder (n=71) or depression (n=20) completed a validated emotional faces interference task (EFIT) before and after 12 weeks of CBT. Thirty healthy controls completed the task at the same time points. EFIT involved identifying a target (X or N) in a string of letters superimposed on threat (v. neutral) faces during low and high perceptual load. At least a >50% pre-to-post reduction in HAM-A (for anxiety) or HAM-D (for depression) denoted CBT response. Pre-CBT EFIT activity for 32 anatomy-based regions comprising frontal, occipital, and parietal systems were submitted to logistic regression with responders (vs. non-responders) as the DV.
Results: 42% responded to CBT. For low load, regression revealed the majority of regions predicted responders ($p<0.05$); overall percentage correct=80.2%. Chi-square showed diagnosis was equivalent across responder/non-responder groups $p=0.66$. Responder group showed both a reduction in anxiety (HAM-A) and depression (HAM-D) ($p<0.001$) and significant increases ($p<0.013$) in pre-to-post activation after completing CBT. The non-responder and control groups showed stable activity in all regions ($p>0.05$) over 12-week period. Regression analysis was not significant for high load ($p=0.14$).
Conclusions: In responders, activation to threat distractors during low, but not high, perceptual load increased after CBT. In contrast, non-responders and controls showed no change after 12 weeks.
Supported By: K23MH093679, R01MH101497, R01MH112705-01
Keywords: Anxiety Disorder, Unipolar Major Depression, Psychotherapy, Cognitive Control

T83. Subjective Response to Alcohol in Young Adults With Bipolar Disorder and Associated Frontolimbic Gray Matter Volume and Alcohol Use

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Background: Alcohol Use Disorders (AUDs) occur three to five times more often in bipolar disorder compared to the general population. Previously, lower gray matter volume (GMV) in the ventral, rostral, and dorsal prefrontal cortex (PFC) was reported in adolescents with bipolar disorder who subsequently developed alcohol problems. It remains unclear how alterations in regional GMV relates to risk for AUDs. This preliminary study is investigating self-report subjective response to alcohol, alcohol use, and associations with PFC GMV in young adults with bipolar disorder and typically developing youth.
Methods: To date, 35 young adults (18 with bipolar disorder and 17 healthy comparison participants, 80% female, mean age+stdev= 20.8+1.9 years) completed structural magnetic resonance imaging, measures assessing alcohol sensitivity, and quantity and frequency of recent alcohol use. These included the Self-Rating of the Effects of Alcohol Questionnaire and the Daily Drinking Questionnaire.
Results: Increased sensitivity to alcohol was associated with lower GMV in the ventral PFC (vPFC) in bipolar disorder ($p<0.005$, >20 voxels). This relationship was not observed in the healthy comparison group (group x SRE interaction $p<0.005$). There was no significant difference between the two groups in their sensitivity to alcohol, frequency of drinking days, or total drinks consumed during their heaviest drinking week.
Conclusions: Preliminary results from this ongoing study suggest variations in vPFC GMV may be associated with altered sensitivity to alcohol. Longitudinal investigations are needed to further examine how variations in GMV, sensitivity to alcohol, and their interactions may then relate to increased risk for AUDs in bipolar disorder.
Supported By: The University of Texas at Austin, Dell Medical School, Department of Psychiatry
Keywords: Bipolar Disorder, Alcohol Use Disorder, Young Adulthood, Magnetic Resonance Imaging

T84. Characterizing Signal Transduction Networks in Postmortem Depressed-Suicide Subjects

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Background: Suicide is one of the top 20 causes of death worldwide, but few interventions consistently reduce suicidal thoughts and behaviors. Our limited understanding of the neurobiology of suicide hinders development of efficacious and safe interventions. Kinases fine-tune signaling in complex biological networks. Kinase gene and protein expression levels are reduced in depressed subjects who die by suicide. Measuring individual kinase expression alone is not sufficient to understand the kinome, the complex network of kinase interactions which represents the intrinsic state of kinases. The kinome has not been studied in subjects who died by suicide.
Methods: We investigated changes in serine/threonine kinase activity in the frontal cortex of depressed subjects who died by suicide and comparison subjects (n=20 per group) using a kinome peptide array-based system (PamGene12).
Results: We demonstrate large scale abnormalities in activity (fold change >1.15 or <0.85) of kinases in depressed subjects who die by suicide, including p53 related protein kinase (PRPK), AMP-activated protein kinase (AMPK), and protein kinase C (PKCd). The kinase data undergo connectivity mapping using the Library of Integrated Network-based Cellular Signatures (LINCS) database. Connectivity mapping links changes in patterns of gene expression induced by altered kinase network activity in depressed-suicide subjects, with chemical perturbagens that induce similar and opposing patterns of change in gene expression.
Conclusions: Kinases have the potential to modulate complex behaviors like suicide but are yet to be exploited therapeutically. Studying the kinome will increase our understanding of the neurobiology of suicide and may lead to the development of novel interventions for suicide.
Supported By: MH107487
Keywords: Postmortem Human Brain, Kinase, Depression

T85. Frontal EEG Asymmetry Evoked by Sad Movies Predicts Relapses After Antidepressant Discontinuation

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Background: Antidepressant discontinuation is associated with a high risk of relapse. Robust predictors of relapse risk after antidepressant discontinuation could support clinical decision-making and possibly help reduce long-term prescriptions. Here, we examined whether frontal EEG asymmetry in the alpha band evoked by sad movies might index relapse risk after antidepressant discontinuation.
Methods: We recruited 35 healthy control subjects and 47 individuals who had achieved stable remission from Major Depressive Disorder while taking antidepressants, and were now intent on discontinuing them. Participants were tested prior to discontinuation and followed up for 6 months after discontinuation to ascertain relapses. All participants underwent EEG recording while viewing sad and neutral movie clips. We compared frontal asymmetry in alpha band power (8-13 Hz) at electrodes F5/F6 during neutral movies vs sad movies.
Results: Patients with remitted MDD did not differ in sadness-induced frontal asymmetry from healthy controls at electrodes F5/6. However, those who went on to relapse (n=14) after discontinuation did differ significantly from those who remained stable (n=33) over the observation period ($p=0.004$, Cohen's $d'=0.93$). Simple thresholding of the F5/6 asymmetry

could be used to predict relapse with an accuracy of 83% (AUC 0.71).
Conclusions: EEG signals from a pair of frontal electrodes during the viewing of sad movies prospectively distinguished those who would and would not go on to relapse after antidepressant discontinuation. This simple procedure has potential to be translated for clinical use and warrants further investigation.
Supported By: Swiss National Science Foundation grant to QH 320030L/153449 / 1; EMDO grant 868 to QH; Stiftung Deutsche Depressionshilfe grant to HW and QH.
Keywords: Frontal Alpha Asymmetry, Antidepressant Discontinuation, Depression Relapse

T86. Clinical Trajectories Over More Than 15 Years Are Associated With Reward Activity Identifying Potential Regions of Neural Compensation in Bipolar Adults

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Background: Childhood onset of bipolar disorder shows severe clinical, social, and developmental outcomes that may be explained by neural abnormalities that develop over the course of the illness. Identifying these abnormalities may provide neural targets for remediation during the course of the illness to improve functioning in this debilitating disorder.
Methods: Adults with childhood onset BD, in the Course and Outcome of Bipolar Youth (COBY) study, have been clinically followed for more than 15 years providing longitudinal data from which three clinical trajectories assessing severity of depression and hypomania over-time were derived using SAS/PROC-TRAJ. Over time, Trajectory 1 participants (n=15) were persistently euthymic, Trajectory 2 (n=20) were moderately ill, and Trajectory 3 (n=12) were persistently ill. HC (n=12) were also recruited. Mean age=26.65 (4.6), 30 female.
Results: Using a whole brain factorial model in SPM12, voxelwise threshold = .001, k=35, during a reward task, we found that HC and the three BD trajectories differed primarily in frontal-parietal activity, with higher activity in HC than in BD-Trajectories 1 and 2 (all ps<.006). HC were similar to BD-Trajectory 3 (ps>.167) in this neural activity.
Conclusions: These results were unrelated to current levels of depression, mania, and medication use (ps>.09), suggesting that frontal-parietal activity to reward was abnormally affected by repeated depression and hypomanic events. Additionally, right-sided dorsolateral prefrontal-parietal activity in persistently ill BD showed compensatory top-down cognitive control function. Thus, activity in this frontal-parietal network may hold potential to be strengthened through intervention in persistently euthymic and moderately ill BD adults with childhood onset BD.
Supported By: R01 MH059929-18
Keywords: Bipolar Disorder, Brain Imaging, fMRI, Frontoparietal Network

T87. Mindfulness Training Increases Intrinsic Connectivity Between the Default Mode and Frontoparietal Control Networks: Positive Consequences for Self-Kindness in Breast Cancer Survivors

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Background: Mindfulness training is suggested to be an effective strategy for reducing depression risk in breast cancer survivors. A recent study proposes that the beneficial effects of mindfulness training on health may be mediated, in part, by self-kindness, or a compassionate attitude towards the self in the face of suffering. While mindfulness and self-kindness have been repeatedly shown to be positive predictors of psychological health, the neural mechanisms underlying these factors are not well understood.
Methods: Here, we use functional MRI to examine neural correlates of self-kindness following a standardized mindfulness meditation intervention for young breast cancer survivors (n = 20). Participants completed resting-state fMRI and questionnaires before and after the 6-week intervention and completed questionnaires at a 3-month follow-up.
Results: We found that the mindfulness intervention resulted in increased functional connectivity between two large-scale intrinsic neural networks, the Frontoparietal Control Network (FPCN) and the Default Mode Network (DMN) ($t(19) = 2.16$, $p < .05$). The DMN is most consistently implicated in self-processing, and the FPCN is implicated in executive control; thus, results may potentially indicate increased top-down executive control of self-referential processes at rest. We also found that positive changes in connectivity between FPCN and the MPFC node of the DMN related to increased self-kindness at the 3-month follow-up compared to baseline (beta = .11, $p < .05$).
Conclusions: Overall, results suggest that mindfulness training in breast cancers survivors may result in increased inter-network functional interactions and that these network-level changes are associated with positive consequences for thoughts and feelings about the self.
Supported By: Breast Cancer Research Foundation
Keywords: Depression, Self-Control Networks, Mindfulness Intervention, Self-Regulatory Control, Cancer

T88. Human and Non-Human Primate Investigations of Approach-Avoidance Conflict: Relevance to Depression and Anxiety Disorders

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Background: Major depression and anxiety disorders have been associated with abnormal approach-avoidance behaviors, which have been implicated in the onset, maintenance and relapse of these prevalent disorders. In spite of the clinical significance of these abnormalities, their neural circuitry dysfunctions remain poorly understood. Partially responsible for modest progress in this area is the fact that preclinical and clinical studies typically use different paradigms to probe approach-avoidance behaviors.
Methods: To circumvent limitations of prior studies in this area, in the present study, we developed an approach-avoidance conflict task based on recent work in non-human primates (Amemori & Graybiel, Nat Neurosci 2012;15:776-785) for use in humans and functional magnetic resonance imaging. Using functionally analogous tasks, 42 unmedicated individuals (18 with MDD) and two female Macaca mulatta monkeys were investigated using fMRI and electrorheological recordings, respectively.
Results: Across species we found shared neural correlates of approach-avoidance conflict and aversiveness in the anterior cingulate cortex (ACC), most prominently in the pregenual anterior cingulate cortex. In addition, in both species, avoidance activated similar ACC regions (humans: $p < .05$, whole-brain corrected). Among the MDD group additional evidence of abnormal task-related activations emerged in the prefrontal cortex, striatum and ACC. Notably, in the human sample, task-related activations correlated with current symptoms and predicted perceived stress months later (all ps $< .03$).
Conclusions: The present results highlight shared cross-species mechanisms of approach-avoidance conflict, and thereby, point to promising candidates for translational biomarkers.
Supported By: NIMH R37
Keywords: Depression, Anterior Cingulate Cortex (ACC), Non-Human Primates, Motivation, Conflict Resolution

T89. Abnormal Functional Connectivity of Frontopolar Subregions in College Students With Depressive Symptomatology

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Background: The frontopolar cortex (FPC) has particular importance in the treatment of major depression and recent neuroimaging studies suggested that the FPC further subdivides into distinct subregions, with each serving distinct functional roles. Study exploring nodes of functional networks showing abnormal connectivity to the FPC subregions could be useful in understanding depression pathology.
Methods: Sixty-five college students, including 31 with depressive symptoms and 34 without depressive symptoms, were recruited for exploring the functional connectivity involving FPC subregions. Mood and anhedonia measures were correlated with brain connectivity.
Results: Results showed that compared with participants without depressive symptoms, participants with depressive symptoms showed a decreased connectivity from the right lateral FPC (lFPC) to the caudate and supplementary motor area and from the left medial FPC (mFPC) to the dorsolateral prefrontal cortex and the right thalamus. Enhanced connectivity observed in the left lFPC and bilateral mFPC to various brain areas including some key nodes in the default mode network (DMN). And, among participants with depressive symptoms, the severity of anhedonia was associated with increased functional connectivity between the left lFPC and the right medial caudate and decreased functional connectivity between left lFPC and the right inferior temporal gyrus, while depression severity was related to decreased functional connectivity from the right mPFC to the right cerebellum.
Conclusions: These results provide preliminary evidence that the lFPC may contribute to symptoms of anhedonia related to abnormal reward processing and the mFPC may engage in enhanced DMN activity among participants with depressive symptoms.
Supported By: National Natural Science Foundation of China (81501177)
Keywords: Frontal Pole, Functional Connectivity, Resting State, Anhedonia, fMRI

T90. Poster Withdrawn

T91. Deep Brain Stimulation for Depressive Episodes: A National Study for Regional Variation of Utilization Across the United States

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Background: DBS is an investigational treatment for treatment-resistant depression (TRD) that is sometimes supported by insurance companies. The objective of this study is to evaluate the utilization pattern of DBS for major depressive disorder (MDD) by sociodemographic and hospital characteristics, and region across the United States (US).
Methods: Patient data were drawn from 2012−2014 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project. Sample included 4,411 hospitals from 45 states; and 116,890 patients (age, 20-65).
Results: The rate of DBS utilization was 0.03% (N=40) in MDD inpatients. Patients who received DBS were older (49±7.85 years). Lower rates of DBS were observed for Medicare/Medicaid beneficiaries and those with median household income <50th percentile. The rate of DBS use was highest in the South, followed by the Northeast and West regions. Majority of DBS patients in the South were <45 years and females. All the DBS patients were from high-income families and covered by private insurance in the Northeast and self-pay in the West. Three-fourths of patients in the South were from low-income families and were Medicare and private

insurance beneficiaries. DBS was performed in public and private hospitals in the South, but only in private hospitals in the Northeast and West. There was a marked variation in the hospital cost for DBS, with the highest in the West ($99,978) and lowest in the Northeast ($12,540).
Conclusions: There is a wide variability of utilization of DBS depending on the region, type of hospital, and type of insurance carrier.
Supported By: Office of Academic Affairs, Medical College of Georgia at Augusta University
Keywords: DBS, Deep Brain Stimulation, Depression, Treatment-Resistant Depression, Utilization

T92. Reduction in Anhedonia Mediates the Relationship Between Left Ventral Striatal Reward Response and 6-Month Improvement in Life Satisfaction in Young Adults

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Background: Anhedonia, the difficulty experiencing pleasure, is a common symptom of multiple psychiatric conditions in young adults that is associated with poorer mental health and psychosocial function and abnormal ventral striatum (VS) reward processing. Aberrant neural reward circuitry function is well-documented in anhedonia and other psychiatric disorders. Longitudinal studies to identify potential biomarkers associated with a reduction in anhedonia are necessary for the development of novel treatment targets.
Methods: Participants, ages 18-25 and experiencing psychologic distress, were recruited into a longitudinal study. Participants were evaluated at baseline and six months. At baseline, participants underwent functional magnetic resonance imaging during a card guessing monetary reward task. Participants completed measures of affective symptoms and psychosocial function at each visit. Neural activation during reward prediction error (RPE) was determined using SPM12. Regions with significant RPE activation were entered as predictors of future symptoms in multiple linear regression models.
Results: 52 young adults [42F/10M, 21.7±2.3yrs] completed the study. Greater RPE activation in the left VS predicted a decrease in anhedonia symptoms over six months (β=-6.094, p=0.037). The decrease in anhedonia between baseline and six months mediated the relationship between left VS activation to RPE and improvement in life satisfaction between baseline and six months (c-path: □=-0.522; p=0.010; c' path: □=-0.308; p=0.157; ab path: 95% CI:-0.551,-0.028). Results were not impacted by psychotropic medication.
Conclusions: Greater left VS responsiveness to RPE may serve as a biomarker for, or potential target for novel treatments to improve, the severity of anhedonia, overall mental health, and psychosocial function.
Supported By: This work was supported by the National Institute of Mental Health (R01MH100041 to MLP) and the Pittsburgh Foundation (to MLP).
Keywords: Anhedonia, Young Adulthood, Quality of Life, Longitudinal Brain Imaging

T93. Higher Concentrations of Interleukin-6 Are Associated With Smaller Nucleus Accumbens Gray Matter Volume and More Severe Symptoms in Depressed Adolescents

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Background: Preclinical and clinical research in adults has demonstrated that psychosocial stress elicits inflammatory responses and is a potent risk factor for the development of depression. The inflammation model of depression has been proposed as a possible mechanism driving brain changes, including smaller limbic gray matter volumes (GMVs), underlying depressive symptoms; however, this model has not been tested in adolescents.
Methods: Twenty-nine depressed adolescents (21 females; mean±SD age:16.15±1.35 years) completed a T1-weighted MRI scan, from which we performed automated tissue segmentations to estimate GMVs of nucleus accumbens (NAcc), amygdala, and hippocampus. Blood drops were collected on 3MM paper and dried overnight; cytokine analysis was performed with a Luminex multiplex bead array as part of a larger immunoassay panel. Depression severity was measured using the Reynolds Adolescent Depression Scale (RADS-2). Linear regression was used to estimate bilateral GMV for each subcortical structure and RADS-2 scores from concentrations of interleukin-6, covarying for BMI and total intracranial volume.
Results: Higher concentrations of interleukin-6 were associated with smaller NAcc GMV (B=-1.697±0.769; t=-2.208; p=0.043). No other GMVs were associated with interleukin-6 (all ps>0.05). Higher levels of interleukin-6 were also associated with more severe dysphoric mood and somatic symptoms on the RADS-2 (all Bs>0.097±0.043; all ts>2.225; all ps<0.05).
Conclusions: Given the role of the NAcc in reward-based and motivational deficits in depression, we propose that higher levels of pro-inflammatory cytokines are associated with reduced striatal dopamine availability and, in turn, reward responsivity and effort-based motivation. Future studies are needed to test this formulation more explicitly.
Supported By: K01; R37
Keywords: Neuroscience, Adolescent Depression, Neuroinflammation, Neuropsychology, Developmental Psychopathology

T94. Lower Subcortical Entropy is Associated With Worse Depressive Symptomology and Suicidality in Adolescents With Mood Disorders

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Background: Depression and suicidality often arise in adolescence. Suicide is the second leading cause of death in adolescents. Depression and suicidality are related to a narrowed attentional focus and perseverative thinking that could reflect entrenched, inflexible neuronal functioning. Entropy of resting-state fMRI signals is a novel approach for measuring neural flexibility.
Methods: Adolescents aged 13-18 years with a mood disorder with (SI; n=15) and without (no SI; n=9) present suicidal ideation and healthy controls (HC; n=15) completed a resting-state fMRI scan. A subset (n=13) completed a second visit one year later. We calculated entropy in subcortical brain regions to assess neural flexibility. We conducted an analysis of variance to examine group differences in subcortical entropy, and tested correlations between subcortical entropy and clinical measures (depression severity and suicidality).
Results: The SI group trended toward lower entropy in the right amygdala, $F(2, 36)=2.01$, $p=.15$, and right thalamus, $F(2, 36)=1.80$, $p=.18$ (SI < HC < no SI). Depression severity was negatively correlated with entropy in the right caudate ($r=-.42$, $p=.007$) and right accumbens ($r=-.32$, $p=.046$). Longitudinal analyses revealed that after 1 year, increased entropy in the right amygdala was associated with improved depression ($r=-.74$, $p=.004$).
Conclusions: The findings suggest low entropy in subcortical regions may serve as a marker of depression symptomology and suicidality both concurrently and longitudinally. Low entropy may interfere with flexibility in problem-solving and the ability to break out of perseverative negative thinking patterns. These results suggest an avenue for treatments designed to enhance subcortical entropy as a target.
Supported By: Ontario Mental Health Foundation, Engdahl Family Research Fund
Keywords: Adolescent Depression, Suicidal Ideation, Resting State fMRI, Entropy

T95. A Serotonin Axon Related Abnormality in Major Depression

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Background: Serotonin transporter binding studies in major depressive disorder (MDD) report disparate findings. Traditional image analysis approaches use regions of interest not based on serotonin anatomy. Brainstem serotonin neuron cell bodies project to frontal pole before projecting to occipital pole. There is excess serotonin synthesis capacity in the cell bodies in MDD and deficient serotonin transmission in projection areas. We sought to determine if MDD has a serotonin system abnormality that varies with distance along the axon from the cell body.
Methods: Serotonin transporter (5-HTT) binding was estimated by positron emission tomography with [11C]DASB in 26 healthy volunteers and 59 medication-free current MDD subjects. Voxel-level binding potential (BPP) was calculated by empirical Bayesian estimation in graphical analysis, and a brain-wide estimate of radiotracer non-displaceable distribution volume (VND), obtained using hybrid deconvolution approach. A statistical model examined the relationship between MDD diagnosis and DASB binding as a function of distance along a tract following serotonergic axons.
Results: 5-HTT binding in both groups decreases along axon tract ($p<0.0001$). The interaction of axon distance and diagnosis is significant ($p=0.0010$). Closer to brainstem raphe, binding is numerically lower in MDD than healthy volunteers. Binding along the axon declines faster in controls than MDD, the two groups converging from front to back of the brain.
Conclusions: Consideration of the anatomy of the serotonin system reveals a potential abnormality in MDD that is not readily detectable using traditional ROIs selected on the basis of high 5-HTT binding. If confirmed, future studies need to elucidate its cause.
Supported By: RO1:R01MH074813; P50MH090964: RO1 MH040695.
Keywords: Unipolar Major Depression, Serotonin Transporter, PET Imaging

T96. Blunted Cardiac Interoception in Suicide Attempters

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Background: An emerging theoretical literature suggests a contributory role for internal sensory deficits in suicidal behavior, although empirical findings in this area are limited. In the current study we examined whether individuals with a history of attempted suicide show evidence of interoceptive dysfunction within the cardiovascular system.
Methods: Psychiatric patients with a history of attempted suicide (n=34) were identified from the Tulsa 1000 dataset and matched to patients without a history of suicide attempts (n=68) on self-reported indices of depression, anxiety, substance use, and eating disorder symptomology. To index cardiac interoception, participants completed a heartbeat tapping task outside of the MRI scanner, and a BOLD fMRI task aimed at localizing brain activity during interoceptive attention directed towards naturally-occurring cardiac sensations. Group differences in the accuracy of heartbeat perception on the heartbeat tapping task were examined using a

linear mixed-effects ANOVA, and differences in BOLD signal during interoceptive attention were analyzed in AFNI using 3dttest++.
Results: Suicide attempters exhibited reduced interoceptive accuracy during the heartbeat tapping task ($F(1,98)=5.10$, $p=0.02$) and hypoactivation in the right dorsal posterior insula during the cardiac interoceptive attention task (small volume threshold of <0.005 within the insula, ACF corrected at $\alpha<.05$). There were no significant group differences in age, sex, or BMI, and no diagnostic differences between groups.
Conclusions: Suicide attempters exhibit blunted cardiac interoception at the brain and behavioral levels. These data suggest that further investigation is warranted to determine whether impaired interoception is etiologically involved in suicide attempts, and/or whether it may distinguish individuals at risk for suicide.
Supported By: NIH/NIMH K23MH112949; NIH/NIGMS P20GM121312; Brain and Behavior Foundation (NARSAD) Young Investigator Award; William K. Warren Foundation
Keywords: Interoception, Suicide Attempts, BOLD fMRI

T97. Predicting Functioning and Quality of Life Using Objective and Subjective Measures of Sleep and Biological Rhythms in Major Depressive and Bipolar Disorder

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Background: Disruptions in biological rhythms and sleep are a core aspect of mood disorders; sleep and rhythm changes frequently occur prior to and during mood episodes.
Methods: A comprehensive study using subjective and objective measures of sleep, biological rhythms was conducted in 111 participants (40 healthy volunteers [HC], 38 major depressive disorder [MDD], 33 bipolar disorder [BD]). Participants completed 15-day actigraphy, first-morning urine sample to measure 6-sulfatoxymelatonin. Questionnaires were administered: Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN), Munich Chronotype Questionnaire, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, Functioning Assessment Short Test (FAST) and World Health Organization's Quality of Life Assessment-BREF (WHOQOL-BREF). Actigraph data were analyzed for sleep, circadian activity rhythms, light exposure, likelihood of transitioning between rest and activity.
Results: Mood groups had worse subjective sleep quality (PSQI), biological rhythm disruptions (BRIAN), higher objective mean nighttime activity than controls. BD group had longer total sleep time (TST), higher circadian quotient, lower 6-sulfatoxymelatonin than HCs. MDD group had longer sleep onset latency, higher daytime probability of transitioning from rest to activity than HCs. Mood groups displayed later mean light exposure timing. Multiple linear regression analysis with BRIAN scores, circadian quotient, mean nighttime activity during rest, daytime probability of transitioning from activity to rest explained 43% WHOQOL-BREF score variance. BRIAN, TST, probability of transitioning from activity to rest explained 52% of FAST score variance (all $p<0.05$).
Conclusions: Our results support that sleep and biological rhythm disruptions are trait markers of mood disorders which negatively impact functioning and quality of life.
Supported By: This work was supported in part by the Canadian Biomarker Integration Network in Depression (CANBIND), an Integration Discovery Program carried out in partnership with, and partially sponsored by the Ontario Brain Institute under Grant [number 00000], an independent nonprofit corporation, funded partially by the Ontario government. The opinions, results and conclusions are those of the authors and no endorsement by the Ontario Brain Institute is intended or should be inferred. This work was also supported in part by the Ontario Ministry of Research and Innovation (Early Research Award – Dr. Frey) under Grant [number ER13-09–229].
Keywords: Biological Rhythms, Mood Disorders, Quality of Life, Functioning, Actigraphy

T98. Small Conductance Calcium-Activated Potassium Channels (SKCs) as Novel Targets for the Development of Rapid-Acting Antidepressants

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Background: The rapid-acting antidepressant (RAD) effects of ketamine and scopolamine (SCP) have recently been described. Despite divergent upstream pharmacological action, recent evidence suggests a downstream convergence point involving small conductance calcium-activated potassium channels (SKCs), which directly regulate neuronal activity and plasticity.
Methods: Fisher344 rats (n=5-6/group) underwent chronic unpredictable stress (CUS), and the effects of SCP and SCP+EBIO on behaviours were assessed. Brain-wide [125I] apamin autoradiography was performed on CUS rats. SK3 knockout mice (WT=10, Hom=12) underwent behavioural testing. Three novel SKC antagonists were assessed in forced swim test (FST) following intracerebroventricular (ic.v.) infusion in Sprague Dawley rats (n=7-8/group). Results were corrected for multiple comparisons where appropriate.
Results: SCP (4 μg/kg, i.v.) reversed CUS-induced reduction of sucrose preference ($P=0.003$), and CUS-induced

prolongation of feeding latency in the novelty-suppressed feeding test (P=0.001). Co-administration of the SKC positive modulator EBIO (4 mg/kg, i.v.) abrogated the effects of SCP. CUS increased [125I]apamin binding of SKCs in the CA1 (P=0.04) and prelimbic cortex (P=0.006). SK3 knockout did not produce effects in the elevated plus maze (EPM), but produced a trend towards decreased hyponeophagia in the novelty-induced hypophagia test (NIHT) (p=0.07), and reduced passive behaviour in the FST (P=0.048). All three novel SKC antagonists (10 ng, ic.v.) reduced passive behaviour in the FST (P<0.001).

Conclusions: SKC-specific compounds offer promising new targets for the development of RADs, which may circumvent the addiction liability and adverse effects associated with ketamine and scopolamine.

Supported By: Centre for Collaborative Drug Research

Keywords: Rapid Anti-Depressant Effect, Small Conductance Calcium-Activated Potassium Channels, Ketamine, Scopolamine, Affective Disorders

T99. Reduction of Frontal and Temporal Cortical Thickness in Patients With Suicidal Behavior but Not With Suicidal Ideation Only

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Background: Abnormalities in fronto-parietal and temporal regions, substrates of cognitive control, decision-making, and emotional regulation deficits have been linked to suicidal thoughts and behavior. However, the structural changes are generally examined in the context of presence of lifetime suicidal events (ideation and attempt). In this study, we aimed to extricate the structural differences between individuals with recent and remote suicidal thoughts and behavior.

Methods: Data was pooled from two separate studies (total N=243) and included individuals with lifetime suicide attempts (Remote-SA), individuals with lifetime suicidal ideation only (Life-SI), individuals who recently attempted suicide (Recent-SA), and individuals who meet criteria for major depressive episode (depressed group) without lifetime suicidal behavior (SA and SI). Whole-brain surface-based morphometry analyses were performed with FreeSurfer 5.3.0.

Results: Lifetime presence of suicidal behavior (Recent-SA+Remote-SA) was associated with lower cortical thickness (CT) in the orbitofrontal, superior frontal and temporal cortices and lower thalamic volume. There were no significant differences in presence of either lifetime of current suicidal ideation. Higher CT in the dorsal anterior cingulate (dACC) and lower hippocampal and thalamic volume were observed in Recent-SA compared to Remote-SA.

Conclusions: Our findings of structural brain changes with suicidal behavior but not with suicidal thoughts support the notion of qualitative distinct phenomena, with the former associated considerably more reduction of brain tissue. Changes in the thickness of the dACC and hippocampal and thalamic volume in patients after a recent suicide attempt may provide a substrate for the deficits in conflict monitoring and pain processing found in these individuals.

Supported By: This work was partially funded by the Clinician Scientist Program of the University Arkansas for Medical Sciences, NCATS UL1TR000039, NIGMS P30 GM110702, and NIH/NIA AG12411.

Keywords: Suicidal Behavior, Anterior Cingulate Cortex, Structural Brain Imaging, Cortical Thickness, Recent Suicide Attempts

T100. Reactivity to Uncertain Threat is a Marker of Suicidal Ideation in Individuals With Depression and Anxiety

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Background: Identifying neurobehavioral correlates of suicidal ideation can help detect individuals most at risk for suicide among high-risk groups. One neurobehavioral process that has been implicated in the development of internalizing psychopathology, and may increase risk for suicide, is heightened sensitivity to uncertain stressors or threats (U-threat). The present study examined whether increased sensitivity to U-threat was associated with a propensity to experience suicidal ideation across two samples of individuals with current depression and anxiety.

Methods: Startle potentiation to U- and predictable (P-) threat was measured using a well-validated threat-of-shock paradigm. In Study 1 (N= 99), current suicidal ideation was measuring using self-report and clinician-administered assessments, the Beck Depression Inventory-II (BDI-II) and Hamilton Depression Rating Scale (HAM-D). In Study 2 (N=102), lifetime history of suicidal ideation was measured using the Structured Clinical Interview for DSM-5 (SCID-5).

Results: In Study 1, current suicidal ideation on the BDI-II and HAM-D was associated with heightened startle potentiation to U-threat, $F(1, 95)=6.22$, $p< 0.05$ and $F(1, 95)=5.30$, $p< 0.05$, respectively. Similarly, in Study 2, a lifetime history of suicidal ideation was associated with heightened startle potentiation to U-threat, $F(1, 97)=4.69$, $p< 0.01$. This relation was specific to U-threat, relative to P-threat (p's $> .09$) across both samples.

Conclusions: Heightened startle potentiation to U-threat is associated with both current and past suicidal ideation across treatment-seeking and non-treatment seeking samples with depression and anxiety. Heightened reactivity to U-threat may characterize those prone to suicidal ideation within high-risk groups and could represent a risk factor for suicidality.

Supported By: RO1

Keywords: Startle, Uncertainty, Suicidal Ideation, Internalizing Disorders, Threat

T101. A Randomized Controlled Trial of Repetitive Transcranial Magnetic Stimulation for Chronic, Treatment Resistant Major Depressive Disorder

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Background: Treatment options in individuals with major depressive disorder (MDD), who are depressed for at least 2 years and are treatment resistant for more than two different types of intervention, remain scarce. Being less invasive than electroconvulsive therapy, repetitive transcranial magnetic stimulation (rTMS) might be an alternative treatment option.
Methods: We conducted a randomized controlled trial investigating the effect of twenty sessions of real or sham-rTMS, during 4 consecutive weeks. Relevant clinical measurements were the Hamilton depression rating scale (HDRS) at baseline, and 1 week after end of treatment and the Dutch method for quantification of treatment resistance in Depression (DM-TRD) at baseline.
Results: Due to the absence of difference in antidepressant response between the treatment conditions (active/sham), we stopped the RCT after 31 patients. The mean difference of the HDRS score between baseline and post-treatment was -3.65 (+/-). There were neither significant effects across time nor between treatment groups. However, we found a negative correlation between the change in HDRS score and DM-TRD in the active rTMS group.
Conclusions: Additional rTMS treatment may not be effective in chronic, treatment-resistant depressed patients. While a replication of our data in this patient group may be ethically difficult, further research with less treatment resistant patients might help positioning rTMS in the stepped care model of depression.
Keywords: Depression, HF-rTMS, Clinical Trials

T102. White Matter Integrity in Bipolar Disorder: Relationship to Cardiovascular Function and Comparison to Major Depressive Disorder

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Background: We sought to compare white matter integrity (WMI) in bipolar disorder (BD) with both healthy volunteers (HV) and major depressive disorder (MDD). We also aimed to determine the relationship of bipolar specific differences in WMI to cardiovascular function.
Methods: 32 participants with BD, 44 with MDD, and 41 HV were recruited. All BD and MDD participants were in a major depressive episode, and all but 12 BD participants were medication free. 64-direction diffusion tensor imaging (DTI) and arterial spin labeling (ASL) sequences were obtained on a 3T MRI scanner. Tract-based spatial statistics (TBSS) on four DTI indices were employed to distinguish patterns of DTI in BD relative to HV and MDD groups. Body mass index (BMI) and blood pressure were obtained for the BD participants.
Results: A cluster of lower axial diffusivity (AD) was found in BD participants in comparison to the HV group in the left posterior thalamic radiation, superior longitudinal fasciculus, inferior longitudinal fasciculus, fronto-occipital fasciculus, and internal capsule. Mean AD in the significant cluster was not associated with cerebral blood flow in the region as measured by ASL and was not associated with BMI or blood pressure of participants. A cluster of lower AD was also found in the BD group when compared to MDD that had spatial overlap with the HV comparison.
Conclusions: The results confirm past studies that WMI is more disrupted in BD than in MDD. Our results showed no evidence of a link between cardiovascular function and disruptions of WMI in BD.
Supported By: K23MH104688; Independent Medical Education Grant from Sunovion Pharmaceuticals
Keywords: Bipolar Disorder, Diffusion Tensor Imaging (DTI), Cardiovascular Disease, Major Depressive Disorder (MDD)

T103. White Matter Microstructure and Related Difficulties in Emotion Regulation: Differentiating Vulnerability and Disease Marker in Bipolar Disorder

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Background: Bipolar disorder (BD) has been associated with aberrant white matter (WM) microstructure. However, it is not clear whether these aberrancies represent a trait marker of the disorder, are a manifestation of an abnormal developmental process and relate to difficulties in emotion regulation.
Methods: A sample of N=108 youth (8-21 years; BD: n=36; unaffected relatives of individuals with BD (REL): n=36; healthy volunteers (HV): n=36) underwent diffusion tensor imaging and provided information regarding difficulties in emotion regulation.
Results: Individuals with BD showed widespread reductions in fractional anisotropy (FA) including the superior corona radiata/ corticospinal tract (SCR/CST; 1119 voxel, pmin=0.02) and the body of the corpus callosum (CC; 33 voxel, pmin=0.048), two clusters where we also observed reduced FA in REL. In the genu and body of the CC only, we observed less age-related FA increases (p=0.002) in

individuals with BD and REL. Both individuals with BD and REL reported more difficulties in emotion regulation ($p<0.001$); 53% of the variance in the difficulties in emotion regulation was explained by FA in the bilateral anterior thalamic radiation and SCR/CST, a finding that replicated in random subsamples.
Conclusions: In sum, our results suggest that alterations in the SCR/CST and the body of the CC represent a trait, rather than a disease, marker of BD. Further, our results support the role of aberrant developmental trajectories of WM microstructure in the risk architecture of BD, and confirm the relevance of these alterations for difficulties in emotion regulation, a core characteristic of BD.
Keywords: Bipolar Disorder, Diffusion Tensor Imaging (DTI), Emotion Regulation, Neurodevelopmental Trajectories

T104. Gaze Behavior Among Patients With Major Depression Disorder When Looking at Own Face

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Background: Self-face processing plays a vitally important role in the study of complex conceptions of self as well as its aberration in depression.
Methods: Adult patients with MDD (n= 57) and controls (HC, n=37) participated in the study. Eyes were tracked while participants viewed centrally displayed for 15 s emotional and self-face expressions. Gaze data were analyzed using traditional measures of fixations over the upper and lower face areas (UFA, LFA).
Results: Being presented with their self-faces, overall patients manifested significantly stronger gaze preference toward the LFA whereas controls showed mostly the UFA preference. Dynamically, HC peaked with visiting the UFA at the intervals of early and late cognitive appraisal, whereas patients mostly dwelled into the UFA all the time ($p = 0.02$). Fixation time scores in the LFA for the late time window positively correlated with the HDRS-17, the RRS's pathological rumination subscale of brooding, anhedonia, and loss of interest (range $r = 0.27$ to 0.24, $p = .02$). In HC the self-face elicited emotion of appeasement, whereas patients manifested dominating sadness and guilt (at $p < .01$). Self-assessed appeasement negatively correlated with HDRS-17, brooding, anhedonia and loss of interest while sadness and guilt were positively associated with the same scales (range from $r = 0.52$ to $r = 0.34$ at $p = .01$).
Conclusions: Attentional strategy for dwelling in the LFA along with perceived negative emotionality of the self-face may be regarded as important potential markers of a distorted self-concept in MDD distinctive "social signature" of emotional self-identification in depression.
Supported By: Research was supported by Russian Science Foundation grant #16-15-00128 to
Lyubomir Aftanas
Keywords: Major Depressive Disorder (MDD), Eye Tracking, Anhedonia, Rumination, Self-Perception

T105. Childhood Maltreatment and Associated Prefrontal-Paralimbic Activity During Emotional and Cognitive Processing in Adolescents/Young Adults With Familial Risk for Bipolar Disorder

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Background: Previous studies have established childhood maltreatment increases risk for bipolar disorder, alcohol use disorders, and their comorbidity. Yet, few studies have investigated neurofunctional consequences following childhood maltreatment that may mediate increased risk for these outcomes. Greater structural and functional abnormalities within prefrontal-paralimbic systems in bipolar disorder following childhood maltreatment are suggested. The mechanisms that contribute to prefrontal-paralimbic abnormalities remain unclear. As bipolar disorder is highly heritable, familial factors may be one mechanism contributing to abnormalities and outcomes.
Methods: To date, 39 adolescents/young adults (19 with familial risk for bipolar disorder, 20 healthy comparison participants, 77% female, agemean+stdev=20+9 years) completed a Continuous Performance fMRI Task with Emotional and Neutral Distractors, the Childhood Trauma Questionnaire (CTQ), and a battery of drinking-related measures. This preliminary analysis investigated the relationship between total CTQ scores and prefrontal-paralimbic activity while viewing targets and emotional distractors.
Results: A negative association was observed between total CTQ score and ventral prefrontal and anterior cingulate activity in individuals with familial risk for bipolar disorder. Specifically, greater total CTQ was associated with lower ventral prefrontal and anterior cingulate responses to targets and lower ventral prefrontal responses to emotional distractors ($p<0.005$, >20 voxels). These negative associations were not observed in the healthy comparison group, with a significant group by total CTQ interaction observed for ventral prefrontal responses ($p<0.05$).
Conclusions: Preliminary results from this ongoing study suggest familial risk factors may contribute to altered prefrontal-paralimbic activity following childhood maltreatment. Longitudinal study examining mood-related and drinking outcomes is needed.
Supported By: Department of Psychiatry Dell Medical School
Keywords: Childhood Maltreatment, Bipolar Disorder, Prefrontal Cortex, MRI, Functional, Familial Risk

T106. Higher Levels of Subclinical Depression in Adolescents Are Associated with Greater Volume of the Hippocampus, Thalamus and Nucleus Accumbens Across Time Than Lower Levels

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Background: Subclinical depressive symptoms (StD) are frequent in adolescence and are related to functional impairment and suicidality, however their neurobiology is poorly understood.

Methods: 178 adolescents (118 Female) aged 14, representative of race, ethnicity and socioeconomic status completed the Revised Children's Anxiety and Depression scale (RCADS) and underwent MRI at time 1 and two years later. FreeSurfer-initiated Large Deformation Diffeomorphic Metric Mapping of structural 3T MRI obtained volumetric measurements of the left and right hippocampus, amygdala, thalamus, caudate, putamen, nucleus accumbens and pallidum. We measured StD with the RCADS Major Depressive Disorder (MDD) scale T score (gender and grade adjusted), binarized according to the standard mean. Repeated measures MANCOVAs of volume for each subcortical structure included StD group as the between-subjects factor, time and hemisphere as within-subjects factors, and covariates of age, gender, race, ethnicity, puberty, intracranial volume and socioeconomic disadvantage.

Results: Low StD group (n=121) mean MDD T score= 41.69, high StD group (n=53) mean MDD T score= 59.03. Repeated measures MANCOVAs revealed significant main effects of StD group for the hippocampus, thalamus and nucleus accumbens, with higher volumes in the high StD group.

Conclusions: Our study was the first to examine the relationship between StD and multiple subcortical structures in adolescents. We argue that our finding of increased volume of the hippocampus, thalamus and nucleus accumbens in higher StD reflects inflammatory processes that occur prior to neurotrophic effects of HPA axis dysregulation, as part of the same mechanism. Additional longitudinal studies are needed.

Supported By: NHLBI (PI: Miller) R01 HL122328, and in part by NIH grant R01 EB020062, NSF grants 1734853 and 1636893.

Keywords: Subcortical Volume, Adolescent Depression, Nonclinical Sample, Longitudinal Brain Imaging

T107. Neurological Predictors of Symptom Trajectories During and Following Treatment of Adolescents With a Primary Diagnosis of Major Depression

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Background: Structural abnormalities in the anterior cingulate, orbitofrontal, prefrontal and insula regions are associated with treatment non-response. These observations are not consistent in depressed adolescents. Definitions of treatment non-response are non-standardised and arbitrary, contributing to variations across studies. We aimed to classify depressed adolescents into different trajectories of symptomatic change using a data-driven approach; and conduct a preliminary investigation of structural brain predictors of class membership.

Methods: 465 depressed adolescents received psychological therapies in the IMPACT trial. Structural magnetic resonance imaging was conducted on 109 patients. Growth mixture modelling (GMM) was used to plot the trajectories of depressive symptoms measured over 86 weeks from randomisation. We used FreeSurfer to extract cortical thickness (CT) and surface area (SA) measures of 4 regions-of-interest (ROI). Logistic regressions were used to investigate their ability to predict class membership.

Results: Piecewise GMM of the total cohort revealed two classes. Continued-improvers (84% of sample) reported a persisting decrease in their depressive symptoms. Halted-improvers (16%) showed improvement up to 18 weeks, but no further improvement thereafter. Neither CT nor SA of any ROI significantly predicted class membership.

Conclusions: Capitalising on repeated symptom assessments with longitudinal data-driven modelling may improve the precision of revealing patient groups with differential responses to treatment. Differences in response trajectory for adolescent depression may not be apparent until after 18 weeks of treatment. CT/SA however, was not associated with subsequent symptom trajectory. This may be due to developmental issues or small effect sizes. A greater sample size is needed in future work.

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SED was funded by a doctoral studentship awarded by the Neuroscience in Psychiatry (NSPN.Org) Consortium itself was funded by a strategic award from the Wellcome Trust (095844/Z/11/Z) awarded to IG and PF.

Keywords: Adolescent Depression, Cortical Thickness, Cortical Surface Area, Treatment Response, Growth Mixture Modelling

T108. The Effect of Deep Brain Stimulation of the Medial Forebrain Bundle on Reward Processing in Treatment-Resistant Depression- A Mode of Action Study

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Background: Deep brain stimulation (DBS) of the medial-forebrain-bundle (slMFB) is under research for treatment-resistant depression (TRD). The slMFB plays a key role in reward processing. Five functions of the reward system were operationalized with behavioral tasks. To assess reward functioning in TRD and to dissociate a direct stimulation effect from placebo effects, the performance of patients was compared to healthy controls before and during DBS, and patients' performance was contrasted during active vs. sham DBS.

Methods: 16 TRD patients were treated with slMFB-DBS and compared to healthy controls with t-tests at t1 (baseline), t2 (DBS active vs. sham: direct effect of DBS) and t3 (chronic DBS) in behavioral tasks (liking: pictures ratings; reinforcement learning: probabilistic reward task; risk: lottery game; effort: winning probabilities; temporal delay: immediate vs. delayed reward).

Results: At baseline, patients showed differences in valence ratings (liking: p=0,009, t=2,837, df: 25), risk taking (p=0,023, t=-2,420, df: 26), learning (p=0,002, t=-3,467, df: 26) and effort (p=0,012, t=2,666, df: 25) as compared to controls. Liking, risk taking, and effort were normalized at t3 (liking: p=0,831; risk: p=0,707; reaction time: p=0,347). Learning remained reduced in patients at t3 (p=0,010, t=-2,775, df: 25). Only in effort (reaction time: p=0,002, t=4,003, df: 13), a difference between stimulation and sham group (t2) was found.

Conclusions: TRD patients showed typical dysfunctions of the reward system. Chronic DBS, which resulted in an antidepressant response, was associated with a normalization of most reward functions. A differential effect of acute DBS vs. sham on reward was not proven.

Keywords: Brain Reward Circuit, Treatment-Resistant Depression, Deep Brain Stimulation, Cognitive Neuroscience, Medial Forebrain Bundle

T109. Short Lived Mixed Affective States in Bipolar Disorder

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Background: We examine the prevalence and associations of subjectively reported states of simultaneously high sadness and high energy that fluctuate within the course of a day, termed here as Short Lived Mixed Affective States (SLMAS), using baseline data from an ongoing longitudinal study of subjects with Bipolar Disorder (BDs) and Healthy Controls (HCs).

Methods: Sample included 50 BDs and 91 HCs. Affective ratings were gathered 3 times per day for 14 days using mobile phone surveys. SLMAS were defined as instances with simultaneously high sadness/depression (>4) and high energy (>4) ratings (on a scale of 0-7). The proportion of total reported ratings with SLMAS (P-SLMAS) were calculated for all subjects. We examined the association of P-SLMAS with demographics, suicidality, symptom severity, cognition and inflammation using correlations and ANOVAs.

Results: BDs had significantly higher P-SLMAS compared to HCs: 9.7% vs 3.5%, p <0.001. Proportion of subjects with at least one SLMAS was also significantly higher in BDs (60.0% vs 38.5%, p=0.014). In the BD group, P-SLMAS was significantly correlated with Brief Psychiatric Rating Scale total score (r=0.373, p=0.012), Hamilton Depression Rating Scale total score (r=0.413, r=0.004), and 36-Item Short Form Health Survey mental component score (r=-0.430, p=0.011), as well as Cognitive Failures Questionnaire and Brief Symptom Inventory Anxiety Scale scores. Correlations remained significant on linear regression. No significant correlation was found with YMRS, suicidality, cognitive performance, and inflammatory markers.

Conclusions: SLMAS appear to be a marker of depressive pathology in bipolar disorder (akin to 'agitated depression') and are associated with greater symptom severity.

Supported By: NIMH grant R01 MH103318; Desert-Pacific Mental Illness Research, Education, and Clinical Center

Keywords: Bipolar Disorder, Mixed Symptoms, Agitated Depression, Short Lived Mixed Affective States

T110. Human Brain Proteomics Signature of Psychosis in Bipolar Disorder: A Preliminary Study

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Background: The molecular underpinnings of psychosis in bipolar disorder (BD) and related brain morphological distinction from BD without psychosis remain elusive. This preliminary study aimed to identify the proteomic differences associated with BD with psychosis history in the dorsolateral prefrontal cortex (DLPFC).

Methods: Postmortem brain tissues (DLPFC gray matter) from five pairs of age-matched male BD cases with and without psychosis history were procured for this preliminary study. Tissue proteomes were identified and quantified by label-free liquid chromatography tandem mass spectrometry. Detected protein group intensities were then normalized and compared between groups by t-test. Significant differential protein group expression was considered at p<0.05 and FDR-adjusted p<0.50 with detection in all samples. These protein groups further underwent Reactome pathway analysis.

Results: A total of 51 protein groups (out of 5647 detected) were significantly differentially expressed between BD cases with and without psychosis history, out of which 21 protein groups with an absolute fold change (FC) >1. We detected the reductions of aggrecan core protein (FDR=0.411, log2FC=-1.48) and myelin-associated oligodendrocyte basic protein (FDR=0.411, log2FC=-2.07) and the elevations of BAI1 associated protein 3 (FDR=0.241, log2FC=2.10) and synaptosomes associated protein 29 (FDR=0.492, log2FC=1.04) in the psychosis cases compared to the no-psychosis cases. The top overrepresented pathways ($p<0.05$ with ≥3 hits) were neurotransmitter receptors and postsynaptic signal transmission, neutrophil degranulation, and innate immune system.
Conclusions: These preliminary results suggest that proteins involved in neuroplasticity, neurotransmission, myelin sheath integrity, and immune response may be dysregulated in the DLPFC of BD patients with psychosis history.
Supported By: NIGMS; NIMH; Mayo Foundation for Medical Education and Research; J. Willard and Alice S. Marriott Foundation; James D. and Pamela S. Deal family.
Keywords: Bipolar Disorder With And Without Psychosis, Proteomics, Human Postmortem Brain

T111. Patient-Reported Health-Related Quality of Life Correlates Inversely With Depressive Symptoms in a Pivotal Trial of SAGE-217 in Major Depressive Disorder

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Background: Major Depressive Disorder (MDD) significantly impacts patient health-related quality of life (HRQoL). HRQoL was assessed as an exploratory endpoint in a pivotal trial of the investigational, oral GABAA receptor positive allosteric modulator SAGE-217 in MDD.
Methods: Subjects (N=89) with MDD and a Hamilton Rating Scale for Depression (HAM-D) total score ≥22 were randomized 1:1 to receive SAGE-217 Capsule 30 mg or placebo for 14 days, with four weeks follow-up. Depressive symptoms were assessed by the HAM-D and Montgomery-Åsberg Depression Rating Scale (MADRS). HRQoL was assessed using the Short Form survey (SF-36v2). Adverse events (AEs) were reported through Day 42.
Results: At Day 15 (primary endpoint), significantly greater least-squares mean HAM-D total score reduction was observed for SAGE-217 (-17.4) versus placebo (-10.3; $p<0.001$). SAGE-217 showed significant improvements in SF-36v2 scores for the General Health, Vitality, and Mental Health domains at Day 15 (global $p<0.05$). In the total study population, changes in depressive symptom scales (HAM-D and MADRS) were moderately or highly correlated with changes in Vitality (>-0.71 Day 15 and Day 42) and Mental Health (>-0.69 Day 15; >-0.77 Day 42) domains. The Mental Component Summary was moderately to highly correlated (>-0.68 Day 15; >-0.77 Day 42), while a moderate correlation was seen with Social Functioning and Role Emotional domains (>-0.52) The most common AEs (≥5% in SAGE-217 group) were headache, nausea, dizziness, and somnolence.
Conclusions: Domains of patient-reported HRQoL were moderately- to highly-correlated with depressive symptoms, providing further evidence that improvement in depressive symptoms results in improvement in HRQoL.
Supported By: Sage Therapeutics, Inc
Keywords: Major Depressive Disorder (MDD), Quality of Life, GABA, Adverse Effects, Depression

T112. Changing the Past: Finding Positive Meaning in Past Negative Events Adaptively Updates Memory

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Background: Finding positive meaning in past negative events is central to therapy and associated with enhanced mental health. It is unclear, however, whether it leads to long-lasting updates in the memory representation itself. Since memory enters a labile period during retrieval, this leaves the potential for modification each time it reopens. We tested whether positively reappraising negative memories adaptively updates them, leading to the re-emergence of positivity at future retrieval.
Methods: In Study1 (N=102), participants reactivated 12 negative memories. They wrote descriptions, made emotion ratings, and then elaborated on them by either focusing on each memory's positive, negative, or neutral aspects, or performed a distracting task. To test for changes over time, they recalled their memories again 1-week later.
Results: Notably, only the positive group had enhanced positive emotion at future retrieval ($p<.001$). Individuals with the greatest change in positive content also had the greatest positive emotion increase ($p=.007$). Critically, we replicated these findings across 4 studies. In Study2 (N=73), positive meaning finding only led to updates after a reminder and 24hr, but not 1hr-delay, consistent with a reconsolidation account ($p=.03$). It was also more effective than receiving a monetary reward after retrieval (Study3: N=56, $p=.05$). Finally, adaptive updates were long-lasting, remaining even after 2-months (Study4: N=91, $p=.002$).
Conclusions: This work highlights an efficacious strategy for coping with persistent maladaptive memories via positivity, which promotes wellbeing and resilience to adversity. It may have translational potential for individuals with mood disorders or PTSD who face difficulty in reshaping their negative memories into more positive ones.
Supported By: McKnight; APF
Keywords: Autobiographical Memory, Emotion Regulation, Positive Emotion, Memory Updating

T113. Mindfulness-Based Cognitive Therapy Modulates Functional Brain Activation During Affective Distraction in Treatment-Resistant Depression: A Randomized Controlled Study

To see this abstract, please see Oral Abstract #O17.

T114. Behavioral Changes and Glial Staining in Mice Subjected to the Chronic Social Defeat Stress Followed by Electroconvulsive Stimulation

Michael Kritzer[1], Christopher Lai[2], Joseph Tharayil[2], Wilfredo Rosario[2], Patrick Botros[2], Alexander Lowell[2], Dianne Cruz[2], Ramona Rodriguez[2], William Wetsel[2], Angel Peterchev[2], and Douglas Williamson[2]

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Background: Chronic social defeat stress (cSDS) is a means of modeling depression- and anxiety-like phenotypes in mice. There has been little study of the effects of electroconvulsive stimulation (ECS) on mouse behavior after chronic social defeat.
Methods: We applied cSDS to C57BL/6J mice then assayed their behavior with social interaction test, open field test, sucrose preference test, and forced swim test to evaluate the phenotype. We then exposed defeated and control mice to 10 days of either active (isoflurane 2%, current 50mA, 100 pulses/sec, 0.5msec pulse width, one second duration) or sham (same handling and electrode placement) ECS stimulation and evaluated post-ECS behaviors (pre-ECS tests plus elevated zero maze, acoustic hyperarousal, tail flick, hot plate and the novel object recognition test) for changes in their behavioral phenotype. We used immunofluorescence to investigate the distribution of glial markers (Iba1, GFAP and S100b) across mouse brain regions, including cortical (cingulate, prelimbic, infralimbic, insula), limbic (nucleus accumbens, amygdala, hippocampus) as well as corpus callosum.
Results: After cSDS, defeated mice displayed an anxiety-like phenotype ($p<0.05$ for open field test) with a milder depression-like phenotype ($p<0.05$ forced swim) compared to controls. We observed an ECS-effect on both control and defeated mice, although there was little behavioral differences between sham mice post treatment. Similarly, there was an ECS effect on the amount ($p<0.01$) and branching ($p<0.01$) of GFAP staining in the dorsal and ventral hippocampus as well as the amygdala ($p<0.05$).
Conclusions: These findings will drive further investigation into how these cellular changes regulate neurocircuitry changes in response to ECS.
Supported By: R01
Keywords: Electroconvulsive Therapy, Chronic Social Defeat Stress, Glial Cells

T115. Necroptosis Might be a Time Dependent Neuronal Cell Death Mechanism on Hippocampus After Chronic Restraint Stress

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Background: Chronic stress causes neuronal cell death on the hippocampus and shrinking of the hippocampus is associated with depression. The connection between inflammation-mediated necroptosis and neuronal damage has been suggested by studies demonstrating a protective effect of necroptosis inhibitor on the brain injury. Therefore, we aimed to understand the molecular background of cell death mechanisms in hippocampal tissue isolated from chronic restraint-stressed rats.
Methods: Male Wistar rats received chronic restraint stress (CRS) for 7 and 28 consecutive days ($n=7$ for each group and controls). Tail suspension test was used to determine the depressive-like behaviour, the plasma levels of cytokines (TNF-α, IL1-α, IL1-β, IFN-γ) were measured by Luminex. The expressions of proteins related necroptosis (RIP, RIP3, MLKL), apoptosis (PARP, Bax, Bcl-2) and GR, BDNF, nNOS were measured by Western Blotting.
Results: There was a significant decrease in the level of depressive-like behaviour at the 28-day CRS compared to 7-day CRS. There was an increase in the level of IL1-β ($p\leq0.001$) and TNFα ($p=0.04$) at the 7-day CRS than the 28-day CRS. Concordantly, in the expression of RIP3 ($p\leq0.05$) and GR ($p\leq0.05$) were found increased while in the expression of PARP, BDNF and nNOS were significantly decreased ($p\leq0.05$) at the 7-day CRS than 28-day CRS.
Conclusions: Our data suggested that the duration of chronic stress might differ the pathway of neuronal cell death and the early period may be under the control of inflammatory mechanisms. Targeted prevention of necroptosis may provide a novel therapeutic approach for the treatment of inflammatory diseases including depression.
Supported By: This project was supported by Istanbul Bezmialem Vakif University Research Fund (BAP-12.2017/26).
Keywords: Hippocampus, Necroptosis, Apoptosis, Chronic Restraint Stress Model, Depression

T116. Anti-Inflammatory Parp Inhibitor Demonstrates Antidepressant Activity in Animal Model of Treatment-Resistant Depression

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Background: Major depressive disorder is associated with elevated levels of DNA oxidation, DNA damage, and gene expression of DNA repair enzymes including poly (ADP-ribose) polymerase-1 (PARP1). Elevated PARP1 activity is directly linked to neuroinflammation and PARP inhibitors are anti-inflammatory and neuroprotective. We previously showed that PARP inhibitors produce antidepressant-like effects equivalent to fluoxetine in rodent models. Here, we examined whether the PARP inhibitor 3-aminobenzamide (3AB) is effective in a rat model of treatment-resistant depression.
Methods: Treatment-resistant depression was modeled with injections of lipopolysaccharide (LPS; 0.1 ug/kg/day) and daily chronic unpredictable stress (CUS) for 28 days. Anhedonia and

helplessness were indexed with sucrose preference and forced swim tests, respectively, in 5 groups of rats (n=6-8 rats/group) including unstressed, CUS, and CUS+LPS rats treated with saline, and CUS+LPS rats treated with either 3AB or fluoxetine.
Results: Anhedonia induced by CUS+LPS was significantly attenuated by 3AB (p=0.01), while fluoxetine failed to do so. Likewise, 3AB was superior to fluoxetine in reducing helplessness, where latency to immobility times were significantly lower in CUS+LPS rats treated with fluoxetine (p=0.001) compared to unstressed rats, but not significantly different for 3AB-treated CUS+LPS rats.
Conclusions: The PARP inhibitor 3AB demonstrated robust and unique antidepressant activity superior to fluoxetine in the TRD rat model. PARP is linked to neuroinflammation through release of microglia-activating factors including poly (ADP-ribose) and HMGB1, and through NF-kB activation, pathways under investigation by our lab. PARP inhibitors are currently used clinically to facilitate cytotoxicity of DNA-damaging anti-cancer treatments. Further research could implicate re-purposing non-cytotoxic PARP inhibitors for treatment-resistant depression.
Supported By: East Tennessee State University Research Improvement Fund
Keywords: Treatment-Resistant Depression, Antidepressant, Novel Drug Targets, Neuroinflammation, Drug Re-Purposing

T117. Pro-Cognitive Properties of a Novel GABA-A Receptor Positive Modulator in Animal Models of Depression and Aging

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Background: Although considered an emotional illness, depression also involves significant changes in cognition, very frequent in aging populations. Considering the lack of available treatments targeting cognitive decline, the need for novel therapeutics reached a climax with the current aging population suffering from a combination of cognitive decline and depression.

Altered GABA signaling is frequently reported in psychiatric disorders and aging. Reduced function of GABA Dendritic Targeting Interneurons (DTI) contribute to cognitive and mood symptoms. α5-containing GABA-A receptor mediate the function of GABA-DTI, hence we hypothesize that enhancing α5-containing GABAA receptor activity will alleviate mood and cognitive symptoms in neuropsychiatric diseases and aging.
Methods: Our group developed a new positive allosteric modulator (PAM) targeting α5-containing GABA-A receptor (α5PAM), and tested its efficacy at reversing cognitive decline in mouse models of depression (n=12/group±2; 50% female) and aging (n=12/group±2). Chronic restraint stress and chronic unpredictable mild stress paradigms were used to induce depressive-like phenotypes. Multiple assays were used to attest for working memory performance (spontaneous alternation), anxiety-like phenotype (plus-maze), antidepressant-predictive activity (forced-swim test) and locomotor activity.
Results: Acute and chronic administration of the novel α5PAM increased alternation rates altered in mouse models of depression ($p<0.001$ in both models) and aging ($p<0.01$), increased time spent in the open-arms of the plus-maze ($p<0.05$) and decreased the time spent immobile in the forced-swim test ($p<0.05$).
Conclusions: A novel α5PAM shows robust therapeutic effects (pro-cognitive efficacy, antidepressant and anxiolytic properties without sedation) in models of depression and aging, making it a good candidate for drug development.
Supported By: NARSAD (25637); Campbell Family Mental Health Institute of CAMH
Keywords: Depression, Cognition, Animal Model, Positive Allosteric Modulator, GABAA Receptor

T118. Lack ofCASP1, IFNGR and NOS2 Genes Alter Depressive-, Anxiety-Like Behavior and Gut Microbiota

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Background: Mounting evidence implicates neuro-inflammatory pathways in the development and treatment response of MDD. Pre-clinical and clinical studies suggest that decreasing pro-inflammatory signaling may be beneficial to MDD. Dysregulation of three major inflammatory systems is evident in this condition: A) increased oxidative stress by means of nitric oxide (NO) overproduction, driven by NOS2 (NO synthase 2), B) low-grade chronic pro-inflammatory status driven by caspase 1 (CASP1) overproduction, and C) interferon gamma (INFG) over production driven by type 1 T helper (Th1) cells.
Methods: The chronic unpredictable mild stress (CUMS) paradigm was used to evaluate whether triple knockout male mice lacking the pro-inflammatory CASP1, INFG receptor, and NOS2 (Casp1, Ifngr, Nos2)-/- display altered depressive- and anxiety-like behavior. Gut microbiome studies were performed at baseline after CUMS; we also measured plasma adreno-corticotropic hormone (ACTH) and corticosterone (CORT) levels using ELISA.
Results: Triple knockout mice exhibit decreased depressive- and anxiety-like behavior and increased hedonic-like behavior and locomotor activity at baseline, and resistance to developing anhedonic-like behavior and a heightened emotional state following stress compared to wild-type (wt) mice. Plasma ACTH and CORT levels did not differ between the triple knockout and wt mice following CUMS. The triple knockout mice fecal microbiota differed from that of wt mice at baseline and displayed reduced changes in response to chronic stress.

Conclusions: Simultaneous deficit in multiple pro-inflammatory pathways has antidepressant-like effects at baseline and confers resilience to stress-induced anhedonic-like behavior. Concomitant changes in the gut microbiome composition suggest that CASP1, IFNGR and NOS2 play a role in maintaining microbiome homeostasis.
Keywords: Depressive-like Behavior, Neuroinflamation, Knock-out, Gut Microbiome

T119. Differences in Nucleus Accumbens Dopamine Release via Muscarinic Acetylcholine Receptor Subtypes: Implications for Manifestation of Negative Symptoms

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Background: Motivational dysfunctions are described as the most common psychiatric symptom in general medicine, as they are seen across a host of neuropsychiatric and neurological disorders. Motivational symptoms are difficult to treat with conventional medications, and thus present an important unmet need. Muscarinic acetylcholine receptors have been implicated in the regulation of ventral striatal dopamine release, and therefore may be important mediators in the neurocircuit underlying motivational impairments.
Methods: The present studies characterized the ability of positive allosteric modulators (PAMs) of M1 or M4 to enhance selection of high-effort options in mice and dopamine release in the accumbens was measured by voltammetry.
Results: Administration of the M4 PAM reduces motivated behavior compared to vehicle conditions ($p<0.05$), an effect not due to appetite or febrile response. Application of an M4 PAM reduces ventral striatal dopamine release ($p<0.05$). Whereas, the M1 receptor exerts bidirectional control over dopamine release ($p<0.01$) and subsequent motivated behavior ($p<0.01$).
Conclusions: In summary, M4 PAMs reduce the tendency to work for food. Similar reductions in motivation have been observed with available antipsychotic drugs and may be due to the ability of M4 PAMs to decrease accumbens dopamine release. In contrast to the effects observed with M4, activation or inhibition of M1 increases or decreases motivated behavior, respectively. Additionally, M1 plays an important modulatory role over dopamine release in the ventral striatum, suggesting agents that target M1 may be efficacious for the treatment of motivational dysfunctions. This research also helps to delineate the critical role of the cholinergic system on normal dopamine function.
Supported By: RO1 to PJC (MH073676)
Keywords: Dopamine, Muscarinic Subtype 1 Receptor, Muscarinic Subtype 4 Receptor, Motivation, Effort-Based Decision-Making

T120. Transcriptomic Analysis of Cortical Microcircuit Cell-Types Reveals Differential Cellular Vulnerabilities and Adaptations to Chronic Stress

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Background: Depression is characterized by disrupted gene expression in cortical brain regions. Such genes are involved in GABAergic and glutamatergic signaling, neurotrophic support, oxidative stress, and other functions. Similar changes occur in UCMS, a depression-relevant mouse model. Currently, the coordinated changes occurring within and across cell-types of the cortical microcircuitry (CM) are unknown.
Methods: We examined the transcriptomic changes occurring in the principal 4 cell-types comprising the CM of UCMS-exposed C57Bl/6J male mice versus controls ($n=10$/group). Depressive-like behaviour (emotionality) was assessed through a battery of 7 behavioural tests after 5-weeks of UCMS. Pyramidal (PYR)-cells and GABAergic interneurons expressing somatostatin (SST), parvalbumin (PV), or vasoactive-intestinal-peptide (VIP) were collected using fluorescent in-situ hybridization and laser-capture microdissection. Gene expression was determined by RNA sequencing. Differential expression, biological pathway enrichment, and co-expression network analyses were performed.
Results: UCMS-exposed mice exhibited elevated emotionality versus controls ($p=0.002$). Differentially expressed genes were largely unique to each cell-type. UCMS induced an upregulation of synapse structure and neurotransmission-related genes in PYR-cells and a dysregulation (up/down-regulation) in SST-cells. UCMS increased co-expression between PYR-cells and both PV ($p=0.00048$) and SST-cells ($p=0.0026$) and decreased co-expression between VIP and SST-cells ($p=0.014$). A co-expression hub module of 1048 genes in PYR-cells, enriched in axon guidance-related genes, correlated with emotionality in UCMS-exposed mice ($r=0.78$, $p=0.010$).
Conclusions: CM cell-types undergo different responses to chronic stress. Synaptic changes in between PYR-cells and both SST and PV-cells may underlie the long-term neurobiological adaptations to UCMS. In vivo pharmacological validation studies targeting key disrupted pathways are warranted.
Supported By: CIHR, OGS
Keywords: Chronic Stress, Depression, Animal Models, Microcircuits, Neuroinformatics

T121. Effects of Developmental Omega-3 Fatty Acid Deficiency on Dendritic Spine Density and Plasticity in the Adult Rat Medial Prefrontal Cortex

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Background: Mood disorders are associated with omega-3 fatty acid deficits and structural and functional connectivity abnormalities within prefrontal cortex (PFC) networks. Reciprocal connections between the medial PFC (mPFC) and amygdala undergo robust synaptic pruning during adolescence in rats. Prior evidence suggests that the omega-3 fatty acids promote synaptogenesis and synaptic pruning. However, the role of omega-3 fatty acids in mPFC structural maturation and plasticity is not known. This study investigated whether developmental deficits in brain DHA accrual alter basal and amphetamine (AMPH)-induced increases in dendritic spine density in the adult rat mPFC.
Methods: In-house bred male rats were maintained on a diet with (control, CON) or without (deficient, DEF) the omega-3 fatty acid alpha linoleic acid (ALA) from gestation to adulthood. From P40-P80, rats received thirty injections of AMPH (1 mg/kg) or saline. On P90, dendritic spine density of Golgi-Cox stained pyramidal neurons was determined in the infralimbic (IL) and prelimbic (PL) subregions of the mPFC.
Results: Compared with CON rats, adult PFC DHA levels were significantly lower in DEF rats (-68%, $p<0.0001$). AMPH treatment similarly increased locomotor activity in CON and DEF rats. In saline-treated rats, dendritic spine density was a numerically lower in the PL (-15%, $p=0.17$) but not IL (+2%, $p=0.89$) of DEF rats. Chronic AMPH treatment similarly increased dendritic spine density in the IL and PL of CON and DEF rats.
Conclusions: These findings suggest that robust deficits in perinatal brain DHA accrual does not alter basal or AMPH-induced increases in dendritic spine density in the adult rat mPFC.
Supported By: NIMH R01 MH107378
Keywords: Dendritic Spines, Prefrontal Cortex, N-3 Fatty Acids, Developing Brain

T122. Omega-3 Fatty Acids Modulate Neurochemical and Functional Responses to Acute Ketamine in Rats: A 7 Tesla Multimodal Neuroimaging Study

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Background: Mood disorders are associated with deficits in docosahexaenoic acid (DHA), an omega-3 fatty acid (n-3), dysregulated glutamate homeostatsis, and decreased connectivity within prefrontal cortex (PFC) networks. Acute ketamine has antidepressant-like effects, stimulates glutamate release, and alters synaptic connectivity in the rat PFC. The present neuroimaging study investigated the effects of acute ketamine administration on PFC glutamate levels, regional activation patterns, and resting-state connectivity in rats with varying brain DHA levels.
Methods: Male rats were fed a diet with no n-3 fatty acids (Deficient, DEF, $n=10$), preformed DHA (fish oil, FO, $n=10$), or a control diet fortified with alpha-linolenic acid (CON, $n=11$) from P21-P90. On P90, 1H MRS and phMRI were performed prior to and following acute ketamine (30 mg/kg) treatment. Connectivity analyses were performed with the Brain Connectivity Toolbox. Postmortem brain fatty acid composition was determined by gas chromatography.
Results: Relative to CON rats, PFC DHA levels were significantly lower in DEF rats (-31%, $p<0.0001$) and significantly higher in FO rats (+13%, $p=0.003$). Ketamine decreased PFC glutamate levels and increased the glutamine/glutamate ratio, and these responses were not altered by DHA level. Ketamine-induced increases in the GABA/glutamate ratio and reductions in PFC BOLD were significantly blunted in FO rats. Ketamine significantly increased normalized global efficiency and closeness centrality and decreased path length in FO rats compared with CON rats.
Conclusions: Higher PFC DHA levels alter neurochemical, regional activation, and connectivity responses to acute ketamine. These findings may have implications for understanding the role of DHA in the psychotropic actions of acute ketamine.
Supported By: NIMH R01 MH107378
Keywords: Ketamine, N-3 Fatty Acids, MRI Brain Imaging, Developing Brain

T123. A Psychosis-Altered Glial-Produced miRNA Downregulates Neuronal Gene Expression via Exosomes

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Background: The presence of the small secretory microvesicles known as exosomes in glia and neurons, and their perceived ability to influence various aspects of neuronal and glial development and function, has positioned them as an exciting and novel method of cell to cell communication
Methods: We used miRNA profiling and miRNA and mRNA qRT-PCR in postmortem brain samples from the orbitofrontal cortex (OFC) of patients with schizophrenia (SCZ) and bipolar disorder (BD) and examined the expression of miRNAs in neuronal and glial cultures, as well as their capacity to be secreted via exosomes.
Results: We found that miR-223, a miRNA known to regulate immune system function and to be packaged and secreted in exosomes, was markedly increased in SCZ and in BD patients with psychosis at the time of death. Changes in miR-223 expression in the OFC were positively correlated with inflammatory and glial gene expression yet were inversely associated with deficits in validated miR-223 targets: Glutamate ionotropic receptor AMPA type subunit 2 (GRIA2) and glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B). Notably, analysis of miR-223 expression in rodent primary neuronal and astrocytic cultures, stem cell-derived neuronal and astrocytic cultures revealed that miR-223, which is produced by astrocytes is transferred to neurons via exosomes, where it downregulates Gria2 and Grin2b gene expression. Lastly, its expression and exosomal secretion was shown to be affected by antipsychotic treatment.

Conclusions: Taken together, our results demonstrate that an inflammation-induced, glial-produced miRNA, altered in psychiatric disorders, can regulate disease-related neuronal gene expression via exosome secretion.
Keywords: miRNAs, Schizophrenia, Bipolar Disorder, Exosomes, Postmortem Brains

T124. Proteomic Profiling of the 16p11.2 Microduplication Mouse Model: Implications for Neuropsychiatric Disease

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Background: The 16p11.2 microduplication is a rare form of chromosomal rearrangement that confers risk of multiple neuropsychiatric conditions including, schizophrenia, autism spectrum disorder, intellectual disability, bipolar disorder and Rolandic epilepsy. The 16p11.2 chromosomal region contains 27 protein-coding genes however, the mechanism by which altered gene dosage in this region increases disease risk is still incompletely understood.
Methods: To uncover novel disease-relevant pathways, we undertook a quantitative proteomic profiling of cortical membrane fractions from the 16p11.2 microduplication mouse model (dp/+). To functionally validate our findings we used electrophysiology, calcium imaging and behavioural assays.
Results: We discovered a large set of upregulated synaptic and ion channel proteins, which converged on known epilepsy and intellectual disability risk factors. Using electrophysiology and calcium imaging we demonstrate that cortical neurons in vitro are hyperexcitable and have abnormal spontaneous calcium oscillations, suggesting altered cortical activity in dp/+ mice. In addition, our findings are supported in vivo assays demonstrating that dp/+ mice are much more susceptible to kainate-induced seizures. We searched for potential drivers of these epilepsy-related phenotypes within the 16p11.2 microduplication, and propose that PRRT2, a known monogenic epilepsy gene, may contribute to altered molecular and cellular phenotypes. This hypothesis is supported by molecular evidence linking PRRT2-associated proteins to proteomic dysregulation in the dp/+ mouse model.
Conclusions: Our study shows that proteomics is a powerful discovery tool to identify novel pathways and cellular phenotypes in neuropsychiatric disorders, which improves our understanding of disease mechanisms, and our ability to design rational therapeutics for affected patients.
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Keywords: Epilepsy, Copy Number Variation, Intellectual Disability, Cortical Excitability, Ion Channel

T125. Blood Metabolomics Analysis Identifies Abnormalities in the Glycolytic System and Tricarboxylic Acid Cycle in Bipolar Disorder

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Background: Although offspring of bipolar parents present a fourfold increased risk of developing Bipolar Disorder (BD) compared to offspring of healthy parents, the precise biological mechanisms underlying this increased risk remains unknown. In this study, we performed a metabolomics analyses to quantify plasma levels of 15 metabolites from the glycolysis and tricarboxylic acid (TCA) cycle from children and adolescents BD patients, unaffected offspring of BD parents, affected offspring of BD parents and healthy controls (HCs).
Methods: We used mass spectrometry to analyze 15 distinct metabolites in plasma samples from 18 patients with BD-I, 18 affected offspring, 13 unaffected offspring, and 18 age- and sex-matched healthy controls (HCs).
Results: After univariate analysis of variance, lower levels of glucose/fructose, glycerol 3-phosphate/glycerol 2-phosphate were detected in BD patients, affected and unaffected offspring when compared to HCs, while glucose 1,6-bisphosphate/fructose 1,6-bisphosphate levels were lower only in unaffected offspring. In addition, levels of lactate, pyruvate and citrate were lower in affected and unaffected offspring, but not in BD patients. On the other hand, levels of glutamine, α-ketoglutarate, succinate and oxalate - intermediates that are important in regulating the TCA cycle activity - were lower only in unaffected offspring, suggesting that the energy production via the TCA cycle was less efficient in unaffected offspring.
Conclusions: In summary, our preliminary study provides evidence that peripheral metabolomics analyses could discriminate between youth at high risk, BD patients and HCs, and suggests that abnormalities in the glycolysis and TCA cycle may play a role in the pathogenesis of BD.
Supported By: R01MH085667; Pat Rutherford, Jr. Endowed Chair in Psychiatry; John S. Dunn Foundation from United States.
Keywords: Bipolar Disorder, Mitochondria, Glycolysis, Tricarboxylic Acid Cycle, Metabolomics

T126. Short- Vs Medium + Long-Chain Plasma Acylcarnitine in Phenotypes of Major Depression at Baseline and After Citalopram/Escitalopram Treatment

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Background: Metabolic signatures that align with depression phenotypes could better characterize the neurobiology of major depressive disorder (MDD) and its heterogeneity. We aimed to identify metabolomic markers of MDD phenotypes and their change after SSRI-treatment.
Methods: We evaluated metabolic profiles from the Mayo-Clinic-Pharmacogenomics-Research-Network (PGRN) of 240 subjects with MDD. Targeted metabolomics were quantified using the AbsoluteIDQ®p180-Kit, which measures 186 endogenous metabolites. Metabolites were compared in three depression phenotypes [core depression (CD), anxiety (A), neurovegetative symptom of melancholia (NVSM)], classified by Hamilton Depression Rating Scale sub-scores at baseline and after 8 weeks of treatment with citalopram or escitalopram. Linear mixed effects models were used to model trajectories of metabolite levels over 8 weeks and to assess metabolic changes by phenotype.
Results: Baseline to 8-week change in small chain acylcarnitines significantly increased, driven primarily by a significant increase in the CD phenotype patients (n=31, C0(log2[FC]=0.14, p=0.045); C3(log2[FC]=0.24, p=0.027). The mean medium/long chain acylcarnitines significantly decreased after treatment, driven primarily by decreases in the NVSM phenotype patients (n=17, C8 (log2[FC]=-0.88, p<0.001); C16(log2[FC]=-0.6, p<0.001)). Pairwise differential abundance analysis at week 8 revealed that levels of many acylcarnitines (C2, p=0.022; C6,C4.1.DC,p=0.012; C7.DC, p=0.036; C10, p=0.002; C14.1,p=0.01; C14.1.OH, p=0.002;C14.2, p=0.04;C16; p=0.002; C16.OH,p=0.006; C16.1, p=0.002; C16.1.OH, p=0.038; C16.2, p=0.034; C18.1.OH, p=0.001) were significantly lower in NVSM phenotype patients compared to patients who did not meet criteria for any phenotype.
Conclusions: Altered acyl-carnitine profiles in clinical MDD phenotypes suggested that beta oxidation and mitochondrial energetics status could provide insights into disease heterogeneity and may help guide efforts toward MDD subclassification.
Supported By: Dr Ahmed Research reported in this publication was supported by National Institute of General Medical Sciences of the National Institutes of Health under award number T32 GM008685.
Keywords: Metabolomics, Major Depressive Disorder (MDD), SSRI, Acylcarnitines, Phenotype

T127. TSPO Upregulation and Mitophagic Proteins Downregulation in Association With NLRP3 Inflammasome Activation in Bipolar Disorder

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Background: Bipolar Disorder (BD) is a complex pathology involving several biological pathways. It is becoming increasingly apparent the importance of understanding how dysfunctional mitochondria and mitophagy contribute to cell survival and death in BD. The purpose of this study was to evaluate the mitophagic pathway, NLRP3 inflammasome activation and the TSPO- related pathway in peripheral blood mononuclear cells (PBMCs) of patients with BD and healthy controls (HCs).
Methods: Thirty-one patients with BD-I and twenty-five age- and sex-matched HCs were recruited from the UTHealth Mood Disorders outpatient clinic. Human blood samples were collected in heparin collection tubes and the PBMCs were separated using LeucoPREP brand cell separation tubes. Then, the gene expression and concentration of mitophagic proteins and TSPO, as well as NLRP3 inflammasome activation were assayed.
Results: Our results showed that patients with BD had lower levels of Parkin, p62/SQSTM1 and LC3A and an upregulation of TSPO pathway proteins, both in terms of mRNA and protein levels. Additionally, it was found that the gene expression levels of the NLRP3-related proteins NLRP3, ASC and procasp1 were upregulated in BD patients, followed by an increase in caspase-1activity as well as IL-1β and IL-18 levels.
Conclusions: It is hypothesized that the upregulation of TSPO culminates in an inhibition of the mitophagic pathway, resulting in a pronounced accumulation of damaged mitochondria and excessive NLRP3-dependent inflammation. Moreover, these findings could suggest that alterations in the mitochondrial network may play a role in producing psychiatric symptoms and the decline in functional status experienced by BD patients.
Supported By: R01MH085667 Pat Rutherford, Jr. Endowed Chair in Psychiatry; John S. Dunn Foundation from United States
Keywords: Bipolar Disorder, Mitochondria, TSPO, Mitophagy, NLRP3 Inflammasome

T128. Regulation of Dendritic Spine Morphology by Small Isoform of Ankyrin-G and Homer1

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Background: Genome-wide association studies have shown that ANK3 variants (encoding ankyrin-G, ankyrin-G) are associated with multiple neuropsychiatric disorders, such as bipolar disorder, intellectual disability, and autism spectrum disorder. However, the molecular mechanisms by when ankyrin-G modulate synaptic organization and plasticity, and how these contribute to neuropsychiatric pathogenesis remain unclear. Here, we identified a PPXXF domain, which is recognized by Homer1, in a small isoform of ankyrin-G (ankyrin-G 190) and characterized its effects on spine morphogenesis.
Methods: Ankyrin-G 190 and Homer1c were overexpressed in primary cortical neurons or human embryonic kidney 293

(HEK293) cells or COS-7 cells. The effects of mutated PPXXF domain variants on interaction, dendritic spine morphology and dynamics were examined.
Results: The interaction between ankyrin-G and Homer1 via PPXXF domain was confirmed by immunoprecipitation and in situ Proximity Ligation Assay (PLA). PLA combined with structured illumination microscopy (SIM) revealed the interaction of ankyrin-G and Homer1 closely localized at the membrane of dendrites and spine head, and this interaction significantly affected on the morphological change of spines and the size of spine head.
Conclusions: Taken together, ankyrin-G 190 and Homer1, both neuropsychiatric disorder genes, interact in a complex to regulate spine morphology. These data implicate a potential role for ankyrin-G and Homer1 in psychiatric disorder pathogenesis.
Supported By: R01MH107182-01
Keywords: Ankyrin-G, Homer1, Dendritic Spines, Spine Formation, Psychiatry Disorders

T129. Exposure to Stress Early in Life and BDNF Modulation: Role of miRNAs

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Background: Traumatic stressful experiences during childhood are well-known factors able to mediate the vulnerability to psychiatric disorders later in life, in particular depression. One of the biological mechanisms underlying this stress-related susceptibility is represented by neuroplasticity. The brain-derived neurotrophic factor (BDNF) is one of the leading molecules involved in this signaling and it has also been widely investigated in the context of stress and depression. The identification of miRNAs targeting BDNF and involved in stress response might allow the identification of novel molecular targets for a better treatment efficacy.
Methods: We measured total BDNF levels and its splicing variants both in blood samples of control individuals characterized for childhood trauma and in an in vitro model represented by immortalized multipotent human hippocampal progenitor cell line (HPC) that were treated with the stress hormone cortisol for 72h during the proliferation phase and then harvested after 20 days of differentiation. Moreover, we performed miRNOme analyses in both models to identify miRNAs modulated by stress.
Results: BDNF levels are reduced in blood samples of subjects exposed to childhood trauma (-22%, $p<0.05$) as well as in cells treated with cortisol and harvested after the differentiation phase (-39%, $p<0.05$). Moreover, the miRNOme analyses identified 205 miRNAs significantly modulated in subjects exposed to childhood trauma and, within these miRNAs, miR-583 was found to be up-regulated also in the in vitro model.
Conclusions: Early life stress might induce long-term down-regulation of BDNF and the up-regulation of miR-583 may be responsible for such observed effect.
Keywords: Stressful Events, miRNAs, Genome-wide miRNA Expression Analysis, Childhood Trauma, BDNF

T130. Transcriptome Profile in iPSC-Derived Astrocytes of TCF7L2, a Transcription Factor Associated With Bipolar Disorder, Reveals Relationship With Neural Function

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Background: Bipolar Disorder (BD) has been associated with multiple phenotypic traits, including obesity. We previously performed genome-wide association studies (GWAS) for BMI-dependent BD risk and identified a genome-wide significant SNP mapped to the TCF7L2 gene. This signal was replicated in an independent cohort. TCF7L2 encodes a transcription factor in the Wnt/beta-catenin pathway. Genetic polymorphisms in TCF7L2 have been associated with type-2 diabetes risk. However, the role of TCF7L2 in neuropsychiatric disorders like BD is not well understood.
Methods: To investigate TCF7L2 function in central nervous system cells, we knocked-down (KD) TCF7L2 in human iPSC-derived astrocytes from two healthy subjects, followed by RNA-seq to identify genes regulated by TCF7L2. ChIP-seq using TCF7L2 antibody was performed using the same astrocytes to identify TCF7L2 DNA-binding sites. TCF7L2-regulated genes were then used for pathway analysis.
Results: After TCF7L2 KD, 272 genes were differentially expressed (fold change >1.5, FDR < 0.05), with 106 down- and 166 up-regulated. Pathway analysis showed enrichment in gene networks involved in neuronal viability and the outgrowth of dendrites ($p<0.05$). Enrichment of genes targeted by lithium, valproic acid, and carbamazepine was also observed. ChIP-seq revealed TCF7L2 binding sites in one-third of genes enriched in these pathways, including IMPA2, CDK1, MDK, MET, NFATC2, ZBTB18, and BMP4.
Conclusions: We found that TCF7L2 regulates gene networks critical for neuronal survival and dendritic growth. These findings, together with previous GWAS results, suggest that TCF7L2 might contribute to neuronal function and, possibly, to BD pathophysiology.
Supported By: This work was supported by the Mayo Foundation.
Keywords: TCF7L2, iPSC-Derived Astrocyte, Bipolar Disorder

T131. Epigenetic Mechanisms Underlying the Stress-Induced Activation of SGK1

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Background: Serum/Glucocorticoid Regulated Kinase 1 (SGK1) is involved in stress responses and in the vulnerability for stress-related psychiatric disorders. We reported a significant increase of SGK1 mRNA levels in peripheral blood of drug-free depressed patients and in the hippocampus of rats exposed to different stress paradigms. We also showed that SGK1 mediates the effects of cortisol on neurogenesis in an in vitro model of human hippocampal progenitor cells (HPSCs). The mechanisms associated with the long-lasting effect of stress on SGK1 are unknown, but DNA methylation and miRNAs could be involved.
Methods: We measured SGK1 methylation levels in the hippocampus of prenatal stress (PNS) rats and in peripheral blood of depressed subjects exposed to childhood trauma. We analyzed by Real-Time PCR the modulation of miRNAs targeting SGK1 (miR-19a; miR-19b; miR-20b; miR-21; miR-28; miR-29a; miR-29b; miR-29c) in brain samples of PNS rats, in blood cells from subjects characterized for childhood trauma and in HPSCs treated with cortisol.
Results: We observed an increased methylation status in SGK1 locus both in animals and in depressed subjects in association with early life stress. We found decreased levels of miR-19b, miR-29c and miR-28 ($p<0.01$) in PNS rats and a trend of downregulation, although no significant, in subjects exposed to childhood trauma. Cortisol reduced miR-19b, miR-29a, miR-29b and miR-29c levels (all $p<0.05$) in proliferating HPSCs, but only miR-29a decreased after differentiation ($p<0.05$).
Conclusions: The long-lasting expression alterations of SGK1 are associated with changes in miRNAs rather than in DNA methylation. Treatments acting on these miRNAs may prevent the SGK1 stress-related vulnerability.
Supported By: Italian Ministry of Health (MoH) (Ricerca Corrente)
Keywords: Early Life Stress, Epigenetic Biomarkers, Mood Disorders, Glucocorticoid Receptor, microRNAs

T132. Differential Effect of Lithium on Glutamate Induced Apoptosis in Human Olfactory Neuroepithelial Progenitors Derived From Bipolar and Non-Bipolar Subjects

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Background: Bipolar disorder (BD) is characterized by marked parenchymal brain loss. The lack of necrosis in post mortem examination suggests an apoptotic process. There is emerging evidence supports that lithium has antiapoptotic actions. Glutamatergic system abnormalities have been consistently associated with BD. But the mechanisms of glutamate excitotoxicity and protection by lithium in BD are still elusive.
Methods: Olfactory neuroepithelial progenitors (ONPs) were obtained by biopsy from type I bipolar patients and non-bipolar controls matched for age, gender, and passage number ($n=3$ and $n=6$, respectively). ONPs were exposed to 0.1M glutamate alone for 6 hours, 1mM lithium alone, or pretreated lithium for 3days, 5days, 7days followed by glutamate. The apoptotic rate was measured by DNA fragmentation assays using an ELISA kit. The protein levels relevant to apoptotic pathway were determined by western blotting, such as BCL-2, AKT, B-RAF, GSK-3, cleaved-caspase-3, cleaved-PARP.
Results: ONPs treated with 0.1M glutamate for 6h did not undergo apoptosis more compared to controls (BD: 0.040 ± 0.004 MSGX6h vs. 0.038 ± 0.008 control, $P=0.737$; Non-BD: 0.050 ± 0.001 MSGX6h vs. 0.030 ± 0.004 control, $P=0.238$). The proapoptotic protein levels of cleaved-caspase-3 and cleaved-PARP were significantly higher in BD-ONPs compare to non-BD-ONPs with glutamate treatment (14.61 ± 2.66 vs 8.77 ± 1.81 and 5.11 ± 0.62 vs 2.61 ± 0.55, $p<0.05$). Lithium (1mM) pretreatment 3 days significantly increased the antiapoptotic protein levels of phospho-B-RAF and BCL-2 in BD-ONPs compared to non-BD-ONPs (1.70 ± 0.35 vs 0.95 ± 0.11, 5.49 ± 1.25 vs 0.81 ± 0.11, $p<0.05$).
Conclusions: Lithium is more effective in increasing B-RAF and BCL-2 expression in BD-ONPs compare to non-BD-ONPs with 0.1M glutamate treatment for 6h.
Keywords: Bipolar Disorder, Apoptosis, Glutamate, Lithium, Olfactory Neuroepithelial Progenitors

T133. Glutamate-Induced Apoptosis on Olfactory Neuroepithelial Progenitors Derived From Bipolar and Non-Bipolar Subjects

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Background: Post-mortem studies have linked bipolar disorder (BD) with increased brain matter loss due to higher levels of cellular apoptosis. Apoptosis may be related to glutamatergic cytoxicity and studies have suggested BD subjects may have higher levels of glutamate. Higher levels of glutamate increases cytoxicity and activates the cellular apoptotic process. Drugs that normalize glutamate levels may slow the apoptotic process and lead to improved outcomes for BD subjects. Lithium has been established to prevent glutamate-induced cytoxicity in olfactory neuroepithelial progenitor cells (ONPs) cultured from BD subjects.
Methods: The aim of the current study is to examine if ONPs from BD subjects are more sensitive to glutamate-induced apoptosis and to quantify the rate of ONPs undergoing glutamate-induced apoptosis within a cell population. In addition, the study aims to replicate previous findings that suggest BD subjects have increased sensitivity to glutamate-induced apoptosis compared to control subjects using ELISA Cellular DNA Fragmentation Assays and flow cytometry.
Results: Analysis of ELISA assays showed no significant difference between BD subjects ($n=3$) and controls ($n=3$) but did significantly differ within-group when ONPs were treated with 0.1M glutamate for 24 hours ($P<0.05$). Flow cytometry data were inconclusive due to a heterogeneous cell population.
Conclusions: Results obtained from ELISA Cellular DNA Fragmentation Assays did not confirm results from previous ELISA histone-associated assays suggesting increased sensitivity to apoptosis in BD subjects. Further experimentation is being conducted to determine if flow cytometry can be used to

study apoptosis in ONPs and to confirm the ELISA DNA Fragmentation Assay or previous ELISA histone-associated results.
Supported By: National Institute of General Medical Sciences of the National Institutes of Health
Keywords: Glutamate, Apoptosis, Bipolar Disorder

T134. Neurophysiological Correlates of rTMS Treatment Response in Youth With Major Depressive Disorder

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Background: Conventional treatments for youth MDD have only modest efficacy. Recent evidence suggests that rTMS may have potential as an alternative therapy in this population. As part of a novel clinical trial using Theta Burst Stimulation (TBS) in the treatment of youth MDD, we explored the neurophysiological correlates associated with treatment response to rTMS.
Methods: 20 youth with MDD and 20 healthy controls between the ages of 16 − 24 were recruited. Youth with MDD received 10 rTMS (bilateral DLPFC TBS) treatment sessions over 2 weeks. Using TMS-EEG, cortical excitation and inhibition was probed at six cortical sites: bilateral DLPFC, bilateral motor cortex, and bilateral parietal cortices. ANOVAs were used to assess changes in neurophysiology following rTMS treatment. We also investigated associations between baseline measures of neurophysiology and treatment response, as well as associations with changes in depressive symptoms.
Results: Youth with MDD exhibited an average decrease on HRSD-17 scores by 38.4% following treatment ($p < 0.05$). The right parietal cortex N45, a measure of cortical inhibition, decreased following treatment ($p < 0.01$). We also found reductions in depressive symptoms to be negatively correlated with baseline left DLPFC N45 and positively correlated with changes in right parietal cortex N100 following treatment.
Conclusions: rTMS was efficacious in reducing depressive symptoms in youth with MDD. Cortical inhibition, specifically in the DLPFC and parietal cortices, was found to be related to rTMS treatment response. Our findings suggest that the GABAergic system is in part implicated in the efficacy of rTMS treatment for youth MDD.
Supported By: CIHR
Keywords: Adolescent Depression, rTMS, TMS-EEG, Neurophysiology, Cortical Inhibition

T135. Combination Theta-Burst Stimulation and Cognitive Training for Youth Depression

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Background: Major Depressive Disorder (MDD) affects an estimated 11% of North American youth. Current treatments (medication and psychotherapy) are limited in efficacy and accessibility and are associated with significant side effects (i.e. suicidal ideation). They often fail to improve associated cognitive impairment.

In this double-blind placebo-controlled feasibility study, we examine the safety and tolerability of combination TBS and a novel, ipad-based, cognitive training (CT) suite as an alternative for conventional interventions in youth MDD.
Methods: Youth aged 16-24, with a diagnosis of major depressive disorder, were randomized to receive 4-weeks (daily on weekdays) of TBS (1800 iTBS to the left DLPFC, and 1800 pulses cTBS to the right DLPFC) followed by active or sham CT. Baseline neurophysiology and clinical evaluations were repeated 1-week after final treatment. Stakeholders and neuroscientists designed the CT suite together to optimize engagement and executive function.
Results: Twenty-eight participants were recruited and randomized over 14 months (Oct 2017-Dec 2018). TBS and CT were well-tolerated with no significant adverse events (i.e. no seizures) and only some reports of headache (<8%), nausea (<4%), and site discomfort (<5%), none of which spurred study withdrawal. Twenty-six participants (93%) completed the trial in full. Two youth (7%) dropped out − one after baseline testing (before receiving any treatment), and one after 11 treatments (citing the commute as the termination reason).
Conclusions: These data suggest that 4-weeks of combined TBS and CT is a feasible, safe, and tolerable treatment approach for youth MDD. CT may also uniquely serve to enhance accessibility and improve MDD-related cognitive impairment.
Supported By: Caskey-Francis Family, CAMH Foundation Grant
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Keywords: Theta Burst, Neural Plasticity, Adolescent Depression, Cognitive Impairment

T136. Safety and Efficacy of Intravenous Ganaxolone in Severe Postpartum Depression: Results From a Double-Blind, Placebo-Controlled Phase 2 Study

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Background: Postpartum Depression (PPD) affects more than 400,000 women each year in the United States but effective treatment options are limited. We report the results of a double-blind, placebo-controlled Phase 2 study of ganaxolone, a synthetic analog of allopregnanolone and a potent positive allosteric modulator of GABAA-receptors, in severe PPD.
Methods: Women diagnosed with severe PPD (N=58; Baseline HAMD17=26.4, SD 3.8) were randomized (1:1) to receive a 60 hr intravenous (IV) infusion of ganaxolone or placebo. Three

fixed ganaxolone doses were evaluated. HAM-D17 was assessed at various times during the infusion and at Day 11 and Day 34.
Results: A dose response was observed with the highest ganaxolone dose (140 μg/kg/hr, n=10 at baseline) generally performing the best over placebo. Patients in this dose group experienced a 15.1, 16.9, and 15.7 point HAM-D17 reduction from baseline at 48 hrs, 60 hrs, and Day 34, respectively. These HAM-D17 reductions reflect clinically-meaningful 5.6, 4.2, and 4.1 point improvements over placebo (n=28 at baseline) at the corresponding timepoints. Ganaxolone was safe and well-tolerated with the most common reported AE's of mild sedation and dizziness. There were no reports of syncope of loss of consciousness.
Conclusions: Ganaxolone IV in severe PPD demonstrates preliminary evidence of rapid and durable antidepressant action with a favorable safety profile. Although the 60hr infusion paradigm presents an encouraging treatment option, future ongoing studies plan to assess a short course IV infusion followed by daily oral ganaxolone to provide a more convenient treatment paradigm while maintaining acute and durable antidepressant effects.
Supported By: Marinus Pharmaceuticals
Keywords: Postpartum Depression, Antidepressant Trial, GABA-A PAM, Ganaxolone

T137. Psilocybin-Assisted Group Therapy for Demoralization in Long-Term AIDS Survivors

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Background: Long-term AIDS Survivors (LTAS) are people with HIV diagnosed prior to the advent of antiretroviral therapy. LTAS suffer high rates of multiple psychiatric illnesses; demoralization is a syndrome common in LTAS and is characterized by a sense of helplessness, hopelessness, and a loss of meaning and purpose in life. Psilocybin is a 5HT2A agonist and classic psychedelic that can improve depression and anxiety in cancer patients when combined with individual psychotherapy, possibly by decreasing demoralization.
Methods: We are conducting an open-label trial of psilocybin-assisted group therapy for gay-identified LTAS with moderate-to-severe demoralization. Participants complete four group-based preparatory sessions, followed by an individual psilocybin administration session (0.3mg/kg po), followed by six group-based integration sessions. Primary outcomes include safety and feasibility. Secondary outcomes include self-reported demoralization, grief, and symptoms of depression and PTSD.
Results: 18 individuals enrolled in the trial with 100% retention. Zero Serious Adverse Events related to psilocybin occurred and no medical interventions were required. Changes from Baseline to Endpoint were found in Demoralization Scale-II (mean difference (SD): 6.67 (6.51), p=0.0004, Hedge's g=0.99); Center for Epidemiologic Studies of Depression Scale-Revised (8.94 (14.73), p=0.02, g=0.76); Inventory of Complicated Grief-Revised (6.22 (6.74), p=0.001, g=0.52); and PTSD Check List-5 (9 (11.47), p=0.004, g=0.74).
Conclusions: This is the first trial to demonstrate the safety, feasibility, and preliminary efficacy of administering psilocybin as an adjunct to group (vs. individual) psychotherapy for any disorder. Preliminary results resemble prior findings of rapid improvement in mood and anxiety symptoms in cancer patients. Placebo-controlled trials are needed.
Supported By: Gift fund
Keywords: Psilocybin, Mood Disorders, HIV

T138. Augmentation Treatment With Dopaminergic Compounds in Major Depression and Bipolar Disorder: A Systematic Review and Meta-Analysis

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Background: Dopaminergic compounds (DC) are often used as adjunct treatment in mood disorders. We conducted a systematic review and meta-analysis to evaluate the efficacy of augmentation with DC pramipexole, lisdexamphetamine/methylphenidate, and ar/modafinil in major depressive disorder (MDD) and bipolar depression (BD).
Methods: A comprehensive search of major electronic databases was conducted to identify relevant randomized controlled trials (RCT). Data for response/remission and all cause discontinuation rate were analyzed. Effect size was summarized by relative risk (RR) using the Random effects model.
Results: Of 44 potentially eligible studies, 21 RCTs, MDD (13 studies, N=1102, N=1028 placebo) and BD (8 studies, N=828, N=827 placebo) were analyzed. Augmentation with DC exhibited a significantly greater response and remission rate vs placebo (RR, 1.21; 95% CI, 1.12−1.31; P< 0.00001; RR, 1.26; 95% CI, 1.10−1.44; P=0.0005, respectively) with no differences between MDD and BD (I2= 0%, P= 0.73; I2= 47.3%, P= 0.17). Only ar/modafinil achieved significant remission rates (RR, 1.31; 95% CI, 1.09−1.59; P=0.0005). All cause discontinuation did not differ between DC vs placebo (RR, 1.02; 95% CI, 0.90−1.16; P= 0.76) or between MDD and BD (RR, 1.05; 95% CI, 0.89−1.25; P= 0.50).
Conclusions: The meta-analytic data supports the efficacy of DC as an augmentation strategy in mood disorders without increasing rates of discontinuation. There may be merit in further analyzing differential response/remission rates by mood disorder subtype based on drug mechanism of action (i.e. agonist, transporter reuptake inhibition, vesicular monoamine transporter) reinforcing the importance of enhancing dopaminergic neurotransmission in depressive disorders.
Supported By: This project received funding from a grant from Marriott Foundation.

Keywords: Bipolar Disorder, Dopamine, Major Depression, Treatment Efficacy, Meta-Analysis

T139. Dissecting the Impact of Depression on Decision-Making During a Probabilistic Reward Task

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Background: The broad cognitive deficits seen in depression may reflect a fundamental problem with decision-making. To investigate this possibility, we analyzed data from 281 unmedicated adults with Major Depressive Disorder (MDD) and 61 healthy controls as they performed the probabilistic reward task (Pizzagalli et al., 2005).
Methods: Data came from two samples (Study 1: 258 MDD, 36 controls; Study 2: 23 MDD, 25 controls). On each trial, the participant indicated which of two similar stimuli was briefly presented. Quantile-probability plots and the Hierarchical Drift Diffusion Model (HDDM; Wiecki et al., 2013) were used to examine the impact of MDD on response times (RT), speed of evidence accumulation (drift rate), and the width of decision thresholds, among other parameters. Internal consistency of the HDDM results was also assessed.
Results: RTs were more positively skewed in depressed adults, suggesting slower evidence accumulation during decision-making. Indeed, the HDDM revealed slower drift rates (qs < 0.04) and wider decision thresholds (qs < 0.005) in both MDD groups. In Study 1, depressed adults earned fewer rewards than controls ($\beta = -0.13$, $p = 0.029$). When the HDDM parameters were added to the model, however, the Group effect became non-significant ($\beta = -0.05$, $p = 0.30$) and drift rate emerged as the strongest predictor of cumulative reward ($\beta = 0.39$, $p < 0.001$). All HDDM parameters showed good to excellent reliability (Spearman-Brown rs > 0.77).
Conclusions: MDD was characterized by slow evidence accumulation. The resulting decision-making deficits may help explain its broad negative effects on cognition.
Supported By: NIH grants R00MH094438, R01MH68376, U01MH092221, U01MH092250
Keywords: Depression, Computational Modeling, Computational Psychiatry, Reinforcement Learning, Reward

T140. Intrinsic Network Connectivity Reliably Distinguishes Retrospective Risk for Suicidal Behavior in Individuals With Mood Disorders

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Background: Little is known about the neural substrates of suicide risk in mood disorders. Improving the identification of biomarkers of suicide risk, as indicated by a history of suicide-related behavior (SB), could lead to more targeted treatments to reduce risk.
Methods: Participants were 112 young adults with a mood disorder with no history of suicidal behavior (MD), 18 individuals with a mood disorder with a history of SB (as indicated by endorsing a past suicide attempt), and 82 healthy comparison participants (HC). Resting-state functional connectivity within intrinsic neural networks, including cognitive control network (CCN), salience and emotion network (SEN), and default mode network (DMN), was compared between groups.
Results: Several fronto-parietal regions ($k > 57$, $p < .005$) were identified in which individuals with SB demonstrated distinct patterns of connectivity within (in the CCN) and across networks (DMN-CCN and DMN-SEN). Connectivity with some of these same regions also distinguished the SB group from the MD and HC groups when participants were re-scanned after 1-4 months. Patterns of connectivity generally were specific to history of suicidal behavior rather than history of suicidal ideation. Extracted data defined group membership with good accuracy, sensitivity, and specificity.
Conclusions: These results suggest that individuals with a history of SB in the context of mood disorders may show reliably distinct patterns of intrinsic network connectivity, even when compared to those with mood disorders without SB. Resting-state fMRI is a promising tool for identifying subtypes of patients with mood disorders who are at risk for suicidal behavior.
Supported By: This work was supported by NIMH grant MH 091811 and MH 101487 (SAL), and UIC Clinical and Translational Science Awards Program NCATS UL1TR000050 and 1S10RR028898. Jonathan P. Stange was supported by grant 1K23MH112769-01A1 from NIMH and a NARSAD Young Investigator Award.
Keywords: Resting-State Functional Connectivity, Intrinsic Connectivity Networks, Suicide, Mood Disorders, Suicidal Ideation

T141. Suicidality and Emotional Inhibitory Control in Dually-Diagnosed Adolescents

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Background: Dually-diagnosed adolescents, presenting with a substance use disorder and at least one additional psychiatric diagnosis, are at elevated risk for suicidal behaviors. As impulsivity has been linked to suicidal behaviors, particularly in young people, the aim of this study was to examine the relationship inhibitory control and suicide attempt in dually-diagnosed adolescents.
Methods: Dually-diagnosed adolescents were assessed upon admission to the McLean Hospital Acute Residential Treatment program. All participants included in the current analyses

reported lifetime suicidal ideation, assessed via the MINI-KID structured clinical interview. Participants (N=335, 196 female, age=16.9±1.2) performed an emotional Go-NoGo task to measure inhibitory control in the presence of distracting images that were emotionally negative, neutral, positive or scrambled.

Results: Results showed individuals who reported at least one lifetime suicide attempt (N=164) had significantly lower accuracy on inhibitory (NoGo) trials across all background conditions. In a sub-sample reporting suicidal ideation within the past month (N=201), a significant group x background interaction effect was observed (p=.012) with individuals reporting suicide attempts (N=69) within the past month showing significantly increased impulsive errors on negative background trials (p=.020) and neutral background trials (p=.025) only.

Conclusions: These data demonstrate that impulsivity measures may help identify adolescents at highest risk for suicide attempt and that inhibitory control in negative and neutral emotional contexts is particularly associated with recent suicidal actions. Further studies are necessary to parse out relationships between suicidality, inhibitory control and emotion in order to develop targeted interventions to help reduce suicidality in dually diagnosed adolescents.

Supported By: NIAAA K01 AA022392

Keywords: Adolescence, Suicidal Behavior, Inhibitory Control, Substance Use Disorders, Dual Diagnosis

T142. Insulin Resistance Impacts the Relationship of Depression Severity on Cognitive Control

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Background: Deficits in cognitive control - the ability to switch attention between stimuli — is associated with Major Depressive Disorder in some, but not all patients. This heterogeneity is poorly understood and likely has significant clinical implications. Insulin resistance is also associated with deficits in cognitive control, but the effects of cognitive control and insulin resistance have sparsely been investigated in a depressed population.

Methods: The sample for this analysis includes the first 108 participants from the Dallas 2K (D2K) longitudinal depression study with complete psychometric data and available plasma. Plasma glucose and insulin were used to estimate insulin resistance using the Homeostatic model assessment of insulin resistance (HOMA-IR). Participants were categorized as insulin resistant if their HOMA-IR was >2.5, whereas those below 2.5 were considered insulin sensitive. Depression severity was measured using the Quick Inventory of Depressive Symptomology (QIDS) and the Flanker task Z-score (NIH Toolbox) was used to assess cognitive control. In both the insulin sensitive and resistant populations, linear regressions models were used to test whether QIDS predicted flanker task performance.

Results: In the total sample or in the insulin sensitive subgroup, we found QIDS did not predict flanker task performance (n=108, r =-0.09, p =0.3348 and n=89, r=0.13, p=0.2421 respectively). In the subgroup of participants with insulin resistance however, we found QIDS strongly predicted cognitive control (n=29, r =-0.67, p<0.001).

Conclusions: These results suggest insulin resistance alters the relationship between depression and cognitive function. These findings may explain some of the heterogeneity seen in cognitive performance among depressed patients.

Supported By: R25MH101078

Keywords: Cognitive Neuroscience, Insulin-Resistance, Major Depressive Disorder (MDD), Diabetes, Flanker

T143. Dissecting a Specific Role for Dorsal Anterior Cingulate Cortex in Effort-Based Decision-Making With Computational fMRI

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Background: Effort-Based Decision-Making (EBDM) has emerged as an important translational paradigm for studying motivational deficits in psychiatric populations. While a number of preclinical and clinical studies have identified the dorsal anterior cingulate cortex (dACC) as critical for EBDM, its specific computations remain unclear. Prior work suggests that dACC may encode the need to alter an existing strategy (e.g., switching from one option to another) or the difficulty of choosing between two similarly valued options. Importantly, these processes are often highly collinear in many decision-making paradigms, making it difficult to determine which may be most responsible for dACC activity. Determining the specific role for dACC in the context of EBDM is a critical step towards a greater understanding of dACC abnormalities in clinical populations.

Methods: 20 healthy controls (Mage=25.20, SDage=4.10) completed a sequential effort-based decision-making task while undergoing fMRI. The task utilized alternating high and low reward value blocks aimed to dissociate strategy updating and choice difficulty. Participants were also asked to provide ratings of choice difficulty following a subset of decisions.

Results: We observed increased dACC activation (peak pFWE=0.004) for difficult choices compared to easier decisions. Importantly, when comparing easy choices that required a strategy shift to difficult choices that did not, dACC clearly showed significantly more engagement during the latter.

Conclusions: The current study demonstrates that when strategy updating and choice difficulty are dissociated, dACC engagement is most strongly explained by choice difficulty. These results may prove critical in furthering our understanding of disrupted decision-making so often observed in psychiatric disorders.

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Keywords: Effort-based Decision-making, Neuroimaging, Neuroeconomics, BOLD fMRI, Computational Psychiatry

T144. Targeted vmPFC Modulation With fMRI Neurofeedback Changes Functional Connectivity in Depression

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Background: Ventromedial prefrontal cortex (vmPFC) is part of the default mode network (DMN), serves an important role in processing emotion, and is implicated in many psychiatric disorders. We examined the effect of real-time fMRI neurofeedback (rtfMRI-nf) modulation of the vmPFC and assessed training effects on resting-state functional connectivity (rsFC).
Methods: Major depressive disorder (MDD) patients (N=6) completed one fMRI session in which they were trained to upregulate vmPFC activity during episodic future thinking, involving vividly imagining future positive events. Before and after rtfMRI-nf, rsFC was evaluated by GLM analysis with mean vmPFC signal as a regressor, and the beta maps were entered into group-level analysis. We used AFNI's 3dttest++ to examine changes in vmPFC connectivity and its association with changes in POMS total mood disturbance (TMD).
Results: The participants succeeded in vmPFC activity upregulation (effect size = 0.41, compared to 0 value), which was also associated with increased rsFC with the right thalamus, and decreased rsFC with the left parahippocampal gyrus. Moreover, vmPFC increased connectivity with left middle frontal gyrus, and decreased connectivity with left superior frontal gyrus, left thalamus, right insula and right cingulate gyrus significantly correlated with TMD reduction [$p < 0.005$ (uncorrected)].
Conclusions: The connectivity between vmPFC and limbic structures represented by thalamus and parahippocampal gyrus was changed after just one rtfMRI-nf session. Mood improvement was correlated with connectivity between vmPFC and both executive and salient networks. Because vmPFC is part of the DMN, rtfMRI-nf vmPFC modulation has a potential to change network interactions between DMN and other brain networks.
Supported By: This study was supported by the Laureate Institute for Brain Research and William K. Warren Foundation, and in part by the P20 GM121312 award from National Institute of General Medical Sciences, National Institutes of Health. The funders were not involved in the study design, data collection and analysis, and interpretation of results.
Keywords: Real-Time fMRI Neurofeedback, Ventromedial Prefrontal Cortex, Default Mode Network, Depression, Treatment Response

T145. Association Between Hand Digit Ratio and Bipolar Disorder

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Background: The 2nd- to 4th-finger ratio (2D:4D) has been proposed as a potential indicator of greater androgen exposure during fetal development. While smaller digit ratios, suggestive of stronger perinatal androgen action, have been associated with male-linked disorders (e.g., autism), problematic video gaming behavior, larger digit ratios, suggestive of weaker perinatal androgen action, have been associated with depression, schizophrenia, and eating disorders. We investigated association between the (2D:4D) and bipolar disorder.
Methods: 53 bipolar subjects were invited among Bipolar Clinic patients. 52 non-bipolar subjects were invited. Data was collected between February 2017- February 2018. A structured interview (M.I.N.I.) was performed on both bipolar group and control group to assess bipolar sign and symptoms, substance use, personality traits. Impulsivity was assessed with Barratt Impulsivity Scale. Both hands of subjects were scanned by photocopier and measured with following Digit Ratio Measurement Guide.
Results: Bipolar group has higher impulsivity scores in all impulsivity sub-types compared to control group. Right hand 2D:4D ratio is significantly higher in bipolar group. There is no difference on left 2D:4D ratio between bipolar group and control group.
Conclusions: Our findings indicate that right hand 2th- to 4th-finger ratio is significantly higher in bipolar group.
Keywords: Digit Ratio, Bipolar Disorder, Androgen Exposure

T146. Altered Resting-State Connectivity of the Amygdala in Acute HIV

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Background: Diagnosis of a serious illness, including HIV, can trigger an acute stress response. Neuroimaging research has shown altered resting-state functional connectivity (rsFC) following acute stress exposure, including rsFC of the amygdala. In the present study, we looked to see if a similar rsFC stress response would be found in individuals recently diagnosed with acute HIV (AHI).
Methods: Thai participants with AHI and age-matched controls received resting-state functional magnetic resonance imaging scans. We computed rsFC for bilateral amygdala seed regions of interest (ROIs) and performed a t-test to compare amygdala rsFC between the AHI and control groups. The rsFC values for significant clusters from the group analysis were then correlated with two self-report stress/anxiety measures and four HIV-related viral measures for the AHI group.
Results: Compared to the control group (n = 30), the AHI group (n = 74) displayed significantly increased connectivity between the amygdala and bilateral parahippocampal gyri, and significantly altered connectivity with areas of the cerebellum. Significant rsFC findings were family-wise error (FWE) corrected at the whole-brain level, pFWE<0.025. However, these findings were not significantly correlated with any stress or viral measures.

Conclusions: The present study suggests that, compared to controls, rsFC of the amygdala in individuals with AHI was similar to the neural response to acute stress. Within the AHI group the rsFC findings were unrelated to self-report measures of stress or virus relevant measures. Further research is warranted to determine whether early alterations in amygdala connectivity in AHI predict worse long-term outcomes, despite early antiretroviral treatment.
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Keywords: HIV, Resting State fMRI, Amygdala

T147. Resting State MRI Measures of Insular Connectivity and Duration of Chronic Pain

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Background: Veterans report chronic pain (CP) at two to three times the rates of civilians. Longer CP duration has been associated with negative health outcomes including depression, insomnia, and suicide. The insula, a critical node of the salience network, has been closely linked to the perception, and chronicity of pain. The current study utilized rs-fMRI imaging with insula as the seed region to examine insula connectivity associated with duration of pain.
Methods: Sixty-one veterans between the ages of 18 and 55 with chronic pain were assessed by interview for CP onset and duration. CP duration had a mean duration of 25.55 (16.41) for longest pain present. BOLD echo planar images were obtained during an 8-minute resting-state protocol using a 3T Siemens Verio scanner and analyzed using SPM8. Regression analyses were completed between rs-fMRI data and pain duration as reported on the pain history measures ($p < .05$, FDR corrected and $k > 20$ voxels).
Results: Resting state connectivity showed significant negative associations with pain between both the left and right insula ($p < .05$). Connectivity with occipital, temporal and supplementary motor regions showed the strongest associations with pain duration.
Conclusions: The results indicate that connectivity strength varies with duration of pain. Previous research has suggested that prolongation of pain in fibromyalgia patients was associated with temporal lobe involvement. The current findings suggest that connections between insula and temporal regions may be associated with prolongation of pain in additional pain conditions.
Supported By: Military Suicide Research Consortium (MSRC), an effort supported by the Office of the Assistant Secretary of Defense for Health Affairs (W81XWH-10-2-0178 PI: Yurgelun-Todd)
Keywords: Resting State fMRI, Chronic Pain, Insula

T148. Structural and Functional Brain Differences in Children With the FTO Obesity Risk Allele

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Background: Brain mechanisms underlying observed associations among the FTO gene, food intake, and obesity are not fully understood. Studies in adults suggest genotypical structural and functional brain differences. Studies in children are few and methodologically limited.
Methods: We examined associations between FTO genotype and brain structure and function in a sample of non-obese children (body fat %ile $\leq$ 95%). DNA extracted from saliva was used to genotype (C/T alleles) at rs1421085. Grey matter (GM) morphology, white matter (WM) fiber density, and resting-state functional connectivity (rsfMRI), were assessed using deformation-based morphometry, fixel-based morphometry, and seed-based analyses, respectively. Ninety-three children (age=9.12±1.17 years) were studied (genotypes: 15 CC, 31 CT, 47 TT). Age [p=0.69], sex [p=0.83], and body mass index (BMI) [p=0.63] did not vary across genotypes.
Results: C/X individuals showed greater GM volume bilaterally in the cerebellum, temporal gyrus and occipital cortex (whole-brain corrected $p < 0.05$; adjusted for sex, age, BMI), altered WM fiber density in the inferior cerebellar peduncle tract (FWE corrected $p < 0.05$, same co-variates), increased positive rsfMRI between the L-cerebellum, L-superior frontal gyrus, and R-thalamus and increased negative rsfMRI between the cerebellum and the temporal fusiform cortex (voxel threshold $p<0.001$ (uncorrected), cluster threshold $p<0.05$ (FDR); same co-variates).
Conclusions: Multimodal analyses suggest prominent differences in cerebellar structure/function related to FTO genotype. As the cerebellum has been implicated in reward-based learning and cerebellar activity has been related to BMI, future research is needed to explore the effects of the FTO genotypes on brain development, food intake, and obesity susceptibility.
Supported By: NIDDK grant R01-DK097399
Keywords: FTO, Obesity, Brain Imaging, Cerebellum

T149. Gabapentin Glycolimia: A Treatment for Cancer Cachexia?

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Background: Gabapentin induced Glycolimia has not heretofore been reported.
Methods: Case 1: This 56-year-old right-handed female presented with a three-year history of gradually increasing difficulty tasting sweet. After daily treatment of 100 milligrams of gabapentin, she noticed new onset of craving for sweet foods. Through her lifetime she disliked sweet foods, would never eat desserts; she now would eat after each meal and multiple times a day. This craving for sweets continued, until discontinuation of gabapentin, the craving for sweet food resolved.

Case 2: This 34-year-old male presented with recalcitrant anxiety, for which he was begun on gabapentin, 100 milligrams, three times a day. Within one week of initiating this, he observed a marked increase in his desire for sweet foods, including desserts, cakes and candies. Prior to use of gabapentin, he disliked sweet foods and would avoid them. This craving for sweets persisted for six months on gabapentin.
Results: Case 1: Abnormalities in Neurological examination: Decrease vibration and hyporeflexia in both lower extremities Gustatory testing: Taste Quadrant testing: severe weakness to sucrose and salt throughout.

Case 2: Abnormalities in Neurological examination: Normal.
Conclusions: Gabapentin may act directly on the ventromedial nucleus of the hypothalamus to enhance craving or on the uncus in the temporal lobe, pontine nucleus solitarius, or primary/secondary gustatory cortex for taste perception to induce enhanced hedonics towards sweet taste. A trial of gabapentin in conditions of anorexia, for instance associated with cancer, may be warranted to enhance sugar intake and associated weight gain.
Keywords: Gabapentin, Cancer, Cachexia, Glycolimia, Treatment

T150. Evaluating the Effects of Ketamine and Midazolam Using Enigma Resting State fMRI Pipeline

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Background: We used ENIGMA resting state fMRI (rsfMRI) workflow to map the effects of ketamine and midazolam on the activity of functional networks. We pursued to a) identify functional networks affected by the two drugs that have both similar and diverging pharmacological functions. b) rank the effect sizes of ketamine and midazolam for three methodological approaches (seed-based, dual regression and regional homogeneity (ReHo)) to map functional connectivity.
Methods: N=30 healthy volunteers undergone a double-blind, randomized cross-over experiment consisted of three randomized rsPhfMRI scanning sessions: each session included an infusion of saline followed by the infusion of: ketamine, midazolam or saline. Functional connectivity (FC) measures were quantified using three methods incorporated in the ENIGMA rsfMRI pipeline. Correlation analysis was used to study the relationship between these resting state FC (rsFC) measures.
Results: Effect sizes were highly consistent across three rsfMRI approaches: Ketamine showed significant reduction in salience (SN, Average across three methods Cohen's d: 1.13±0.28), auditory (AN: 0.67±0.26) and default mode networks (DMN: 0.42±0.26); Midazolam effect was only significant in the DMN (0.77±0.27). Kendall coefficient of concordance (KCC) values from ReHo maps showed the strongest effect for SN, executive control network (ECN), and AN for ketamine and the strongest effect for SN and DMN for the midazolam.
Conclusions: Ketamine and midazolam are dissociative agents and have significantly disrupted rsFC on the DMN. In addition, ketamine, disrupted connectivity in the SN and AN in healthy volunteers. The rsFC measures are consistent across three analysis approaches and are promising endophenotypes for future studies.
Supported By: NIH grants U54EB020403, U01MH108148, 2R01EB015611, R01MH112180, R01DA027680, R01MH085646, and T32MH067533.
Keywords: Resting State Functional Connectivity, Effect Size, Functional Networks

T151. Childhood Parental Loss, Maltreatment and Metabolic Risk in Healthy Young Adults

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Background: Childhood adversity and trauma are risk factors for psychiatric and medical conditions. Early life stress (ELS) may confer risk through progressive dysregulation of physiologic processes leading to systemic dysfunction and disease. Current research is limited by small sample sizes, limited data regarding early experiences and is often confounded by other illnesses or medications. This study examined ELS, psychiatric/physical symptoms, and health measures in young adults with and without parental loss and childhood maltreatment.
Methods: Adults ages 18-40 (N=124) recruited via community advertisements, phone interview assessed eligibility. Cases (N= 60) experienced parental loss before age 11 and childhood abuse/neglect. Controls (N=64) had no ELS or psychiatric history. Standardized interviews and self-reports assessed demographics, medical/psychiatric history, childhood adversity, health behaviors. Participants had no acute/chronic medical conditions, current medications, bipolar/psychotic disorder/OCD. Fasting blood samples collected for hemoglobin A1C (HgbA1C), cholesterol, triglycerides.
Results: Controlling for age/sex, parental loss and maltreatment were significant positive predictors of HgbA1C and white blood cell count (p's<.05), and negative predictors of high-density lipoprotein (HDL; p's<.05). Recent stressors/perceived stress were not associated with metabolic measures. Individuals with current/lifetime trauma-related disorders had lower HDL (p<.05) and current trauma-related disorder had

higher HgbA1c ($p<.05$). Controlling for lifetime trauma-related disorders, some associations of adversity with metabolic processes remained.
Conclusions: These findings demonstrate the importance of ELS as a risk factor for future disease. Participants were physically healthy, without medical comorbidities/medications. Associations of ELS with metabolic changes suggest a risk process that may underlie poor downstream health outcomes. Further investigation will assess resilience and social support.
Supported By: R25 MH101076 (T.D.); 5R01MH101107-04 (A.R.T.)
Keywords: Early Life Stress, Metabolic Dysregulation, Inflammation, Early Risk Detection

T152. Optimized Volume Censoring in Simultaneous Multi-Slice (Multiband) Resting-State fMRI

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Background: Simultaneous multi-slice (multiband) fMRI is a novel acceleration technique that allows for dramatically improved spatiotemporal resolution. However, BOLD signal artifacts due to motion remain a critical confound in studies of functional connectivity that must be addressed to produce reliable and reproducible findings in psychiatric neuroimaging. While volume censoring of high-motion volumes (scrubbing) is an effective technique, empirically-validated bases for determining optimal censoring thresholds are unclear, particularly in multiband fMRI.
Methods: Using data from the Human Connectome Project (HCP500), standard volume censoring approaches were compared to a novel approach that employs low-pass filtering (LPF) of motion parameters prior to estimation of framewise motion to eliminate the impact of respiration-related motion. To determine optimal values of maximum tolerable framewise displacement (FD), we developed average mean squared error (MSE) across ROI pairs as a metric of sample data quality and minimization target for optimization. Change in MSE, decomposed into bias and variance, was calculated for each ROI pair across subjects. Bias was estimated as the absolute change in mean ROI pair correlation averaged across ROI pairs due to volume censoring, minus the change due to randomly removing an equivalent number of randomly selected frames.
Results: Both LPF and standard censoring thresholds were varied across possible values. Optimal thresholds for LPF-based volume censoring produced substantially greater reduction in MSE and greater changes in RSFC correlations across ROI pairs than standard volume censoring.
Conclusions: LPF-based volume censoring and optimization of censoring thresholds offer novel methods for reducing the effect of motion artifacts in multiband fMRI.
Supported By: NIH/NIMH Grant T32 GM 008444 (Stony Brook University Medical Scientist Training Program), NIH/NIMH Grant K01 MH 107763 (Dr. Van Snellenberg)
Keywords: Simultaneous Mutli-slice (Multiband) fMRI, Resting State fMRI, Functional Connectivity, Functional Magnetic Resonance Imaging, Biostatistics

T153. Resting-State Connectivity in U.S. Service Members With Mild Traumatic Brain Injury Versus Posttraumatic Stress Disorder

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Background: Mild traumatic brain injury (mTBI) is highly prevalent in military and civilian populations and is often associated with somatic, cognitive, and emotional symptoms. Posttraumatic stress disorder (PTSD) symptoms have been shown to predict worse global outcomes in mTBI. While functional neuroimaging studies have characterized abnormalities in resting-state functional connectivity (rsFC) in mTBI, few studies have examined rsFC in U.S. service members with mTBI versus PTSD.
Methods: U.S. service members ($n = 137$; ages 19-59) underwent resting-state fMRI scans. After exclusion for motion ($n = 7$), remaining participants were divided into three study groups: mTBI ($n = 48$), PTSD only ($n = 24$), and orthopedic-injured controls, OI ($n = 58$). Analyses investigated differences group differences in rsFC for cortical networks: default mode (DMN), frontoparietal (FPN), salience, somatosensory, motor, auditory, and visual. Analyses were family-wise error (FWE) cluster-corrected at the whole brain level ($pFWE < 0.002$).
Results: Both mTBI and PTSD groups had reduced rsFC of DMN and FPN regions compared with OI controls. These group differences were largely driven by diminished rsFC in the PTSD group. rsFC between dorsolateral prefrontal cortex of FPN and middle frontal gyrus was increased in the mTBI group versus PTSD and OI groups.
Conclusions: Our findings of reduced rsFC of DMN and increased rsFC within prefrontal regions in mTBI are consistent with previous studies. Results of diminished rsFC in PTSD suggest that severe PTSD symptoms may worsen neural dysfunction in mTBI. Future studies will be necessary to further investigate interactions between mTBI and PTSD for rsFC and neuropsychological functioning.
Supported By: Defense and Veterans Brain Injury Centers (USAMRMC; W81XWH-13-2-0025; CENC; PT108802-SC104835)
Keywords: Resting-State Functional Connectivity, Mild Traumatic Brain Injury, PTSD - Posttraumatic Stress Disorder, Default Mode Network, Frontoparietal Network

T154. Functional Connectivity of the Anterior Cingulate Cortex in Veterans With Mild Traumatic Brain Injury

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Background: Traumatic brain injury (TBI) is one of the most prevalent injuries in the military with mild traumatic brain injury

(mTBI) accounting for approximately 70-80% of all TBI. TBI has been associated with diffuse and focal brain changes to structures and networks underlying cognitive-emotional integration. Although the anterior cingulate cortex (ACC) plays a critical role in emotion regulation and executive function and is susceptible to mTBI, studies focusing on ACC resting state functional connectivity (rsfc) in veterans are rare.
Methods: Veterans with mTBI (n=53) and with no history of TBI (n=25), ages 20 to 54 completed clinical assessments and an 8-minute resting state functional magnetic resonance imaging (rs-fMRI) on a 3T Siemens scanner. Imaging results were analyzed with left and right ACC as seed regions using SPM8. Regression analyses were performed with time since injury ($p<0.05$ FDR corrected and $k>20$ voxels)
Results: Seed-based analysis showed increased connectivity of the left and right ACC with thalamus, caudate, preceneus, and occipital regions in the mTBI compared to the non-TBI group. In the mTBI group, regression analyses showed a negative relationship between the right ACC-occipital lobe connectivity with both time since most recent injury and time since most severe injury.
Conclusions: The rs-fMRI results are in agreement with previous studies showing ACC hyperconnectivity in recently concussed athletes. Enhanced top-down control of attention necessary to compensate for the microstructural damage following TBI may explain ACC hyperconnectivity post-TBI. Results from regression analyses suggest that ACC hyperconnectivity may reduce as time since injury increases.
Supported By: W81XWH-10-2-0178
Keywords: Mild Traumatic Brain Injury, Anterior Cingulate Cortex (ACC), Resting State Functional Connectivity, Veterans

T155. Variational Autoencoder Identifies Clinically Meaningful Latent Features in Neurodegeneration and Neuropsychiatry Based on Blood Gene Expression and Genetically Regulated Gene Expression Across Tissue-Types

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Background: Deep learning can inform the understanding of complex neuropsychiatric traits that are clinically heterogeneous and the prediction of their progression or treatment response. Variational Autoencoder (VAE) is a deep generative model that allows for automatic engineering of non-linear features while learning a reduced dimensional manifold.
Methods: We applied a VAE to the observed blood and imputed transcriptome based on genotype (across 48 tissues) of neuropsychiatric traits (multiple sclerosis/MS, posttraumatic stress disorder/PTSD and traumatic brain injury/TBI). The most variable genes were selected and encoded to 100 features and then recoded back to the original number of variable genes. We investigated state transitions from the latent dimensions of the model to determine the extent to which the approach learned a manifold representation that could be interpreted from a biological perspective.
Results: In the study of MS-relapse, including 362 patients that were untreated or treated with one first-line treatment, VAE latent features were able to capture i) patient gender, ii) previously discovered subtypes of MS and iii) time to relapse. All of this was achieved in an unsupervised manner, meaning that the phenotypic information was not used in the modelling process. Further, the trained models' weights were investigated to determine the contribution of the genes to each learned node in the encoded layer. Genes driving gender were located on sex chromosomes, and those driving MS subtypes in immune signalling pathways. The equivalent analyses of the PTSD and TBI datases are ongoing.
Conclusions: VAE show promise in identifying lower representations of high dimensional biological data that are interpretable.
Supported By: Cohen Veteran Biosciences Inc.
Keywords: Deep Learning Technology, Genetics, Transcriptomics, Transcriptomic Imputation, Machine Learning

T156. A Manualized Eight-Week Virtual Cognitive Behavioral Therapy (CBT) Group Delivered via Secure Video Conference for Chronic Low Back Pain (CLBP)

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Background: Chronic low back pain has deleterious effects on mood, sleep, functioning, and quality of life. Long-term opioid analgesic use compounds these effects, introducing further psychiatric, cognitive, and social consequences. CBT has shown efficacy for CLBP symptoms, but many patients cannot readily access treatment.
Methods: For this ongoing, prospective, open-label pilot study, we adapted a validated pain CBT paradigm (Jamison 1996). Participants received a manualized 8-session CBT program via secure WebEx with an MD or PhD facilitator. Participants were 18-75 years old with diagnosed CLBP of mean daily intensity $\geq$4/10 at least half the time. Participants rated baseline (M0), month 2 (M2), and month 4 (M4) prescription opioid misuse (POM) risk (Current Opioid Misuse Measure [COMM]), pain catastrophizing (PCS), pain interference (Brief Pain Inventory [BPI]), CLBP-related disability (Oswestry Disability Inventory [ODI]), and sleep quality (Insomnia Severity Index [ISI]), as well as study-specific satisfaction.
Results: As of November 2018, the study has enrolled 34 participants (68% female) with mean ($\pm$ standard deviation) age 55.2$\pm$14.3 years. Mean scores decreased for COMM (M0: 11.1$\pm$9.7; M2: 7.7$\pm$5.6: M4: 3.6$\pm$2.3), PCS (M0: 21.0$\pm$13.3; M2: 18.3$\pm$11.7; M4: 14.8$\pm$9.3), BPI severity (M0: 5.8$\pm$1.8; M2: 5.5$\pm$1.7; M4: 5.1$\pm$1.6), BPI interference (M0: 6.1$\pm$2.2; M2: 5.3$\pm$2.4; M4: 4.8$\pm$2.3), ODI (M0: 45.3$\pm$15.9; M2: 45.3$\pm$13.1; M4: 43.8$\pm$14.8), and ISI (M0: 14.6$\pm$6.7; M2: 13.1$\pm$6.7; M4: 11.0$\pm$7.6). Most participants were highly satisfied with the course (71.6$\pm$17.6%).
Conclusions: Our preliminary results suggest that virtual group CBT could be a low-cost way to extend care to CLBP

patients with limited mobility or located in remote or under-resourced areas.
Supported By: Harvard Medical School Zinberg Fellowship in Addiction Psychiatry
Keywords: Chronic Low Back Pain, Cognitive Behavioral Therapy, Opioid Use Disorder, Telepsychiatry

T157. Neurocomputational Plasticity of the Self-Other Distinction

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Background: Healthy social development is underpinned by an ability to distinguish self from other. In order to investigate this, we recently applied computational neuroimaging to healthy adults engaged in a novel Theory-of-Mind task. We found prediction-error signals in distinct, agent-specific neural patterns. Variability in the agent-specificity of these signals predicted a wide range of subclinical psychopathological traits (Ereira et al. PLOS Biology, 2018). In the present study we explore the source of this variability by testing whether neural self-other distinctions are susceptible to experience-dependent plasticity.
Methods: 47 healthy adults were trained on a probabilistic false-belief task, with two different agents, in a within-subjects design. Subjects were required to attribute belief-updates to self and other at the same time when playing with agent-1, but not at the same time when playing with agent-2. We then tested subjects on this task, with no difference between agent-1 and agent-2, whilst they underwent fMRI. We also tested participants on a visual perspective-taking task with the same two agents.
Results: In the test session, subjects could better distinguish their own beliefs from another agent's beliefs when playing with agent-2 versus agent-1 [$t(40)=-2.13$, $p=0.01$]. This training transferred to the visual perspective-taking task [$F(1, 40)=8.24$, $p=0.006$]. Pattern-based fMRI measures showed a neural self-other distinction that was modulated by agent-identity.
Conclusions: Healthy adults can distinguish their own cognition and from another person's with agent-specific neural learning signals. The degree of agent-specificity of these signals can itself be learned through cognitive training in a general manner that transfers to different cognitive domains.
Supported By: Wellcome Trust; Max Planck Society
Keywords: Social Cognition, Computational Psychiatry, Computational Modeling, Statistical Learning, fMRI

T158. Borderline Personality in Bipolar Disorder: Prevalence and Early Trauma Relationship

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Background: Many factors, including childhood abuse and trauma, have been implicated in the development of Borderline Personality Disorder (BPD) [1, 2]. The present study used the Early Trauma Inventory Self-Report Short Form (ETI-SR-SF) and The Borderline Personality Questionnaire (BPQ) to examine the prevalence of early trauma and BPD, respectively, as well as their potential relationship in patients with Bipolar Disorder.
Methods: 494 patients admitted to a psychiatric facility with a primary diagnosis of Bipolar disorder (BP) per DSM-IV-TR criteria between 8/11 and 6/18 completed the BPQ and the ETIRS-SF. Univariate, bivariate (Chi-square and t-tests) and regression analyses were conducted to examine the relationship between early trauma events and BPD. Demographic co-variates were also investigated including race, gender, age, number of admissions and 30-day readmission rates.
Results: 17.6% (87/494) of Bipolar inpatients also met criteria for BPD (BPQ score $\geq$ 56). Linear regression revealed a statistically significant relationship between the number of early trauma events in the general trauma ETI-SR-SF subscale and the total BPQ score ($\beta=1.62$, $p<0.05$) as well as the BPQ suicide and self-mutilation subscales ($\beta=0.130$, $p < 0.05$).
Conclusions: While less than 20% of Bipolar inpatients met full criteria for BPD, a greater number of childhood traumatic events was associated with more BPD traits particularly those related to increased suicidality and self-injurious behavior. Though preliminary, these results suggest that early trauma not only increases the risk for BPD traits in Bipolar patients but may also predict those at risk for self-injurious behavior.
Keywords: Borderline Personality Disorder, Bipolar Disorder, Early Trauma, Bipolar Spectrum Disorders

T159. The Impact of Maternal and Paternal Incarceration on Impulsive and Psychopathic Traits in Female Offenders

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Background: With the increase in rates of incarceration there is a growing concern about the short-and long-term influence this may have on children of incarcerated parents. Prior research has shown that children of incarcerated parents are more likely to suffer from substance use, delinquency, home instability, and externalizing and internalizing behaviors. However, few studies have explored the long-term psychological effects of parental incarceration. The present study assessed the impact of childhood exposure to parental incarceration on psychopathic and impulsive traits in second generation female offenders.
Methods: We recruited an ethnically diverse sample of 175 female offenders from a women's correctional facility that houses maximum, medium, and minimum custody level offenders. We assessed the association between the 3-facet

model of psychopathy using the Levenson Self-Report of Psychopathy and the 3-facet model of the Barratt Impulsiveness Scale, and maternal and paternal incarceration during childhood. Data were analyzed using multinomial logistic regression.
Results: Female offenders with higher levels of interpersonal psychopathic traits were more likely to have experienced paternal incarceration as a child, whereas female offenders who had higher levels of antisocial psychopathic traits were more likely to have experienced maternal incarceration as a child. Affective psychopathic traits were unrelated to parental incarceration. Impulsivity was related to parental incarceration, but this was limited to attentional impulsivity, which increased the likelihood of having an incarcerated father.
Conclusions: The results provide preliminary evidence that exposure to both maternal and paternal incarceration during childhood has long-term effects on women's impulsive and psychopathic traits.
Keywords: Impulsivity, Psychopathy, Women, Offenders

T160. A Single Minimal Dose of an Antipsychotic Reduces the Drive to Play Extraordinary Social Roles Associated With Behavioural Disorganization

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Background: Personal drives to engage in extraordinary social roles (ESRs) were previously found to be an independent factor of the behavioural disorganization assessed by the Schizotypal Personality Questionnaire (SPQ). In this study, we replicated those findings and explored the effect of an antipsychotic on the drive to play social roles.
Methods: A total group of 92 healthy participants was split into those who received 2.5 mg of olanzapine and those who received a fully deceptive placebo. They were tested before (session 1) and during (session 2) the sizeable effect of the medication. Both times, participants were presented with 200 SRs names, which were either ordinary or not, and favourable or not. For each role, participants had to decide whether they would consider performing it at any moment of their life. For the statistical analysis, participants were divided into high and low subgroups according to median splits of the percentages of accepted ESRs.
Results: These percentages predicted again the SPQ disorganization scores, both for favourable ESRs ($p = .008$) and unfavourable ESRs ($p = .0004$). Olanzapine high ESR acceptors became faster at rejecting extraordinary ($p = .00006$, $p = .002$, for each favourability category) and at accepting ordinary ($p = .001$, for both favourability categories) roles at session 2.
Conclusions: Olanzapine reduces the drive to play ESRs and might thus have an effect on factors of behavioural disorganization. The antipsychotic appears to influence neurocognitive mechanisms at a single and a minimal dose.
Supported By: Social Neuroscience, University of Paris VIII
Keywords: Schizotypy, Antipsychotics, Disorganization, Social Roles, D2 Receptor

T161. Effects of Ketamine Administration on the P300 Event-Related Potential: Implications for Schizophrenia

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Background: N-methyl-D-aspartate receptor (NMDAR) hypofunction has been implicated in the pathophysiology of schizophrenia and its associated cognitive impairments, including auditory processing deficits reflected by the P300 event-related potential (ERP) component. P300 amplitude reduction is one of the most widely replicated brain abnormalities observed in patients with schizophrenia. To test the hypothesized contribution of NMDAR hypofunction to P300 abnormalities, we examined the effects of the NMDAR antagonist ketamine on auditory P300 amplitudes in healthy individuals and compared these effects with those of schizophrenia.
Methods: We examined two variants of P300, including the P3b elicited by target stimuli and the P3a elicited by novel distractor stimuli, during a three-stimulus auditory oddball paradigm. 30 healthy volunteers received ketamine or placebo on two test days in a double-blind, counterbalanced manner, and P300 amplitudes were assessed each day. P300 amplitudes from 37 schizophrenia patients were also measured.
Results: There were no differences between the effects of ketamine and placebo on task performance (ps $> .05$). Ketamine decreased the amplitude of P300, regardless of whether P300 was elicited by a target or novel stimulus (ps $< .0001$, Cohen's $d = .96$ and $d = .97$, respectively). Moreover, ketamine produced similar decrements in P300 to those observed in schizophrenia patients.
Conclusions: Results provide evidence that glutamatergic neurotransmission at NMDARs contributes to P300 generation in response to both target (P3b) and novel (P3a) stimuli. Furthermore, results suggest that ketamine and schizophrenia produce similar P300 effects, consistent with the NMDAR hypofunction model of schizophrenia and its possible role in mediating P300 abnormalities.
Supported By: AstraZeneca; R01 MH58262; UL1 RR024139, P50 AA012879
Keywords: Schizophrenia, P300, NMDAR Hypofunction, Ketamine

T162. Association of Semantic Priming Deficits With Role Functioning in Persons at Clinical High Risk for Schizophrenia: Evidence From Event-Related Brain Potentials

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Background: Persons exhibiting clinical high-risk (CHR) symptoms similar to but less severe than those of schizophrenia have an elevated risk of developing this disorder. We previously found that CHR patients have reductions in the N400 event-related brain potential (ERP) semantic priming effect, indicating deficits in using meaningful stimuli to activate related concepts in semantic memory. We sought evidence that this abnormality is associated with real-world functional impairment in CHR patients, hypothesizing that N400 semantic priming deficits would correlate with lower social and role functioning in this group.
Methods: We recorded continuous EEGs in 36 help-seeking CHR patients and 25 healthy control participants while they viewed 80 strongly related and 80 unrelated prime-target word pairs, and 160 word-nonword pairs, in a fixed randomized order, with stimulus-onset asynchrony (SOA) of 300 ms or 750 ms. Functional status was measured with the Global Functioning: Social and Role Scales.
Results: There was a significant reduction in the N400 priming effect at the 750-ms SOA in CHR patients compared to controls ($p=0.049$). In the patients, smaller N400 priming effects at the 300-ms (but not the 750-ms) SOA correlated with lower role functioning (Spearman's $p = -0.37$, $p=0.03$).
Conclusions: The results suggest that although CHR patients in general are deficient in maintaining activation of related concepts over longer intervals after meaningful stimuli, a subset of patients with deficits in activating related concepts even at shorter intervals may be the most functionally impaired.
Supported By: Ontario Ministry of Health Foundation
Keywords: Schizophrenia, Event Related Potentials, N400, Role Functioning, Clinically High Risk

T163. Effects of Nicotine on Cognitive Remediation Training in Schizophrenia

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Background: Cognitive remediation training can alleviate cognitive deficits associated with schizophrenia, but its impact is limited by small effect sizes. We aimed at enhancing the beneficial effects of the training challenges by administering nicotine prior to some of the training sessions. Nicotine-induced facilitation of sensory processing, alertness/attention, and learning/memory was expected to promote training benefits.
Methods: Twenty-five people with schizophrenia completed a 10-week, 5 days/week, computerized auditory and visual cognitive training regimen. Every Monday and Thursday, participants randomized to the nicotine group received a nicotine polacrilex lozenge (2 or 4 mg, depending on smoking status) prior to the training, and participants in the placebo group a placebo lozenge. Outcome measures were taken on a no-lozenge day at baseline and every 3-4 weeks thereafter.
Results: The MATRICS Consensus Cognitive Battery (MCCB) composite score improved over time, but there were no group differences in this effect. When exploring the seven MCCB sub-domains, only the Reasoning/Problem Solving domain displayed a Group x Time interaction ($P=0.003$); the placebo group improved over time, but not the nicotine group, suggesting that intermittent nicotine exposure negatively impacted training benefits on higher-order cognitive processes. Psychiatric symptoms did not change from before to after the training intervention in either group. However, significant improvements from pre- to post-intervention were seen on the Quality of Life Scale ($P<0.05$) and the Cognitive Assessment Interview ($P<0.001$), both measuring real-life functional outcome. These effects did not differ between treatment groups.
Conclusions: In conclusion, there was no evidence that nicotine exposure during cognitive remediation training may potentiate training benefits.
Supported By: R21 MH095824 (B. Hahn)
Keywords: Schizophrenia, Cognitive Deficits, Cognitive Remediation Training, Nicotine, Clinical Trial

T164. Auditory Hallucinations in Patients With Severe Mental Illness With and Without Hearing Impairment

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Background: In view of increased prevalence of auditory hallucinations in hearing impaired patients, we investigated whether it is arising out of the pathology in brain secondary to auditory deficits and whether it shares the same phenomenology as patients without any hearing impairment.
Methods: We evaluated the phenomenology of auditory hallucinations in the patients having Severe Mental Illness with ($n=20$) and without Hearing Impairment ($n=20$). The experience was evaluated across 62 domains and compared across both groups using MUPS (The Mental Health Research Institute Unusual Perceptions Schedule) and PSYRATS (Psychotic Symptom Rating Scale).
Results: Irrespective of the hearing status, patients heard voices mainly in the language that they had learnt first (80%). However, a few experienced hallucinations in languages they did not know (7.5%). Most reported hearing voices of males or both- male and female together (85%). The Hearing impaired population experienced auditory verbal hallucination in the hearing impaired side (5/20), coming from inside the mind over the course of their illness ($p=.025$), more close to their ears ($p=.025$), voices of crowds talking to them ($p=.011$), and 'as if' stuck or repetitive (9 patients reported repetition as 5/5) and more frequent nonverbal hallucinations ($p=.011$), and had no emotional salience with the voices($p=.044$).Use of hearing aids attenuated the intensity of the hallucinations(5 out of 7 patients who used hearing aids improved).
Conclusions: The phenomenology of auditory hallucination differs among the two groups. In hearing impaired patients how the brain locates events and sensations in space and time may be a fundamental defect, underlying the experience of hallucinations.

Keywords: Severe Mental Illness, Auditory Verbal Hallucination, Phenomenology, Hearing Impaired

T165. Metabolic, Inflammatory, and Sleep Changes in Patients Receiving Antipsychotics: A Cross-Sectional Comparative Study

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Background: Cardiovascular disorders and metabolic syndrome are common in patients with irregular sleep patterns or maintained on Antipsychotics (AP). On the other hand, Inflammation and oxidative stress might lead to many psychiatric disorders, sleep changes, metabolic abnormalities, and cardiovascular diseases. This study aimed to assess the relationships between the sleep patterns, metabolic profile, and inflammation of patients maintained on antipsychotics.
Methods: We recruited three groups for this cross-sectional study: 1) patients with a chronic mental disorder (CMD) kept on AP for at least six months (CMD+AP, n=112), 2) another group of patients not taking antipsychotics (CMD/no AP, n=101) and healthy controls (HC, n=126). We collected clinical data, anthropometric measures, self-reported sleep patterns, and fasting blood samples. Multiplex MAP platforms were used to measure multiple cytokines.
Results: Participants on AP showed more obesity and a higher prevalence of metabolic syndrome. Subjects sleeping more than eight hours were mostly patients on atypical AP and showed increased obesity measures. Analysis revealed significant changes for Brain-Derived Neurotrophic Factor (BDNF), Intercellular Adhesion Molecule1 (ICAM-1), Interleukin-8 (IL-8), Monocyte Chemotactic Protein 1 (MCP-1), and Vascular Endothelial Growth Factor (VEGF) with variable patterns. For example, BDNF decreased in patients off AP but increased in those on AP; ICAM-1 and IL-8 increased in both patients' groups when compared to HC.
Conclusions: Patients on AP should be monitored for sleep patterns in addition to metabolic changes. Inflammatory markers could be potential targets to prevent or treat the side effects of AP and psychiatric disorders.
Supported By: Qatar National Research Fund (QNRF); National Priority Research Program #: NPRP 4-267-3-085
Keywords: Metabolic Syndrome, Antipsychotics, Sleep Disturbances, Inflammatory Cytokines, Mental Disorders

T166. Effect of Genome-Wide Methylation Changes on Emergent Suicidal Ideation

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Background: Patients with schizophrenia have a significantly increased risk of suicide. The prevailing stress-diathesis theory postulates that suicidal behavior is the product of genetic predisposition and exposure to stressful life events. DNA methylation, an epigenetic mechanism, was found to play a mediating role between stress and suicidal behavior. This longitudinal study attempts to identify specific methylation changes across the genomes that precede the development of suicidal thoughts.
Methods: Clinical assessments were conducted on 136 patients with schizophrenia, during baseline and three-month follow-up visits. Seventeen subjects experienced increased suicidal thoughts (emergent suicidal ideation) at the follow-up visit, as assessed with the Columbia-Suicide Severity Rating Scale. For four subjects with emergent suicidal ideation and five subjects without suicidal ideation, blood was collected at both visits, and genome-wide methylation analysis of extracted DNA was performed using bisulfite pyrosequencing and the MethylationEPIC chip.
Results: We found six CpG sites that were suggestive of genome-wide methylation changes associated with emergent suicidal ideation in response to stress. Increased methylation at the follow-up visit in CpG cg13833988 on chromosome 9 was associated with emergent suicidal ideation at the three-month visit ($p = 0.0000004$).
Conclusions: This is one of the first studies investigating epigenetic changes across the genome that are associated with emergent suicidal thoughts. We identified, previously unpublished, promising differentially methylated sites that could predict emergent suicidal ideation in schizophrenia. This line of research can further serve to establish molecular biomarkers to monitor for suicidal thoughts in patients with schizophrenia.
Keywords: Schizophrenia, Suicidal Ideation, Epigenetics, DNA Methylation

T167. Age-Related Reductions of GluA2 RNA Editing in Schizophrenia

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Background: Accumulating data indicate that abnormal glutamatergic signaling plays an important role in the pathophysiology of schizophrenia. RNA editing is a key developmental process in the brain that regulates the trafficking of AMPA glutamate receptors to the synapse, a process that is impaired in aging. In this study, we have tested the hypothesis that GluA2-AMPA receptor RNA editing is abnormal in schizophrenia.
Methods: We extracted RNA from the gray matter of the dorsolateral prefrontal cortex (DLPFC) of postmortem subjects with schizophrenia (total n=12, 7 males, 5 females) and controls, (total n=27, 15 males, 12 females). We quantified RNA editing of GluA2 at the R/G site using an RFLP assay that we validated using next generation sequencing. We measured the expression of the RNA editing enzymes, adenosine deaminase acting of RNA (ADAR), subtypes 1-3, using commercial QPCR assays. Statistical analyses were performed using SPSS v. 24, MS Excel and GraphPad Prism v. 7.04.
Results: We observe negative correlation between GluA2 R/G RNA editing and age in both the controls (n=38, R=-0.410, p=0.01) and schizophrenia subjects (n=14, R=-0.680,

p=0.007). However, the schizophrenia group showed a steeper decline in GluA2 RNA editing with increasing age, compared with the control group.
Conclusions: We detected a steeper decline in GluA2 R/G RNA editing in the DLPFC during aging in schizophrenia compared with controls. RNA editing is strongly associated with increased GluA2-AMPA receptor trafficking to the synapse. Therefore, these data indicate that reduced GluA2 RNA editing may be a marker of age-related neuropathology in the DLPFC in schizophrenia.
Keywords: Dorsolateral Prefrontal Cortex, AMPA Receptor, Glutamate, Human Postmortem Brain, Gene Expression

T168. Phenome-Wide and Genome-Wide Analyses of Quality of Life in Patients With Psychosis

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Background: Schizophrenia is a severe psychiatric disorder negatively impacting quality of life (QoL). A handful of factors from small studies have been reported to influence QoL of schizophrenia patients but a study comprehensively dissecting the genetic and non-genetic determinants of QoL in these patients is currently lacking.
Methods: Our study population consisted of patients suffering from psychosis (n=1,119), their siblings (n=1,059) and healthy controls (n=586). We performed genome-wide association analyses of QoL and constructed polygenic risk scores (PRSs) for schizophrenia, major depressive disorder (MDD), and subjective wellbeing (SW). We then tested the association of these PRSs and of over 100 independent clinical phenotypes with QoL.
Results: In total, nine clinical phenotypes were significantly and independently associated with QoL. The most significantly associated phenotypes included negative (Beta=-1.17; SE=0.05, P=1×10-83; r2=53%), depressive (Beta=-1.07; SE=0.05; P=2×10-79; r2=51%) and emotional distress symptoms (Beta=-0.09; SE=0.01; P=4×10-59, r2=38%). No genome-wide significant locus was identified for QoL. Schizophrenia and emotional wellbeing (but not MDD) PRSs using various P-value thresholds were significantly associated with QoL (lowest association p-value = 6.8×10-6). Several sensitivity analyses confirmed our results.
Conclusions: Various clinical phenotypes of schizophrenia as well as schizophrenia and emotional wellbeing polygenic risk scores are associated with QoL in schizophrenia patients and their relatives. These factors could be used by clinicians to more easily identify vulnerable schizophrenia patients and optimize their management.
Supported By: The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (Zon-Mw, grant number 10-000-1001), and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen Cilag) and universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psycho-medical center The Hague. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en De Kempen, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan, Virenze riagg, Zuyderland GGZ, MET ggz, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Utrecht: University Medical Center Utrecht and the mental health institutions Altrecht, GGZ Centraal and Delta).
Keywords: Genetics, Schizophrenia, Quality of Life

T169. Distinct Patterns of Schizophrenia, ADHD, and Cognition Polygenic Scores in Schizophrenia Subgroups Defined by Cognitive Development Trajectories

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Background: Different patterns of premorbid vs. current IQ in schizophrenia suggest distinct trajectories of cognitive development through childhood and adolescence, including early life cognitive impairment in some. Different cognitive patterns may reflect different patterns of underlying genetics associated with schizophrenia, cognition, ADHD, and related phenotypes. We tested whether IQ-defined cognitive trajectory subgroups also showed distinct polygenic score (PGS) profiles across schizophrenia, ADHD and cognition PGS.
Methods: Schizophrenia cases and controls provided blood and completed an assessment protocol. Cognitive trajectory subgroups were derived from premorbid (WRAT) and current (WAIS) IQ. In 470 SZ cases and 844 controls (all Caucasian) – separately for schizophrenia, ADHD and cognition – PGS were calculated at ten different p-value thresholds, then concentrated by deriving the first principal component (PC1) for each PGS set. We analyzed the resulting PC1 scores across groups using GLM, controlling for age, sex, and population stratification.
Results: Three premorbid vs. current IQ subgroups, Cognitively Stable, Pre-Adolescent Impairment, and Adolescent Decline, differed on demographic, cognitive, and clinical variables. The schizophrenia subgroups had elevated schizophrenia PGS relative to controls (p's<1x10E-10), with the Adolescent Decline subgroup most elevated. The Pre-Adolescent Impairment and Adolescent Decline subgroups had lower cognitive PGS than the Cognitively Stable and control groups (p's<.002). The Pre-Adolescent Impairment

subgroup, alone, showed an elevated ADHD PC1 relative to the other groups (p's<.003). The PC1s accounted for between 2% and 3% of variance in the SZ subgrouping scheme.
Conclusions: Analyses revealed an interesting convergence between subgrouping based on IQ measures and stratification based on schizophrenia, ADHD and cognitive genetics.
Supported By: NIMH Division of Intramural Research
Keywords: Schizophrenia, IQ, Polygenic Scores, ADHD, Cognition

T170. Effective Multiple Test Correction (MTC) for GWAS With Large Numbers of Correlated Genotypes and Phenotypes

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Background: An important issue affecting genome-wide association studies (GWAS) with millions of single nucleotides polymorphism (SNPs) markers and multiple correlated phenotypes is to find a suitable significance threshold. Straightforward family-wise correction (Bonferroni) of p <0.05 for 4.3 million genotypes and 462 phenotypes would give a threshold of p < 2.51E-11. This and related corrections may prove too conservative because they assume that the hypotheses tested are independent. The effective number of tests, both phenotypic and genotypic, needs to be adjusted for the correlation between them. For validation of MTC, permutation is considered the gold standard.
Methods: Spectral decompositions of a 462 phenotypes correlation matrix (largely structural MRI measures) was used to estimate the effective number of phenotypic tests (Nyholt, 2004, Li and Ji, 2005). Genotypes were corrected for linkage disequilibrium by standard methods. Permutations were performed by shuffling individual IDs (to preserve correlation of phenotypes). There were 4.3 million imputed genotypes, 1,116 unrelated individuals, and 20 shuffles of permutation. GWAS was performed in PLINK.
Results: The 462 correlated phenotypes had 34 independent tests, using the Li and Ji method. The threshold for a single GWAS was 5.5E-8 (method: Li et al, 2011). For 34 GWASs, the significance threshold became 1.62E-09. The permutation threshold for significance was 2.82E-10.
Conclusions: Standard MTC methods are unduly conservative for clinical multi-phenotype GWAS studies.
Supported By: NIMH
Keywords: GWAS-wide Significance Threshold, Multiple Testing Correction, Data Reduction Techniques, Effective Number Of Tests

T171. Implication of FOXP2 and DRD2 in the Associations Between Computerized Device Use and Psychiatric Disorders

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Background: Computerized device uses (CDU; e.g., playing computer games (CompGaming), mobile phone use (minutes/week for the last three months (PhoneUse) and total usage years), hands-free/speakerphone device use). Epidemiological associations between CDUs and psychiatric disorders are frequently reported; the biological mechanisms underlying these observations remain unknown. We investigated genetic overlap and causality between CDUs and psychiatric disorders (attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), autism spectrum disorder, major depressive disorder, alcohol dependence, bipolar disorder, anorexia nervosa, and posttraumatic stress disorder) using LD score regression (LDSC) and Mendelian randomization (MR).
Methods: We performed genetic correlation, polygenic risk scoring, MR, SNP- and gene-based genome-wide analysis, and pathway enrichment analysis using GWAS (genome-wide association studies) summary data from the UK Biobank (up to N=361,194) and Psychiatric Genomics Consortium (14,477<N<150,064).
Results: Genetic correlations were observed between CompGaming vs. SCZ (rg=-0.271, p=7.16x10-26) and PhoneUse vs. ADHD (rg=0.425, p=4.59x10-11). MR detected bidirectional causality in both situations, and a latent causal variable analysis indicated that the genetic correlations are not due to causal relationships but are instead related to shared biology. Mechanisms involving FOXP2 (pADHD=9.32x10-7, pPhoneUse=9x10-11), the DRD2 locus (pSCZ=7.94x10-8; pCompGaming=3.98x10-25), and dopamine transport (GO:0015872; pSCZvsCompGaming=2.74x10-10) were implicated in these associations by SNP- and gene-based GWAS and pathway enrichment.
Conclusions: The genetic associations identified recapitulate epidemiological reports between CDU and psychiatric disorders and elucidate similar (speech/language development in ADHD and PhoneUse) and differential (dopamine transport in SCZ and CompGaming) molecular mechanisms underlying these correlations which may be therapeutically relevant.
Supported By: This study was supported by the Simons Foundation Autism Research Initiative (SFARI Explorer Award:

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Keywords: Schizophrenia, ADHD, Dopamine, FOXP2, Computerized Devices

T172. Short-Term Stress and DNA Methylation of Hypothalamic-Pituitary-Adrenal Axis Genes in Triggering or Worsening Suicidal Ideation: Association Analysis in Schizophrenia

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Background: The molecular mechanisms of stress remain poorly understood, although it has been hypothesized that epigenetic mechanisms are involved in sensitivity to stress and increased risk for suicide. The proposed project investigated the methylation change in the hypothalamic−pituitary−adrenal (HPA) axis genes and short-term stress as predictors of emergent suicidal ideation (SI).
Methods: We assessed 136 schizophrenia patients. Stressful events, SI, and methylation patterns in 11 HPA axis genes (NR3C1, SKA2, CRH, CRHR1, CRHR2, CRHBP, MC2R, POMC, FKBP5, NR3C2, AVP) were assessed at baseline and three-month follow-up. Emergent SI was the primary outcome variable in a logistic regression model including methylation change and stress as the main predictors. Stress exposure was measured using the Social Readjustment Rating Scale (SRRS). DNA was extracted from white blood cells and tested using bisulfite pyrosequencing technique to determine the methylation level of the selected genes.
Results: We found that a higher SRRS score increase the risk of emergent SI ($p<0.0003$). Furthermore, the presence of SI was predicted by lower methylation of CpG 4:149362809 in NR3C2 ($p=0.01$).
Conclusions: This study is one of the first to investigate the role of short-term stress in epigenetic changes in HPA axis genes and the subsequent possible effect on SI. The study was longitudinal and could better investigate the relationship between stress and DNA methylation compared to most of the epigenetic studies of suicidality that adopted a cross-sectional design. Future studies should examine the involvement of DNA methylation changes in HPA axis genes, as a potential risk factor for SI, in a larger sample.
Supported By: AFSP
Keywords: Suicidal Ideation, Hypothalamic Pituitary Adrenal (HPA) Axis, DNA Methylation, Schizophrenia, Stressful Events

T173. Structural Amygdala Nuclei Abnormalities Distinguish Neurobiologically Derived Biotypes With Psychosis

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Background: The amygdala underlies emotional regulation and mediated by nuclei differing in functionality and topographic projections. Post-mortem and neuroimaging studies are inconclusive, and no group has studied nuclei differences in psychosis utilizing an MRI probabilistic atlas. We examined amygdala nuclei in previously defined biotypes and associations with symptomatology and cognition.
Methods: Subjects included controls (n=283) and psychosis participants classified based on cognitive control and sensorimotor reactivity into three biotypes (BT1, n=199; BT2, n=243; BT3, n=298) with BT1 displaying the most impairments. FreeSurfer 6.0 extracted basal (Ba), accessory basal (AB), lateral (La), and central (Ce) nuclei volumes from T1 MPRAGEs. Contrasts were run using a linear mixed-effects model with age, sex, race, and intracranial volume as fixed effects and site as a random effect. Partial correlations were run against symptoms and cognition and p-values were FDR corrected.
Results: BT1 showed the largest distinctions from controls, with significant reductions in all regions. BT1 displayed significantly lower bilateral AB and right Ba, La, and Ce compared to BT2 and right Ba, AB, and Ce compared to BT3. Compared to controls, significant reductions were observed in left Ba and AB for BT2, and bilateral AB, Ba and left Ce for BT3. BT2 did not distinguish from BT3. Larger nuclei were associated with better global functioning in BT1 and BT2, and lower manic symptoms and better cognition in BT2.
Conclusions: This is the first structural-MRI study of amygdala nuclei showing psychosis-related atrophy. We further validate our previous observations that BT1 is a psychosis subgroup with the most functional impairments.
Supported By: NIMH RO1 MH078113, MH077945, MH077852, MH077851, MH077862, MH072767, and MH083888
Keywords: Psychosis Spectrum, Basolateral Amygdala, Central Nucleus Of The Amygdala, Biotypes, FreeSurfer

T174. Examining the Neurobiological Progression of Early Course Schizophrenia

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Background: Schizophrenia (SCZ) is one of the most disruptive disorders in the world, and it is characterized by symptoms such as hallucinations, delusions, and disorganized thought and behavior. While growing amounts of evidence suggest that large scale network disruptions have a major role in the pathophysiology of chronic SCZ, less is known about early course SCZ. Consequently, this study examined the longitudinal progression of non-medicated early course SCZ over a period of two years.
Methods: Non-medicated early course SCZ patients (N=159) and healthy controls (N=116) were recruited at the West China Hospital, in Chengdu, China. A subsample of these participants were followed longitudinally. All imaging data were processed using Human Connectome Project (HCP) Pipelines. Whole brain and seed based individual level functional connectivity maps were analyzed using independent and paired samples t-tests.
Results: Contrary to the prefrontal cortex (PFC) connectivity reduction observed in chronic SCZ patients, our study found a significant increase in resting state functional connectivity in PFC in early course SCZ. Longitudinal follow ups indicated that the PFC connectivity returned to control levels in a subset of the patient group. Importantly, the connectivity normalization coincided with symptom improvement.
Conclusions: This study adds to the existing evidence of large-scale network disruptions by demonstrating alterations in prefrontal cortex connectivity and their relation to symptom severity in early course non-medicated SCZ patients. Thus, it brings us one step closer to characterizing the neural development of early course SCZ and informing the treatment for the early phases of illness.
Supported By: 5R01MH112189-02; 5R01MH108590-03
Keywords: Recent-Onset Schizophrenia, Functional Neuroimaging, Clinical

T175. The Effects of Lorazepam on Resting-State Functional Connectivity

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Background: Benzodiazepines, such as lorazepam, are commonly used to treat anxiety. The pharmacological mechanism of action of benzodiazepines is well understood; however, it remains unclear which neural networks and systems are involved during resting-state functional connectivity. The objective of this study is to investigate the effects of lorazepam administration (12 hours or less prior to rsMRI) compared to non-lorazepam during the resting state in patients with psychosis. We focused our analyses on the effects of lorazepam on corticostriatal connectivity, as we have previously demonstrated that a specific pattern of striatal connectivity, the striatal connectivity index (SCI; Sarpal et al., 2016), was related to antipsychotic drug response.
Methods: Thirty-eight participants (21F, 17M; mean age = 29.34 years; SD = 8.93) were included from 4 study cohorts of patients with schizophrenia. Participants were matched by age, sex, race/ethnicity and study cohort. Patients underwent two 7-minute resting state MRI scans with a 3T Siemens Prisma scanner. Whole-brain functional connectivity maps were generated for each subject from 12 striatal seed regions of interest (Di Martino et al., 2008) and individual SCI values were derived. SCI values for the lorazepam-treated group were then compared to values for the non-lorazepam-treated group.
Results: Preliminary analyses revealed a trend ($t = -1.9$, $df = 36$, $p = 0.07$) indicating that lorazepam-treated subjects exhibited different degrees of striatal connectivity as compared to non-lorazepam-treated subjects.
Conclusions: These data suggest that lorazepam may influence striatal connectivity. However, given the trend-level result more data may need to be required to confirm this hypothesis.
Supported By: R01MH109508; R01MH108654
Keywords: Schizophrenia, Resting State Functional Connectivity, Corticostriatal, Benzodiazepine

T176. Examining Retinal Nerve Fiber Layer Thickness and Microvascular Abnormalities in Psychosis With Swept Source OCT and OCT-A

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Background: Psychosis is characterized by gray matter reduction and neocortical hypoperfusion from normal, yet adequate neuroimaging resolution is difficult to achieve. We used optical coherence tomography (OCT) and OCT-angiography (OCT-A) to identify fine retinal alterations in psychosis.
Methods: Swept Source OCT was performed in 19 psychotic probands (schizophrenia, schizoaffective, bipolar) and 6 controls, with a subset of patients undergoing Spectral

Domain OCT-A. Macula retinal segmentation was performed for individual layer thickness. OCT-A scans were skeletonized to determine vessel density of the superficial and deep retinal plexus, and choriocapillaris. Subjects had clinical, structural and perfusion MRI data. Statistical analyses were performed using R, controlling for age, sex, race, BMI, visual correction and visual acuity.

Results: Probands had significant macular retinal nerve fiber layer (RNFL) thinning in the right, left, and combined eyes (Cohen's d=-4.1 to -2.1) compared to controls. The choriocapillaris density was significantly increased in the left (d=0.93) and combined (d=0.95) eyes compared to controls, but not in the superficial or deep retinal plexus. RNFL was significantly correlated with gray matter thickness (r=0.71). Global gray matter perfusion and retinal vessel density were not correlated. RNFL was significantly associated with verbal fluency (r=0.49, total sample) and digit sequencing (r=0.75, probands). Deep retinal vessel density was significantly associated with duration of psychotic symptoms (r=0.87), psychosis severity (r=0.80) and verbal fluency (-0.61, total sample).

Conclusions: Psychosis patients displayed RNFL thinning by OCT and increased choriocapillaris density by OCT-A that correlated with neuroimaging and clinical measures. OCT may be a fast and non-invasive tool for studying psychosis pathophysiology.

Supported By: 1KL2TR002542-01, Sydney R Baer Jr Foundation

Keywords: Retinal Nerve Fiber Layer, Retinal Vessels, MRI, PCASL, Psychosis

T177. The Effect of the TRKB Polymorphism and Urban Upbringing on Hippocampal Coupling During Episodic Memory

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Background: Childhood urbanicity (Urb) is an environmental factor implicated in risk for illnesses like schizophrenia, and previously shown to participate with BDNF in gene-environment interactions (GxE). BDNF's primary receptor encoded by TRKB (NTRK2) is also critical to memory and its associated physiological processes such as long-term potentiation and synaptic remodeling. We hypothesized that urbanicity would show a GxE interaction with TRKB as evidenced by alterations in hippocampal area function and coupling.

Methods: BOLD fMRI for 213 healthy subjects was gathered at 3T using a memory encoding task. BOLD activation analyses and psychophysiological interactions using a right hippocampal area seed were conducted in SPM12, with a threshold of $p<.001$ uncorrected. TRKB rs2769605 (C/T) genotypes were obtained from whole-genome genotyping.

Results: We observed main effects of TRKB and Urb, and their interaction, on BOLD activity in bilateral parahippocampal gyri. We found the same main effects and interaction for hippocampal-to-inferior parietal lobule (IPL) coupling. Specifically, minor allele homozygotes demonstrated reduced coupling across all Urb classifications, and urban-reared individuals showed increased coupling regardless of TRKB genotype. Minor allele homozygotes had reduced coupling among urban-reared subjects, while the opposite was noted for rural-reared individuals.

Conclusions: We found main effects for TRKB and Urb, as well as TRKB-Urb interactions on BOLD fMRI in parahippocampal regions and in hippocampal coupling to the IPL. These effects suggest that urbanicity, depending on genotype, may disrupt hippocampal area function. These results may highlight novel GxE mechanisms associated with poor hippocampal function in illnesses like schizophrenia where the hippocampal area has been repeatedly implicated.

Keywords: Brain Imaging, fMRI, TRKB Genetic Polymorphism, Hippocampus, Encoding Memory, Schizophrenia

T178. The Utility of Connectivity Phenotypes as Successful Biomarkers for Psychosis Diagnoses

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Background: Psychosis is a consequence of brain dysconnectivity. Connectivity deficits in psychosis, in the form of brain-wide reductions in structural and functional connectivity as measured by MRI, are well-replicated at the group-level in the literature. Such recurrent group differences suggest diagnostic specificity, although the discriminability of connectivity phenotypes on an individual-level, which is necessary for biomarker viability, is unclear. This is likely due to varying methodology compounded with the lack of independent validation samples. We aim to systematically test the viability of connectivity phenotypes as diagnostic predictors by evaluating their individual-level discriminability using supervised machine learning methods and multiple independent samples.

Methods: Whole-brain indices of structural (from DTI; N=672) and functional (from resting state fMRI; N=971) connectivity were extracted from 4 independent datasets with psychosis cases and controls. For each sample and modality, a support vector machine (SVM) with k-fold cross validation (k=5) was used to evaluate the

ability of connectivity phenotypes to classify cases and controls
Results: ROC curves were used to evaluate SVM model performance. Mean AUC across the five folds were significantly above chance for all samples and modalities and ranged from 0.60-0.69, with significant variability between folds for some samples. Functional connectivity measures outperformed structural connectivity measures but this difference was slight.
Conclusions: While connectivity phenotypes showed discriminability greater than chance, predictive ability was well below the threshold needed for clinical use. It's possible that connectivity phenotypes, while discriminative at the group level, are not useful as classifiers for individual cases, making their candidacy as biomarkers unlikely.
Supported By: R01 MH106324
Keywords: Support Vector Machines, Psychosis Phenotype, Diffusion Tensor Imaging (DTI), Resting State Functional Connectivity, Biomarkers

T179. Executive Function and Microstructural Lateralization Alterations in Schizophrenia

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Background: Changes in cortical lateralization are a biomarker of several neurological diseases, including schizophrenia (SZ), and have been previously linked to impaired cognition. In this study, we use diffusion kurtosis imaging (DKI) technique to non-invasively study gray matter (GM) microstructural lateralization in chronic schizophrenia (SZ) compared to healthy controls (HC) and additionally test its relationship with executive function.
Methods: DKI and T1-weighted data was acquired in 18 SZ patients and 19 HCs (right-handed males, 30-55 years old) on a 3T Trio MRI scanner. DKI data was employed to generate three dimensional mean kurtosis (MK) maps for each subject. Mean MK for thirty-four cortical and eight subcortical bilateral regions of interest (ROI) and the four cortical lobes was calculated using the derived maps and FreeSurfer segmentation. Microstructural laterality indexes were calculated for each subject and ROI as the difference in mean MK values in the left and right hemisphere regions normalized by the sum of these values. Executive function was assessed using Wisconsin Card Sorting Test (WCST).
Results: We found significant decreases in MK lateralization in SZ for the lobar, cortical and sub-cortical GM ROIs at the Bonferroni-corrected $p < .001$ level. There was a significant correlation between decreased MK lateralization and poor performance on the WCST.
Conclusions: Our findings suggest that MK, an in-vivo metric of tissue microstructural complexity, is sensitive to abnormal lateralization of GM cytoarchitecture in SZ. Decreased executive function in SZ may stem in part from disorganization of gray matter at both micro and macrostructural levels.
Supported By: R21 MH085228;R01 MH108962
Keywords: Diffusional Kurtosis Imaging (DKI), Schizophrenia, Brain Asymmetry, Cognition, Gray Matter Microstructure

T180. Impaired Theta Phase-Coupling Between Hippocampus and Medial Prefrontal Cortex in Schizophrenia

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Background: A genetic schizophrenia (Scz) mouse model has impaired hippocampal-prefrontal synchrony during spatial working memory (Sigurdsson et al., 2000, Nature). These Df(16)A(+/-) mice (models of the human 22q11.2 microdeletion) have impaired mPFC phase-locking to hippocampal theta (4-8 Hz) oscillations, which predicts performance. This deficit has never been demonstrated in human Scz subjects, however.
Methods: 18 Scz (8 unmedicated) and 26 age, gender and IQ-matched controls performed a spatial memory task whilst undergoing magnetoencephalography (MEG), and a 'paired associates' task dependent on hippocampal function (without MEG).
Results: Oscillatory activity was compared before and after a cue prompting subjects to recall the location of an object. Compared with controls, Scz showed:
i) a mild deficit in spatial memory performance, relating to the position of the furthest object ($p=0.027$),
ii) a marked loss of cue-induced theta (1-8 Hz) power, especially around left frontotemporal sensors ($p=0.002$), which localised to mPFC and left hippocampus (peak pFWE(SVC)$=$ 0.019),
iii) Reduced theta phase-locking value between mPFC and left hippocampus (corrected for medication, movement and power differences: peak pFWE(SVC)$=0.005$) − most marked in those off medication,
iv) A loss of correlation between phase-locking value and memory performance in left hippocampus (corrected as above, peak punc(SVC)$=0.02$).
Scz had a marked impairment in inferring associations ($p=0.003$), and this ability correlated with mPFC-HC phase-locking value in the MEG task across the whole sample ($r=-0.35$, $p=0.02$).
Conclusions: These results indicate that impaired theta phase-locking between hippocampus and mPFC could underlie hippocampal-prefrontal dysconnectivity in schizophrenia, and impairments in the cognitive domains that depend on communication between these areas.
Supported By: Wellcome Trust 202805/Z/16/Z
Keywords: Schizophrenia, Cognitive Dysfunction, MEG, Hippocampal Coupling, Theta Band

T181. Retinal Cytoarchitectural Abnormalities in Schizophrenia and Bipolar Disorder: A Meta-Analysis

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Background: Schizophrenia (SZ) and bipolar disorder (BD) are characterized by reductions in gray- and white-matter. Limitations in brain imaging have led researchers to use optical coherence tomography (OCT) to explore new biomarkers of brain pathology. We investigate the retinal layers that may be associated with SZ or BD.
Methods: Articles identified using PubMed, Web of Science, Cochrane Database. Twelve studies met inclusion for acutely/chronically ill patients. We used fixed or random effects meta-analysis for patients (SZ and BD), SZ or BD pair of eyes versus healthy control (HC) eyes. We adjusted for sources of bias, cross validated results, and report standardized mean differences (SMD). Statistical analysis performed using meta package in R.
Results: Data from 820 patient eyes (SZ=541, BD=279) and 904 HC eyes were suitable for meta-analysis. The peripapillary retinal nerve fiber layer (RNFL) showed significant thinning in SZ and BD eyes (n=12, SMD=-0.74, -0.51, -1.06, respectively) compared to HC eyes. RNFL thinning was greatest in the nasal, temporal, and superior regions. The combined peripapillary ganglion cell layer and inner plexiform layer (GCL-IPL) showed significant thinning in SZ and BD eyes (n=4, SMD=-0.39, -0.44, -0.28, respectively) compared to HC eyes. No statistically significant differences were identified in other retinal or choroidal thicknesses. Clinical variables were unrelated to the RNFL or GCL-IPL thickness by meta-regression.
Conclusions: The observed retinal layer thinning supports the classic gray- and white-matter atrophy observed on neuroimaging in SZ and BD patients. OCT may be a useful biomarker tool in studying the neurobiology of psychosis.
Supported By: 1KL2TR002542-01
Keywords: Optical Coherence Tomography, Schizophrenia, Bipolar Disorder, Retinal Imaging, Meta-analysis

T182. Investigating the Structural Correlates of Apathy Within the Psychosis Continuum

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Background: Apathy, one of the most severe and debilitating symptoms in schizophrenia, is thought to be associated with striatal and orbitofrontal structural abnormalities. However, it is unclear whether this holds across subclinical and early stages of the schizophrenia spectrum. Here, we investigated whether apathy in healthy individuals with schizotypal personality traits (SPT) and patients with first episode psychosis (FEP) is associated with reduced striatal volume and reduced thickness of the orbitofrontal cortex (OFC).
Methods: We analyzed T1-weighted brain images from 27 healthy individuals with high SPT, 26 patients with FEP and 28 controls using FreeSurfer. We evaluated volumes of the nucleus accumbens, putamen, caudate and cortical thickness of the OFC, as well as apathy and diminished expressivity from the Brief Negative Symptom Scale.
Results: In individuals with SPT apathy was negatively associated with lower volume of right nucleus accumbens (r=-.548, p=.007), and right and left putamen (right: r=-.58, p=.003: left: r=-.63, p=.001) accounting for age, gender and intracranial volume. In patients with FEP, apathy was negatively associated with reduced OFC thickness (r=-.644, p=0.001) accounting for age, gender and global cortical thickness. Significant group differences were observed in the right and left OFC, with reduced OFC thickness in patients with FEP compared to individuals with SPT and controls.
Conclusions: Our findings suggest that structural correlates of apathy can already be observed in non-clinical unmedicated populations and early stages of psychosis. These distinct structural correlates of apathy may help to identify symptom specific subgroups within the psychosis continuum and foster progress to develop individualized treatments.
Keywords: Striatum, Apathy, First Episode Psychosis, Schizotypy, Orbitofrontal Cortex

T183. Assessing the Validity of the Human Connectome Project's Identification of Primary Auditory Cortex

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Background: Current automated cortical parcellations are based on anatomy. Accurate parcellation based more on function would be valuable for delineating cortical maps, such as primary auditory cortex (A1). To assess the validity of the Human Connectome Project (HCP) quasi-functional parcellation in delineating A1, we compared A1 alignment within Heschl's gyrus (HG) in Freesurfer-processed data and in new data processed with HCP methods.
Methods: T1w MRI scans from 56 individuals were processed using Freesurfer. HG was defined by the Desikan-Killiany atlas, and HG was also manually edited (Barta 1995). T1w, T2w, and BOLD-rest MRI scans were acquired on 22 different individuals and processed with HCP protocols. HG was defined by the Desikan-Killiany atlas. A1 was defined by the HCP parcellation. Percent overlap of A1 was calculated with Desikan HG for each sample.
Results: A1 had 99.6% overlap with Desikan HG in FreeSurfer with >95% overlap in all individuals, 89.2% overlap with manually-edited HG with 41/56 individuals with >95% overlap, and 95.0% overlap with Desikan HG in HCP data with 13/22 individuals >95% overlap.
Conclusions: The Freesurfer Desikan structural parcellation of HG overlaps well with HCP-derived A1. After adjusting boundaries manually, A1 does not overlap HG as well because some individuals have uniquely shaped HG, e.g. bifurcation. The HCP quasi-functional parcellation has 95% overlap. Future work will investigate if those with poor overlap is

explained by unique HG morphology. The HCP parcellation is largely valid in locating A1 quasi-functionally, but its relation to manually traced ROI remains to be examined.
Supported By: P50 MH103204, R01 MH113533, R01 MH108568
Keywords: Human Connectome Project, FreeSurfer, Parcellation, Auditory Cortex

T184. Anterior Hippocampal Hyperactivity Limits fMRI Activation During Scene Processing in Early Psychosis

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Background: Extant data provide strong evidence for hippocampal hyperactivity in schizophrenia. We have found that volume deficits in early psychosis patients are more prominent in the anterior hippocampus. The origin of functional abnormalities along the hippocampal long axis is unclear. Models of hippocampal function have highlighted a role for the anterior hippocampus in scene processing and construction. Here we test the hypothesis that anterior hippocampal hyperactivity impairs the recruitment of this region during a cognitive task.
Methods: We analyzed fMRI data from 112 individuals (48 early psychosis patients; 64 healthy controls) using a block design 1-back task with scene, face, and scrambled image conditions. We measured BOLD activation in response to scenes and faces compared to scrambled images in each individual. Cerebral blood volume data was collected to measure baseline hippocampal activation from a subset of individuals in the fMRI sample (17 patients; 28 healthy controls).
Results: Relative to healthy controls, we observed decreased activation of the anterior hippocampus in early psychosis patients during scene processing (cluster-wise pFWE$<$0.014) and increased cerebral blood volume in the anterior hippocampus (t(19.7)=2.77, p=0.006). Increased cerebral blood volume in early psychosis patients was associated with less task-related activation during scene processing in the anterior hippocampus (r=-0.46, p=0.03).
Conclusions: We find evidence for anterior hippocampal hyperactivity in early psychosis patients that limits their ability to effectively recruit the hippocampus during scene processing. Our findings provide novel support for the anterior hippocampus as a target in the treatment of cognitive deficits and clinical features of psychosis.
Supported By: NIMH R01-MH70560; Charlotte and Donald Test Fund
Keywords: Early Psychosis, Hippocampus, BOLD fMRI, CBV

T185. Impairment in Prefrontal Connectivity Supporting Cognitive Control State is Associated With Cognition in Individuals With First-Episode Psychosis

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Background: Recent evidence suggests that a background attentional state may support cognitive task-based demands. Background connectivity (BC) during working memory (WM) in schizophrenia has not been explored. The following fMRI study examined BC of the dorsolateral prefrontal cortex (DLPFC) in a group of patients with first-episode psychosis (FEP) to assess its link with psychopathology and cognition.
Methods: We examined BC during a visuo-spatial WM task using fMRI in FEP (N=43) and age-matched healthy controls (HC; N=35). Spherical regions of interest, centered around each participant's peak activation within the left and right DLPFC were seeded in task-independent BC analyses and compared with resting state functional connectivity and task-activation. BC was also assessed in relation to task performance, psychopathology, and cognition (via MATRICS Consensus Cognitive Battery (MCCB)). Significance was defined voxel-wise as p$<$.001, and cluster corrected at p$<$.05.
Results: The FEP group showed significantly lower background DLPFC connectivity relative to HC in bilateral superior parietal lobule (SPL) and left inferior parietal lobule (IPL). Resting-state DLPFC connectivity and WM activation in these regions did not differ significantly between groups, and no fMRI measures were associated with symptoms or task performance. BC with the left IPL was positively associated with overall MCCB score in the FEP group (p=.003) and trended toward significance in our HC group (p=.038; Bonferroni correction set at p $<$0.017).
Conclusions: These results provide novel evidence indicating that the ability to sustain DLPFC connectivity during cognitive engagement, independent of intrinsic connectivity at rest, may underlie cognitive impairments in FEP.
Supported By: NIMH/NIH: K23MH110661, P50MH103204, UL1TR001857
Keywords: First-Episode Psychosis (FEP), Cognition, Functional Connectivity, Visuospatial Working Memory, Schizophrenia Spectrum

T186. The Association Between Processing Speed and White Matter Tract Myelination in Schizophrenia

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Background: Abnormalities in myelin content have been implied in schizophrenia by both histological and diffusion imaging studies. However, diffusion imaging offers only an indirect assessment of myelin content and thus additional data

is necessary to confirm dysmyelination as a contributor to white matter dysfunction in schizophrenia. Moreover, the exact relationship between dysmyelination and behavioral outcomes remains undetermined. The current study employs quantitative magnetization transfer (qMT) imaging, a myelin specific technique, to examine myelin content in schizophrenia and its relationship with processing speed (PS), a prominent deficit of the disorder.
Methods: Twenty-two schizophrenia spectrum patients and 21 age-matched controls participated in the study. Processing speed was measured by the composite score in MATRICS Consensus Cognitive Battery. Macromolecular proton fraction (MPF), which reflects myelin content, was calculated for each subject using qMT data. Group differences in MPF for several white matter regions and tracts as well as the relationship between MPF and PS were investigated.
Results: SZ group had significantly lower PS compared to controls ($p<.001$) and decreased MPF in the occipital area ($p=.024$). Significant positive correlations were noted between PS and MPF for the whole sample in anterior thalamic radiation ($p=.023$), corticospinal tract ($p=.012$), corpus callosum splenium ($p=.009$), and cingulate tract ($p=.037$).
Conclusions: Processing speed appears to be associated with overall myelin content in white matter tracts feeding to motor, sensory, and visual areas. As PS/MPF correlation trends were comparable in the two groups, the behavioral deficits in patient group are likely to reflect reductions in normal function as opposed to fundamental changes in mechanism.
Supported By: R01MH108962
Keywords: Schizophrenia, Myelin, Magnetization Transfer Imaging, Processing Speed

T187. Persecutory Beliefs are Associated With Abnormal Medial Temporal Lobe Responses During Fear Learning

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Background: Psychotic symptoms, particularly persecutory delusions, have been consistently associated with changes in the function of the amygdala and hippocampus. However, the mechanisms underlying these changes remain unclear. To further investigate this abnormality in a population that is naïve to treatment with antipsychotic medication, we collected fMRI and skin conductance data in young adults with varying levels of subthreshold symptoms of psychosis, while they participated in a Pavlovian fear conditioning task. We predicted that subthreshold psychotic symptoms, particularly persecutory beliefs, would be linked to abnormalities in amygdala and hippocampus activity during fear learning.
Methods: During conditioning, two distinct face stimuli were shown; one (CS+) was followed by an electrical shock and the other (CS-) was not. Subclinical delusional beliefs were measured using the 21-item Peters et al. Delusions Inventory. FMRI data were analyzed using anatomically-defined regions-of-interest (FreeSurfer 6.0).
Results: 26 participants endorsed one or more persecutory beliefs (P+ group) whereas 46 participants did not endorse such beliefs (P- group). Both groups showed differential fear conditioning as reflected by skin conductance responses. However, the P- group showed significant differential (CS+ $<$ CS-) responses in the amygdala and hippocampus, whereas the P+ group did not. In a follow-up analysis of amygdala subnuclei, we found that this effect was present (and remained significant after controlling for depressive/anxiety symptoms) in the basal, accessory and cortico-amygdaloid nuclei.
Conclusions: These findings provide further evidence for abnormal medial temporal lobe function in subthreshold psychotic states, supporting the continuum model of psychosis.
Supported By: 4R01MH095904
Keywords: Fear Conditioning, Brain Imaging, fMRI, Subclinical Psychosis, Hippocampus/Amygdala, Positive Symptoms

T188. Thalamocortical Functional Connectivity in Schizophrenia and Schizotypal Personality Disorder

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Background: Resting-state fMRI studies of schizophrenia (SZ) have uncovered a pattern of thalamic hyperconnectivity with sensorimotor and temporal regions, as well as thalamic hypoconnectivity with frontal regions. No studies, however, have examined thalamocortical functional connectivity in schizotypal personality disorder (SPD). SPD is a SZ-spectrum disorder that shares genetic, neurobiological, and behavioral characteristics with schizophrenia. Studying SPD is advantageous as confounds including medication and hospitalization are avoided
Methods: A large, rigorously diagnosed (structured interview) and clinically assessed, demographically-matched SZ-spectrum sample was examined: 24 SZ, 54 SPD, and 48 healthy controls (HCs, without Axis I or II diagnosis). A 3T resting-state fMRI was obtained and bilateral whole thalamic seed-based analyses were conducted. Between-group analyses were performed using FSL FEAT with p-values set to $p<0.05$ (corrected).
Results: The SPD group was intermediate between the HCs and SZ patients in terms of their thalamo-cortical functional connectivity. Compared with HCs, both the SPD and SZ groups showed increased thalamic connectivity with the sensorimotor cortex and temporal lobe, primarily in the middle temporal gyrus. Only the SZ group showed reduced thalamo-frontal connectivity compared with HCs, primarily in the superior frontal gyrus and dorsolateral prefrontal gyrus. When comparing thalamic connectivity between the SPD and SZ groups without reference to HCs, there were no between-group differences.

Conclusions: Our SPD findings are novel and indicate similarities in thalamo-temporal hyperconnectivity across SPD and SZ, suggesting a shared neurobiological trait marker for the SZ spectrum. The lack of thalamo-frontal hypoconnectivity in SPD may serve as a protective factor that spares these individuals from full-blown psychosis.
Supported By: VA Merit Award (I01 CX000609); VA Research Career Scientist Award (1 IK6 CX001738-01)
Keywords: Schizophrenia Spectrum, Schizophrenia, Schizotypal Personality Disorder, Resting State fMRI, Thalamocortical Connectivity

T189. Segmentation of the Superior Longitudinal Fasciculus in First-Episode Psychosis

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Background: Abnormalities in the superior longitudinal fasciculus (SLF), a major white matter association tract connecting all brain lobes, have been identified among individuals at risk for developing psychosis and in psychotic disorders across different illness stages. To date, however, only post-mortem studies have been able to investigate specific subregions of the SLF in psychotic disorders.
Methods: Sixty-three (46M/17F) patients (mean age=21.5, SD=5.0) experiencing a first-episode of psychosis (FES) and 70 (46M/24F) healthy volunteers (mean age=21.4, SD=4.9) completed diffusion tensor imaging (DTI) exams at the onset of treatment with either aripiprazole or risperidone. We employed two tensor tractography, and a novel automated tool (i.e., white matter query language) that consistently identifies white matter tracts across individuals. Four subregions of the SLF (i.e., SLF I-III and arcuate fasciculus), which were first defined in Makris et al., 2004), were the focus of this study.
Results: Patients demonstrated significantly ($p < .05$) lower fractional anisotropy (FA) within SLF II and III compared to healthy volunteers with subsequent analyses revealing higher radial diffusivity and trace in SLF III among patients. These findings were comparable in both hemispheres. There were no significant between group differences in axial diffusivity for the 4 SLF subregions.
Conclusions: Using a novel approach for the consistent identification of white matter tracts we report the first in-vivo study to identify putative abnormalities within specific segments of the SLF in first-episode psychosis. Furthermore, these findings implicate myelin (in contrast to axonal) abnormalities within SLF II and III in the pathophysiology of first-episode psychosis.
Supported By: R01 MH076995
Keywords: Diffusion Tensor Imaging (DTI), First Episode Psychosis, Superior Longitudinal Fasciculus, White Matter

T190. Multivariate Analysis Revealed Shared Brain Patterns With Psychotic Symptom Profiles in Bipolar Disorder and Schizophrenia

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Background: We previously used multivariate analyses of imaging and symptoms to identify gray matter patterns correlated with a profile of increased anxiety, delusions and hallucinations in schizophrenia. That analysis used structural images and the Positive and Negative Symptom Scale (PANSS). We now apply the same methods to a dataset from individuals with bipolar disorder (BD), to determine whether similar patterns are identified.
Methods: We applied parallel independent component analysis (pICA) to gray matter (GM) concentration and the PANSS in 110 BD patients from the Thematically Organized Psychosis (TOP) study. The previously identified SZ GM pattern was also projected onto BD data, and its associations with PANSS items were explored.
Results: pICA revealed grandiosity, lack of judgment and guilty feelings positively associated with a GM component involving front-temporo-parietal areas and the cerebellum ($p = 1.72e-04$, beta = 0.35). The projected pattern showed a trend of association with grandiosity, hostility, poor impulse control, social avoidance, positive, general and total score. Severity differences in delusion, guilty feelings, lack of judgment and preoccupation were observed between BD patients with and without a history of psychotic symptoms. However, none of the above GM pattern loadings showed difference across the subgroups.
Conclusions: The projected PANSS-GM pattern in BD tended to show similar effects as in SZ. The distinct symptom profiles between psychotic and non-psychotic BD can be partly explained by frontal-temporal-parietal-cerebellum GM alterations. Both brain patterns were closely connected to symptom dimensions regardless of current diagnosis. The results also highlight the utility and stability of multivariate methods across disorder studies.
Supported By: NIH 1R01MH094524
Keywords: Multivariate Analysis, Gray Matter Density, Neuropsychiatric Symptoms, Cross-Disorder

T191. Load-Dependent Working Memory Circuity in Early-Onset Psychosis

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Background: Functional neuroimaging studies reliably illustrate working memory (WM) activation patterns in frontoparietal regions in adults. In typical developing (TD) youth, diffuse WM activation has been observed, while in youth with early-onset psychosis (EoP) activation is disrupted. However, the nature of WM disruptions is inconsistent in EoP youth, possibly resulting from differences in task-demands and not accounting for age-related WM performance differences in analyses. This study examined WM circuitry in 53 TD and 29 EoP youth using a novel WM task that accounted for age and diagnosis related confounds in WM abilities.
Methods: Each individual's WM capacity was estimated based on Cowan's formula: k=n*(h+cr-1). Participants then completed a Sternberg style WM task during fMRI at 3 levels of difficulty: below capacity (low: k-1), at capacity (medium: k), above capacity: (high: k+2). To compare neural activation differences between groups in each condition, whole brain analyses were performed and corrected for multiple comparisons.
Results: EoP youth demonstrated greater recruitment of right IFG compared to TD youth in the high condition. Though both groups had stronger frontoparietal activation in the high condition compared to the low condition, EoP youth showed greater differences in bilateral frontoparietal regions between conditions than TD youth. No differences were observed in the low or medium conditions.
Conclusions: This study indicates the importance of accounting for age and diagnosis related differences when examining WM circuitry in TD and EoP youth. Results suggest that when equating performance across groups, EoP youth exhibited hyperactivity to meet increased task demands.
Supported By: MH101506
Keywords: Early-Onset Psychosis, Working Memory, fMRI

T192. Working Memory in Patients With Schizophrenia Revisited by Graph Theoretical Methods

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Background: Disturbances in "functional connectivity" have been proposed as a major pathophysiological mechanism for schizophrenia, and in particular, for cognitive disorganization. Few studies have investigated the disturbances in "functional connectivity" underlying cognitive disorganization from network level or identified the relationship between clinical symptoms, cognitive deficits, and the efficiency of brain network.
Methods: We used graph analysis to examine the functional networks of 155 patients with schizophrenia and 96 healthy controls (HCs) in processing information under working memory (WM) task. The efficiency of functional networks was evaluated by quantifying the small-world network metrics (SWN). We also compared degree and betweenness regional network measures. Additionally, to validate our results, we replicated these analyses in another dataset which collected 81 patients with schizophrenia and 54 HCs but used different scanning parameters. A moderating model was conducted to identify the relationships between the SWN, clinical symptoms, and the behavior data of WM task in patients with schizophrenia.
Results: Both datasets consistently demonstrated brain networks of patients with schizophrenia had significantly increased SWN networks under 2Back. The SWN has a moderating effect between the negative symptoms and the behavior data. Areas emerging in the frontotemporal circuits were detected has altered degree and betweenness in patients with schizophrenia.
Conclusions: The higher SWN organization in patients of schizophrenia suggests that they need to optimize their brain network organization to perform better in demanding cognitive tasks relying on WM. Regional connections in the frontotemporal circuits may play a role in maintaining or adapting to schizophrenia pathology.
Supported By: National Natural Science Foundation
Keywords: Schizophrenia, Functional Brain Connectivity, Small-World, Working Memory

T193. Monetary Incentives Shape Behavioral and Neural Precision of Spatial Working Memory

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Background: Cognitive and motivational deficits co-occur across psychiatric illnesses. To better understand how cognitive and motivational neural systems interact, we designed a novel incentivized spatial working memory (I-sWM) task for functional magnetic resonance imaging (fMRI).
Methods: 33 healthy adults performed the I-sWM task. The possibility for monetary gain or loss was cued before each sWM trial (cued), or instructed before a block of sWM trials (non-cued). Effects of incentives on sWM networks were calculated with general linear models. We regressed blood oxygen level dependent (BOLD) signal change with trial-by-trial sWM accuracy, or monetary feedback, to identify regions where parametrically increasing BOLD signal reflected better accuracy, or increasing money won/lost. All imaging results are whole-brain, $p<0.05$, family-wise-error-corrected.
Results: Cued gain and loss, and non-cued loss conditions improved sWM accuracy ($p<0.01$). For cued incentive trials, BOLD signal increased in intraparietal sulcus (IPS) during memory maintenance, and precentral sulcus (PCS) during location encoding. Effects of non-cued incentives were similar. There was increasing BOLD signal with better trial-by-trial accuracy in IPS, PCS, superior parietal and superior frontal sulci. Increasing BOLD signal in ventral striatum reflected both more money won and less money lost.

Habenula and insula had increasing BOLD signal with more money lost.
Conclusions: Our results suggest that incentives improve sWM, and IPS and PCS enhance incentivized sWM maintenance, encoding and accuracy. In the same task, specific monetary feedback was tracked by ventral striatum, habenula and insula. This study in healthy adults highlights key findings for future translation to psychiatric populations.
Supported By: Thomas P. Detre Fellowship Award
Keywords: Spatial Working Memory, Reward Processing, Motivation, Monetary Loss, Cognitive Neuroscience

T194. Reward-Related Decision-Making in Schizophrenia: A Multimodal Neuroimaging Study

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Background: Schizophrenia is a severe psychiatric disorder characterized by important cognitive deficits, which ultimately compromise the patients' ability to make optimal practical decisions. Unfortunately, the neurobiological bases of impaired reward-related decision-making in schizophrenia have rarely been studied. The objective of this study is to examine the neural mechanisms involved in reward-related decision-making in schizophrenia, using functional magnetic resonance imaging (fMRI).
Methods: Forty-seven schizophrenia patients (DSM-IV criteria) and 23 healthy subjects with no psychiatric disorders were scanned using fMRI while performing the Balloon Analogue Risk Task (BART). A rapid event-related fMRI paradigm was used, separating decision and outcome events. Between-group differences in grey matter volumes were assessed with voxel-based morphometry.
Results: During the reward outcomes, increased activations were observed in schizophrenia patients relative to controls in the left anterior insula, the putamen, the dorsal anterior cingulate cortex and the left dorso-lateral prefrontal cortex (peak threshold: $p<0.001$; cluster threshold: >45 voxels). Reduced grey matter volumes were observed in the left anterior insula in schizophrenia patients which spatially overlapped with functional alterations. Finally, schizophrenia patients made fewer gains on the BART, relative to controls.
Conclusions: The fact that schizophrenia patients had increased activations in sub-cortical regions such as the striatum and insula in response to reward events suggests that the impaired decision-making abilities of these patients are mostly driven by an overvaluation of outcome stimuli. In addition, the coherence of functional and structural alterations in the left anterior insula strongly suggests that this limbic regions plays a critical role in impaired reward-related decision-making in schizophrenia.
Supported By: Eli Lilly Canada Chair on Schizophrenia Research; Réseau de Bioimagerie du Québec

Keywords: Schizophrenia, Neuroimaging, Decision-Making, Reward

T195. Neuroanatomical Heterogeneity of Schizophrenia Quantified via Semi-Supervised Machine Learning Reveals Two Distinct Subtypes: Results From the PHENOM Consortium

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Background: The neuroanatomical heterogeneity of schizophrenia can lead to confounded interpretations of patient-control comparisons by averaging across possible subgroups exhibiting distinct patterns of gray matter volume (GMV) decreases and increases. Our aim was to decompose the neuroanatomical heterogeneity of schizophrenia using newly developed semi-supervised machine learning tools.
Methods: T1-structural images of 671 participants from a subcohort of the PHENOM consortium coming from three sites [controls = 364 (age = 29.5±7.0 years; 44.2% female); schizophrenia = 307 (age = 30.9±7.3 years; 35.2% female)] were analyzed. A recently published semi-supervised machine learning algorithm (HYDRA) was applied to simultaneously cluster and classify patients relative to corresponding control subjects. Voxel-wise analyses were carried out using regionally multivariate discriminative statistical mapping (MIDAS).
Results: We found two neuroanatomical subtypes of schizophrenia. Subtype1 had widespread cortical GMV deficits with larger alterations in medial temporal, medial prefrontal/frontal, and insular cortices (FDR-$p < 0.05$). Subtype2 had GMV increases in striatum but no cortical abnormalities (FDR-$p < 0.05$). Subtype1 had relatively higher negative symptoms and lower educational achievement when compared to Subtype2. GMV correlated

negatively with illness duration in Subtype1 but not in Subtype2.
Conclusions: Our results demonstrate distinctly different neuroanatomical profiles of two schizophrenia subgroups. Subtype1 appeared to be more progressive. Strikingly, Subtype2 did not demonstrate cortical GMV decreases and instead showed subcortical increases, which questions current conceptions of the neuropathology of schizophrenia. Given their notable brain differences, these imaging-defined subtypes may require different clinical treatment planning and intervention approaches.
Supported By: National Institutes of Health grant 1R01MH112070-01A1
Keywords: Structural MRI, Neuroanatomical Correlates, Machine Learning, Schizophrenia, Statistical Analysis

T196. A Longitudinal Study of Relationships Between Resting State Functional Connectivity and Real-Life Functioning in Early Psychosis

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Background: Resting state functional magnetic resonance imaging (rs-fMRI) has emerged as a useful technique to study functional connectivity between spatially distinct regions that are altered in psychiatric illnesses. In this study, we investigated how functional connectivity within specific regions, where changes in patients with psychosis have been observed, correlated with real-life functioning in early psychosis. Two time-points were studied to explore the longitudinal changes that arise as psychosis progresses.
Methods: Rs-fMRI data were collected from 20 early-phase psychosis patients at baseline and a follow-up scan (within 2 years from baseline) on 3-T scanners. Functional data were acquired in 2 runs of 6.2 minutes (124 time-points). Scan images were converted to NIFTI files, and imported into the CONN toolbox for further pre-processing, denoising, and analysis. Domains of functioning (e.g., independence) were assessed using the Multnomah Community Ability Scale (MCAS). Correlation analysis was conducted in GraphVar.
Results: Preliminary analysis revealed that at baseline, different connectivity patterns were correlated with specific domains of functioning. However, connections between the right temporal fusiform cortex, and the parietal cortex, opercular cortex, and the planum polare (all $p < 0.01$) were correlated with multiple domains, suggesting the importance of temporal-parietal connections in real-life functioning. Interestingly, different connectivity patterns were observed at the follow-up time-point for the same measures, where less overlapping connections were correlated across different functioning domains.
Conclusions: Real-life functioning appears to be correlated with connectivity between the temporal and parietal lobes. Specific domains of function activate different neural connectivity patterns and dynamically changes over time in early psychosis.
Supported By: National Institute of Mental Health [1R01MH109687]:Mei-Hua Hall
Keywords: Brain Imaging, fMRI, First Episode Psychosis (FEP), Resting State Functional Connectivity

T197. Reduced Striatal Dopamine Synthesis Capacity Mediates Altered Within-Basal Ganglia Intrinsic Functional Connectivity in Patients With Schizophrenia During Symptomatic Remission of Positive Symptoms

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Background: Basal ganglia circuitry, organized in largely parallel dorsal and ventral/limbic pathways, is modulated by dopamine. We recently reported cortico-basal ganglia intrinsic functional connectivity (iFC) alterations in schizophrenia and identified decreased striatal dopamine synthesis capacity (DSC) in patients with schizophrenia during symptomatic remission of positive symptoms. However, the functional relationship between altered within-basal ganglia iFC and striatal-DSC is unknown in schizophrenia.
Methods: We employed 18F-DOPA positron emission tomography to investigate striatal-DSC (indexed as kicer) and resting-state functional magnetic resonance imaging to examine basal ganglia iFC in 23 patients with schizophrenia during symptomatic remission of positive symptoms and 24 healthy controls. IFC between striatal functional-subdivisions (limbic - LST, associative - AST, and sensorimotor - SMST) and internal (GPi) and external globus pallidus (GPe) was investigated. Pearson correlation and mediation analyses were used to characterize the relationship between striatal-DSC and basal ganglia iFC.
Results: We found reduced AST-GPi and AST-GPe iFC in patients, peaking in the right GPi and GPe, respectively ($p<0.001$). Similarly, reduced LST-GPi and LST-GPe iFC was found in patients, peaking in the right GPi and GPe, respectively ($p<0.001$). Across all subjects, these connectivity-clusters correlated with striatal-DSC, which was reduced in patients (AST-GPi: $r=0.39$, $p=0.01$, AST-GPe: $r=0.45$, $p=0.004$, LST-GPi: $r=0.40$, $p=0.01$, and LST-GPe: $r=0.47$, $p=0.002$). Furthermore, striatal-DSC mediated the disorder's effect on all connectivity-clusters.
Conclusions: Reduced striatal dopamine synthesis capacity mediates altered functional connectivity between ventral and dorsal striatum and internal and external globus pallidus in patients with schizophrenia during symptomatic remission of positive symptoms.
Keywords: Schizophrenia, Dopamine, Basal Ganglia

T198. Evidence for Cerebello-Thalamo-Cortical Hyperconnectivity as a Heritable Trait for Schizophrenia

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Background: Our recent study revealed that cerebello-thalamo-cortical (CTC) hyperconnectivity is a state-independent "trait" alteration for psychosis prediction. One possible cause of such change would be genetic predisposition. Here we tested this hypothesis using two independent twin datasets: the Human Connectome Project (HCP) twin sample and the Swedish Schizophrenia Twin Study (STAR).
Methods: The HCP sample included a total of 137 healthy twin pairs (85 monozygotic, 52 dizygotic). We quantified the similarity of CTC connectivity across twin pairs using intra-class correlation and estimated the heritability of CTC connectivity using structural equation modeling (SEM).

The STAR sample included 40 schizophrenia discordant co-twins (10 monozygotic, 30 dizygotic) and 32 healthy twins. CTC connectivity were compared between the three groups using a linear regression model, in which genetic distance to schizophrenia, age, sex and head motion were modeled as regressors.
Results: The ICC for CTC connectivity among monozygotic and dizygotic twin pairs in the HCP sample were 0.54 and 0.22, respectively. The SEM revealed a heritability of 0.52 (95% CI: 0.36-0.64), where 52% of the variance was attributable to additive genetic effects (a2 = 0.52) and 48% attributable to unique environmental effects (e2 = 0.48).

A significant linear effect of genetic loading for schizophrenia was observed in CTC connectivity in the STAR sample (P = 0.045), where schizophrenia monozygotic co-twins showed the highest connectivity and healthy twins had the lowest connectivity.
Conclusions: The findings from two independent twin cohorts have provided converging evidence that CTC hyper-connectivity is likely to be a heritable trait associated with risk for schizophrenia.
Supported By: NARSAD
Keywords: Schizophrenia, Cerebello-Thalamo-Cortical Connectivity, Heritability, Genetic Risk

T199. Assessing Neurometabolite Alterations in the Anterior Cingulate Cortex of Patients With Schizophrenia: A Multi-Site Proton Magnetic Resonance Spectroscopy Initiative

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Background: Neurometabolite alterations have often been reported in patients with schizophrenia (SCZ). These changes can be difficult to discern using proton magnetic resonance spectroscopy (1H-MRS), as differences are subtle and influenced by study heterogeneity. Thus, we developed and used a standardized approach to examine neurometabolite disturbances through a multi-site 1H-MRS initiative investigating patients with schizophrenia.
Methods: We pooled raw anterior cingulate cortex 1H-MRS data (GE; TE=35ms) from two sites: Toronto, Canada (n=93; 70 SCZ, 23 healthy controls) and Tokyo, Japan (n=80; 58 SCZ, 22 healthy controls). The FID-A toolbox was used to execute a standardized procedure that included the simulation of site-specific basis sets and data preprocessing. Preprocessed outputs were analyzed by LCModel. Glutamate, glutamate+glutamine (Glx), myo-inositol, choline, and N-acetylaspartate were estimated, referenced to creatine, and compared between groups using a linear mixed-effect model from the lme4 package in R 3.5.0, with group as a fixed effect and site as a random effect.
Results: Patients with SCZ had higher levels of glutamate, Glx, and choline (F=4.16, p=0.043; F=4.39, p=0.038; F=9.05, p=0.003). No differences were identified for myo-inositol or N-acetylaspartate (F=2.04, p=0.16; F=0.01, p=0.90).
Conclusions: Using a multi-site standardized analytical approach, we demonstrated elevated glutamate, Glx, and choline in patients with SCZ. Our ultimate goal is to pool additional 1H-MRS data from other research groups (interest already secured from several) to perform further analyses, including subgroup and meta-regression analyses.
Supported By: Healthy Brains for Healthy Lives (Postdoctoral Fellowship)
Keywords: Schizophrenia, Proton Magnetic Resonance Spectroscopy, Multi-Site, Anterior Cingulate Cortex, Glutamate

T200. Abnormal Thalamocortical Functional Connectivity and Sensory Gating Deficits in Psychotic Disorders: Are These Two Biomarkers Related?

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Background: Recent data implicate abnormalities of the thalamic reticular nucleus (TRN) and thalamocortical circuitry in schizophrenia risk. The TRN modulates sensory processing by gating thalamocortical communication. Patients with schizophrenia and first-degree relatives exhibit sensory gating (SG) deficits. Further, abnormal thalamocortical functional connectivity predicts conversion to schizophrenia in high-risk samples. Here, we investigated SG in relation to thalamocortical connectivity in early-course patients with psychotic disorders (PSY) and individuals with familial-high-risk (FHR).
Methods: Ten PSY (4 schizophrenia, 6 other psychoses), 14 FHR and 16 demographically-matched healthy controls (HC), aged 13-32 had resting-state fMRI and an

EEG-auditory-sensory-gating paradigm. We performed a seed based functional connectivity analysis based on the FSL-Oxford thalamic-connectivity-atlas. SG was calculated as the suppression of the auditory P50 event-related potential for the second of a pair of identical clicks. Whole brain regression analyses were used to examine relations of thalamocortical connectivity with SG (we report pFDR≤.05).

Results: Relative to HC, PSY exhibited marginally reduced SG (t(19)=-1.9,p=.07; FHR vs HC non-significant). Reduced SG was associated with weaker thalamocortical connectivity in the right dorsolateral-prefrontal-cortex (DLPFC;MNI:x=44,y=44,z=-2;BA46;164voxels;no slope difference between groups). Thalamus-to-DLPFC connectivity in this cluster was significantly reduced in PSY vs. HC (t(19)=2.2,p=.04; FHR vs HC non-significant).

Conclusions: We demonstrate that an ERP endophenotype of schizophrenia correlates with reduced thalamocortical connectivity in the DLPFC. Previous imaging work in schizophrenia reveal a pattern of thalamic sensory-motor hyperconnectivity coupled with prefrontal hypoconnectivity. We argue that these large-scale perturbations in thalamocortical circuitry result in a failure to gate superfluous sensory information. Future analyses will investigate specificity of these deficits to schizophrenia.

Supported By: K01MH114012

Keywords: Psychotic Disorder, Thalamocortical Circuitry, Resting State Functional Connectivity MRI (fcMRI), Sensory Gating, ERP

T201. Mega-Analysis of Subcortical Structures and Intracranial Volume in Early Onset Psychosis – an ENIGMA Study

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Background: Early onset psychoses (EOP, including early onset schizophrenia (EOS), affective psychosis, and other psychosis) are rare disorders with onset <18 years of age, and with poorer outcome than adult onset psychosis. EOP studies are small with limited power. In this collaborative effort, we investigated subcortical brain structures and intracranial volume (ICV) in EOP compared to healthy controls (HC) and putative differences across EOP subgroups.

Methods: MRI scans from 296 EOP patients (age 16.5±1.4 years; 40.5% females; N EOS=183, Affective psychosis=72, Other psychosis=41) and 360 HC (age 15.9±1.7 years; 45.6% females) were pooled from 11 cohorts worldwide and processed in FreeSurfer following a standardized pipeline. Subcortical volumes (both hemispheres combined) and ICV were extracted. Group differences were analyzed by linear mixed-effects model adjusting for age, sex and ICV, with scanner as random variable. False discovery rate was applied for multiple comparisons.

Results: EOP patients had significantly smaller ICV (d=-0.38), hippocampus (d=-0.23) and amygdala (d=-0.18), and larger caudate (d=0.25), lateral ventricle (d=0.23), putamen (d=0.19) and pallidum (d=0.19) than HC. There was no age or sex interaction for diagnosis. The largest effects were in EOS (smaller ICV (d=-0.34), hippocampus (d=-0.2); larger pallidum (d=0.28), caudate (d=0.2), putamen (d=0.2)), followed by affective psychosis (smaller ICV (d=-0.29); larger lateral ventricle (d=0.28)) relative to the HC group.

Conclusions: EOP patients showed volumetric changes across several subcortical structures, that were more pronounced in EOS patients. The largest negative association was for ICV, with larger effects than in similar adult studies, which suggests that neurodevelopmental factors may play a role in EOP.

Supported By: The Research Council of Norway (grants number 223273); KG Jebsen Foundation; NIH U54 EB020403

Keywords: Brain Magnetic Resonance Imaging (MRI), Child And Adolescent Psychiatry, Neuroimaging, Schizophrenia Spectrum, Early-Onset Psychosis

T202. Atypically Larger Variability of Resource Allocation Accounts for Visual Working Memory Deficits in Schizophrenia

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Background: Working memory (WM) deficits have long been noticed in schizophrenia (SZ) and the majority of existing studies attributed the deficits to decreased capacity compared with healthy control (HC) subjects. However, this decreased-capacity theory ignores contributions of other WM components, such as precision, which have been recently shown very crucial in mediating WM behavior.

Methods: We measured the performance of 60 SZ (31 females) and 61 HC (29 females) in a classical delay-estimation visual working memory (VWM) task. To disentangle different VWM components, we evaluated several influential computational models that embody current theories of VWM.

Results: In contrast to the decreased-capacity account, none of the models revealed group differences in memory capacity and in memory resources across set size levels¬. Model comparisons revealed that the model assuming variable precision (VP) across items and trials can best explain the performance of both groups. The VP model suggested that SZ only exhibited abnormally larger variability of allocating memory resources rather than showing reduced

resources or capacity per se. Finally, we found that estimated resource allocation variability is correlated with symptom severity in SZ, highlighting its contribution to schizophrenic pathology.
Conclusions: Our results propose an alternative account to the widely accepted decreased-capacity theory and demonstrate that elevated resource allocation variability is the major determinant of the atypical VWM behavior in schizophrenia. Our findings also highlight the use of computational models to characterize mechanisms of mental deficits in special population.
Supported By: This work was supported by the National Social Science Foundation of China (17ZDA323), the National Key Fundamental Research Program of China (2013CB329501), the Major Program of Science and Technology Commission Shanghai Municipal (17JC1404100), the Fundamental Research Funds for the Central Universities (2018ECNU-QKT015), and the NYU-ECNU Institute of Brain and Cognitive Science at NYU.
Keywords: Schizophrenia, Visuospatial Working Memory, Memory Precision, Generative model, Bayesian Inference

T203. Poster Withdrawn

T204. Caudate Volume and Emotional Lability in Marijuana Using Adolescents

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Background: Structural imaging studies have found evidence of increased gray matter volume in the basal ganglia in adults with heavy cannabis use. The basal ganglia has been linked to cognitive and emotional regulation impairments. Emotional lability has been shown to predict intensity of marijuana-related problems, but few studies have focused on associated brain regions. The current study examines the association between adolescent marijuana use, emotional lability, and subcortical volume in the basal ganglia.
Methods: Twenty-seven adolescents (mean age17.4 years) with current marijuana use disorder (MJ) and thirty healthy controls completed a structured interview of substance use, the Conners' Parent Rating Scale-Revised (CPRS-R). Magnetic resonance imaging data was acquired on 3T Siemens Verio scanner, and images were analyzed using FreeSurfer to obtain regional brain volumes.
Results: Adolescents with MJ use showed higher emotional lability ($p=0.002$) and greater left ($p=0.038$) and right ($p=0.036$) caudate volume compared to controls. There was a positive correlation approaching statistical significance found between emotional lability CPRS-R T-scores and total lifetime use ($p = 0.060$) and age of first use ($p= 0.067$). However, there was no association between caudate volumes and emotional lability.
Conclusions: Results indicate differences in caudate volume between MJ users and non-users. In addition, MJ users demonstrated greater emotional lability which was associated with total MJ exposure. These pilot data suggest that alterations in lability may be secondary to MJ use and independent of caudate volume.
Supported By: Adolescent Brain and Cognitive Development (ABCD) Study award U01DA041134
Keywords: Marijuana, Adolescents, Emotional Lability, Conners' Parent Rating Scale

T205. Moral Cognition in an Alcohol-Cued Context

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Background: Individuals with alcohol use disorder have an attentional bias towards alcohol stimuli that interferes with neural response to emotional stimuli in the presence of alcohol cues. Previous studies also demonstrate chronic and acute alcohol use is associated with a tendency to make utilitarian moral judgments; however, the extent to which alcohol biases may drive the neural response underlying this pattern has not yet been investigated.
Methods: Preliminary analysis was conducted in adult volunteers ($n = 10$) who completed a magnetic resonance imaging protocol. Recent drinking was assessed using the Alcohol Timeline Followback. Participants were administered a Stroop task in a neutral setting and in a simulated bar environment. During scanning, participants viewed images of moral transgressions. These images were presented alongside pictures of alcohol or non-alcoholic objects.
Results: Number of drinks consumed in the last 90 days was related to alcohol cue interference on the Stroop task. During moral processing in the presence of alcohol compared to neutral distractor cues, last 90 days drinking was related to increased hemodynamic response in occipital and precentral regions as well as decreased anterior cingulate engagement in that condition.
Conclusions: Alcohol cues interfered with task performance and moral processing. This interference was more pronounced in individuals with more recent alcohol consumption. The findings suggest that more alcohol use is associated with greater salience of alcohol images and less suppression of attention to those stimuli. Future work will focus on whether this alcohol-cue interference is more pronounced in alcohol use disorder.
Supported By: NIAAA/NIH Intramural Research Program Funding; NIH Clinical Center Bench-to-Bedside Award
Keywords: Alcohol, Brain Imaging, fMRI, Moral Decision-Making, Attention, Stroop

T206. Interoceptive Dysfunction in Stimulant and Opioid Addiction

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Background: Stimulant (cocaine and amphetamine) use disorder (SUD) has been associated with blunted anterior insula activation during interoceptive perturbations, but no studies have examined interoception in opioid use disorder (OUD). To address this knowledge gap, the current study investigated the evidence for interoceptive dysfunction across SUD and OUD.
Methods: Individuals diagnosed with lifetime SUD (n=71), OUD (n=26) or both (SUD+OUD; n=28) were compared to healthy individuals (CTL; n=58) on brain and self-report responses during a visceral interoceptive attention task (VIA) known to elicit insula activation. Participants selectively attended to interoceptive (heart and stomach) and exteroceptive signals during functional magnetic resonance imaging (fMRI). Groups and conditions were compared on: (1) blood-oxygen-level dependent fMRI signals from probabilistic cytoarchitectonic segmentations of the insula (Brainnetome Atlas); and (2) self-reported stimulus intensity. We hypothesized that SUD and OUD would exhibit interoceptive dysfunction via abnormal sensation intensity and insular activation.
Results: SUD demonstrated lower heart-related dorsal agranular/dysgranular insula activation but higher sensation ratings than CTL, whereas OUD displayed lower stomach-related dorsal agranular/dysgranular insula activation but higher sensation ratings than SUD+OUD and CTL (all $p<.03$). Although SUD+OUD did not differ in insula activation from CTL, they endorsed heightened intensity of: (1) heart sensations similar to SUD; and (2) stomach sensations commensurate with OUD (both $p<.03$).
Conclusions: SUD and OUD exhibit an interoceptive mismatch between perceptual and brain responses when attending to drug-relevant physiological signals. Further studies are warranted to determine whether such discrepancies contribute to craving and relapse within these disorders.
Supported By: William K. Warren Foundation
Keywords: Interoception, Substance Use Disorders, Insular Cortex

T207. Poster Withdrawn

T208. Expression of Striatal Fibroblast Growth Factors in Rats After Escalated Oxycodone Self-Administration

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Background: Oxycodone is a semisynthetic opioid prescribed for moderate to severe pain. Recently, addiction to prescribed opioids has been tragic. Better treatment for opioid addiction is needed. To elucidate the neurobiological underpinnings of addiction to opioid drugs, we have used the model of oxycodone self-administration (SA) in rats. In the present study, we investigated the potential role of growth factors in oxycodone SA and withdrawal.
Methods: Rats were trained to self-administer oxycodone for 4 weeks in SA chambers. After the training sessions, rats were withdrawn from oxycodone and then seeking tests were performed at weekly intervals. The rats were euthanized after one month of withdrawal. Their nucleus accumbens and dorsal striata were then used in PCR analyses to measure mRNA of FGF trophic factors.
Results: Rats, given long access to oxycodone, escalated their drug intake and showed incubation of oxycodone seeking during forced abstinence. These rats exhibited significant dose-dependent increases in FGF2 expression in the dorsal striatum but not in the NAc. However, there were significant dose-dependent increases in FGF9 expression in the NAc but not in the dorsal striatum. Moreover, the expression of other FGFs including FGF receptor 2 was impacted in the dorsal striatum but not in the NAc.
Conclusions: Because changes in FGF expression were more prominent in the dorsal striatum, this suggests that striatal FGFs may be more salient to incubation of oxycodone seeking than those in the NAc. These results suggest that manipulation of the FGF signaling pathway might offer an important approach to the treatment of opioid addiction.
Supported By: NIH Intramural Research Program at NIDA
Keywords: Oxycodone, Fibroblast Growth Factor, Incubation Of Drug Seeking, Incubation Of Craving, Dorsal Striatum

T209. The Amygdala miR-137/LSD1 Axis Confers Risk for Anxiety and Alcohol Consumption After Adolescent Alcohol Exposure

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Background: Repeated binge drinking in adolescence increases risk for alcohol use and anxiety disorders in adulthood. Epigenetic mechanisms such as microRNAs (miRNAs) may contribute to this increased risk in crucial affective structures including the amygdala. Here, we investigated the role of miR-137 and its targeting of the epigenetic enzyme lysine-specific demethylase 1 (LSD1) in the adult amygdala after adolescent intermittent ethanol (AIE) exposure.
Methods: Rats were exposed to 2g/kg ethanol (2 days on/off; AIE) or intermittent n-saline (AIS) during postnatal days (PND) 28-41 and allowed to grow to adulthood for analysis of behavior and biochemical measures. Some adult rats were cannulated in the central nucleus of amygdala (CeA) and infused with miR-137 antagomir with or without concurrent Lsd1 siRNA infusion prior to analysis.
Results: AIE increases miR-137 expression, decreases Lsd1 mRNA levels, and decreases LSD1 occupancy at the brain-

derived neurotrophic factor exon IV (Bdnf IV) promoter in the amygdala at adulthood (n=5-6, p<0.001-0.05). Infusion of miR-137 antagomir directly into the CeA rescues AIE-induced alcohol drinking and anxiety-like behaviors. miR-137 antagomir infusion in the CeA also normalizes the decreased Lsd1 expression, decreased LSD1 occupancy, and decreased Bdnf IV expression due to increased H3K9me2 occupancy seen in AIE adult rats (n=6-8, p<0.001-0.05). Finally, co-infusion of Lsd1 siRNA into the CeA prevents the miR-137 antagomir-induced rescue of AIE-induced anxiety-like behaviors (n=6-7, p<0.001-0.05).
Conclusions: Adolescent alcohol exposure leads to increased miR-137 targeting of LSD1 in the amygdala that influences chromatin organization at crucial genes such as BDNF and increases adult anxiety and alcohol consumption.
Supported By: This work was supported by the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health UO1AA-019971 (NADIA project) & P50AA022538 grants to SCP and F30AA024948 to EJK.
Keywords: Amygdala, Alcohol Use Disorder, Adolescence, Epigenetics, microRNA

T210. Increased Peripheral Blood Levels of microRNA-124 and microRNA-181 Among Females With Smoked Cocaine Use Disorder

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[1]Pontifical Catholic of Rio Grande do Sul RS Brazil, [2]University of Kentucky

Background: There is growing emphasis in the field of psychiatry on the need to identify candidate biomarkers to aid in diagnosis and clinical management of addictive disorders. MiRs are small nucleotide sequences with the ability to regulate gene expression at the transcriptomic level. However, the role of miRs as potential biomarkers for addiction is still underexplored. Based on translational and clinical findings, we compared the expression levels of microRNA-124 (miR-124), microRNA-181 (miR-181), and microRNA-212 (miR-212) between a group of females with smoked cocaine use disorder (CUD; n = 30) and a group of healthy females (HC; n = 20).
Methods: Blood expression levels of miR-124, miR-181, and miR-212 in the HC and CUD group were determined by qPCR, using two miRs as endogenous controls (miR-24 and miR-126). Substance use behavior was assessed by self-report using the Addiction Severity Index (ASI-6) and depressive symptoms severity was measured using the Beck Depressive Inventory (BDI-II). Urine screen test was performed to detect cocaine metabolites.
Results: Mir-124 and miR-181 were upregulated in the CUD group (p > 0.01). Furthermore, increased cognitive/affective depression symptoms were identified among a CUD subgroup with the higher miR-181 expression levels (p > 0.05). No significant difference in expression levels was found for miR-212.
Conclusions: Free-blood miR-124 and miR-181 show promise as biomarkers for CUD. Further investigation is needed to elucidate the possible biochemical mechanisms underlying these associations and the effectiveness of these miRs as predictors of depressive symptoms severity in recovering CUD patients.
Supported By: NIH R01DA044859
Keywords: Cocaine Addiction, microRNAs, Depressive Symptoms

T211. Epigenetics of Cocaine Use Disorder: A Collaborative Case-Control Initiative in Blood and Brain

Consuelo Walss-Bass[1], Gabriel Fries[1], Thiago W. Viola[2], Breno Sanvicente-Vieira[2], Joy Schmitz[1], Diego Rovaris[3], Claiton Bau[3], and Rodrigo Grassi-Oliveira[2]

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Background: Recent studies have implicated a role for DNA methylation in modulating addictive behavior. In this study, we present preliminary data where we investigated blood methylome alterations in patients with cocaine use disorder (CUD, N=99) and controls (N=90) in a cohort from the region of Rio Grande do Sul, Brazil, as well as in blood and brain tissue (BA9) from 11 controls and 32 subjects with polysubstance use disorder, including cocaine, from the Houston area.
Methods: Assessments were made using the Infinium MethylationEPIC BeadChip (Illumina) controlling for age, sex, BeadChip, batch, and blood cell type composition, adjusting for false discovery rate.
Results: In the Brazil cohort we identified significant differences in methylation of 34 genes. Of these, S100A8 (comb.p.adj.fdr p=0.015), a toll-like receptor 4 (TLR4) agonist was found by enrichment analyses to be involved in immune system pathways. In addition, we identified accelerated epigenetic aging in CUD subjects compared to controls, and this was correlated with severity of cocaine consumption. Accelerated epigenetic aging was also identified in BA9 of addiction subjects from the Houston cohort and this correlated with epigenetic aging in blood from the same subjects.
Conclusions: Our findings support a role for inflammation pathways in cocaine addiction and may aid in future development of novel treatments for addiction.
Supported By: R01DA044859; R01DA044859-02S1
Keywords: Epigenetic Aging, DNA Methylation, Blood Epigenomics, Human Postmortem Brain, Cocaine Addiction

T212. No Increase in Chronic Pain Among Opioid-Dependent Individuals Randomized to Treatment With Extended-Release Naltrexone Compared to Buprenorphine-Naloxone

Lars Tanum[1], Zill-E-Huma Latif[1], Kristin Solli[1], Arild Opheim[2], Nikolaj Kunoe[3], Jurate Benth[3], and Peter Krajci[4]

[1]Akershus University Hospital, [2]Haukeland University Hospital, [3]University of Oslo, [4]Oslo University Hospital

Background: It is presently unclear whether extended-release naltrexone hydrochloride treatment induces pain or

aggravates existing pain among individuals with opioid use disorders. We assessed changes in pain among individuals receiving treatment with either extended-release naltrexone hydrochloride or buprenorphine-naloxone hydrochloride.
Methods: This randomized prospective open-label clinical study included 143 participants (aged 18–60 years) with opioid dependencies, recruited from outpatient addiction clinics at five urban hospitals in Norway. After in-patient detoxification from opioids, patients were randomized to 12-week treatment with either long-acting naltrexone (380 mg intramuscularly injected every four weeks) or buprenorphine-naloxone (flexible 4–16 mg sublingual doses daily). This phase was followed by a 9-month open-treatment study with the participant's choice of either naltrexone or buprenorphine-naloxone. Changes in pain were assessed every 4 weeks using the Norwegian Short-Form of McGill Pain Questionnaire.
Results: Throughout the study period, we found no increase in mean sensory pain, affective pain, or present pain intensity on the McGill Pain Questionnaire, in either treatment group, including the subgroups of participants with chronic pain. Participants who switched from buprenorphine-naloxone to extended-release naltrexone treatment after week 12 reported no increase in pain intensity during longer-term treatment. Women experienced significantly more affective pain symptoms than men ($p = .01$).
Conclusions: Among individuals with opioid use disorder, switching from daily opioid use to long-acting naltrexone did not induce pain, or aggravate mild-to-moderate chronic pain. The level of pain was not influenced by opioid agonist or antagonist treatment.
Supported By: The Research Council of Norway; University of Oslo
Keywords: Opioid Use Disorder, Long-Acting Naltrexone, Chronic Pain, Buprenorphine

T213. Cannabis Use Disorder and the Response to Threat

Karina Blair[1], Laura Thornton[1], Stuart White[1], Patrick Tyler[1], Emily Leiker[1], Shah Niraj[1], Kimberly Johnson[1], Matthew Dobbertin[1], and **James Blair**[1]

[1]Boys Town National Research Hospital

Background: Two of the most commonly abused substances by adolescents in the United States are alcohol and cannabis, which are associated with adverse medical and psychiatric outcomes throughout the lifespan. Both are assumed to impact the development of emotional processing though findings on the direction of this impact have been mixed. Pre-clinical animal work and some fMRI work with humans has suggested Cannabis Use Disorder and Alcohol Use Disorder (CUD & AUD) are associated with increased threat responsiveness. However, other fMRI has indicated CUD/AUD are associated with diminished threat responsiveness. Here we report on a study examining the relationship of severity of CUD/AUD and threat responsiveness in an adolescent population.
Methods: The study involved 87 adolescents with varying levels of CUD/ AUD symptomatology (N=45>clinical cut-offs for CUD or AUD). They were scanned during a looming threat task that involved negative and neutral human faces or animals, that appeared to be either looming or receding.
Results: Increasing levels of CUD symptomatology were associated with decreased responding to looming stimuli within regions including rostral frontal and fusiform gyrus as well as the amygdala. There were no relationships with AUD symptomatology.
Conclusions: These data indicate that CUD in particular is associated with a decrease in threat responsiveness possibly related to its putative neuro-toxic impact.
Keywords: Cannabis Use Disorder, Alcohol Use Disorder, fMRI, Threat Processing

T214. Sign-Tracking, Goal-Tracking, and Impulsivity in College-Aged Subjects

Jonathan Morrow[1], Ali Gheidi[1], Lora Cope[1], and Sanjeev Billing[1]

[1]University of Michigan

Background: Sign-tracking is a form of Pavlovian conditioned approach to reward-associated cues. Sign-tracking is often contrasted with goal-tracking, which is cue-triggered approach directed toward the location of reward delivery. Interest in sign-tracking has increased in recent years because individual variation in sign-tracking has been shown to predict addiction-like behaviors in animals. Though sign-tracking has been observed in a wide variety of species, including rodents, primates, fish, cephalopods, and insects, there have been very few attempts to document sign-tracking in humans.
Methods: So far twenty-one healthy college students aged 18-25 have been recruited for this study. We directly translated a rat PCA task for human subjects, using a retractable lever as a conditioned stimulus that predicts reward delivery into a different physical location (reward magazine). Physical contacts as well as eye-gaze directed toward the lever or magazine were recorded as outcome measures. Subjects also completed questionnaire-based measurements of trait impulsivity.
Results: There was significant inter-individual variation in the extent to which subjects interacted with the "sign" (lever) or the "goal" (magazine) during lever presentation. The variation was roughly proportional to that seen in animal studies, with 33% of subjects primarily sign-tracking, 38% primarily goal-tracking, and 28% equally engaging in both behaviors. Analysis of impulsivity in a subset of subjects revealed a positive correlation with sign-tracking behavior ($n=11$, $r=0.65$, $p=0.015$).
Conclusions: These experiments demonstrate that sign- and goal-tracking behavior can be measured in humans. Furthermore, inter-individual variation in sign-tracking behavior appears to correlate well with impulsivity, which is a known risk factor for addiction.
Supported By: NIDA 5-P50 DA037844; MCubed 2.0 Classic Cube Project ID 1037
Keywords: Incentive Motivation, Individual Differences, Addiction, Pavlovian Conditioning, Reward Learning

Friday, May 17, 2019

POSTER SESSION 2
5:00 P.M. - 7:00 P.M.

F1. Reward Learning in the Aging Brain: The Impact of Perseveration on Probabilistic Reversal Learning

Lindsay Victoria[1], Matteo Respino[1], and Faith Gunning[1]

[1]Weill Cornell Medicine

Background: Older adults commonly have deficits in reward learning, including difficulty using previous feedback to predict future rewards and modifying behavior to increase rewarding outcomes. We aimed to study the link between behavioral performance on a Probabilistic Reversal Learning (PRL) task, age-related changes in cognition, and neural circuits involved in reward learning.
Methods: 51 older adults (aged 60-85) performed a PRL task during an MRI scan. Participants had to learn to switch responses to maximize rewarding feedback but inhibit erroneous switches to probabilistic error trials. Differences in behavioral performance and neural activation were analyzed as a function of response (switch vs. non-switch) and feedback (positive vs. negative) and correlated with performance on an outside-of-the-scanner Wisconsin Card Sort Task (WCST).
Results: There was a significant interaction of response and feedback on the PRL task ($F(1,50) = 19.07$, $p < 0.001$). WCST performance was associated with age and PRL performance; more WCST perseverative errors correlated with age ($r(49) = -0.27$, $p = 0.05$), more frequent PRL switches ($r(49) = -0.41$, $p = 0.003$), and more PRL rewards ($r(49) = 0.40$, $p = 0.004$). Distinct patterns of fMRI activation were observed for positive vs. negative feedback in frontal reward processing regions, including DMPFC and OFC.
Conclusions: Perseveration on previous outcomes may drive response selection strategies in the younger old, resulting in more switches but also more rewards. Our findings have implications for understanding the link between cognition, neural abnormalities, and reward learning deficits in healthy aging, towards the goal of improving reward learning in older adults.
Supported By: NIMH R01MH097735
Keywords: Aging, Brain Imaging, fMRI, Reward Learning, Probabilistic Reward

F2. White Matter Lesions are Common in Midlife and Associated With Cognitive Decline

Tracy d'Arbeloff[1], Maxwell Elliott[1], Annchen Knodt[1], Tracy Melzer[2], Ross Keenan[2], David Ireland[3], Sandhya Ramrakha[3], Richie Poulton[3], Avshalom Caspi[4], Terrie Moffitt[4], and Ahmad Hariri[1]

[1]Duke University, [2]New Zealand Brain Research Institute, [3]University of Otago, [4]King's College London; Duke University

Background: As the brain ages, it begins to accrue small microbleeds and lesions in white matter that are readily detectable as white matter hyperintensities (WMH) using FLAIR MRI. Accumulation of WMH is associated with multiple dementia risk factors, including age, hypertension, stroke, and brain atrophy. Longitudinal studies have reported that the spread of WMH coincides with age-related cognitive decline in general populations of older adults. However, the age at which WMH begin to signal cognitive deficits is still unclear.
Methods: We examined links between WMH and cognition in midlife participants from the Dunedin Study (n=850, 50% male), a population-representative birth cohort born in 1972-1973 in Dunedin, New Zealand. WMH volumes were first identified and extracted from FLAIR images using the fully automated pipeline UBO and were then entered into analyses with adult IQ and childhood IQ measures.
Results: We found that WMH were common at age 45 across the entire sample, and correlated with adult IQ ($\beta = -.17$, $p < .001$). In addition, those individuals with greater WMH volume already showed cognitive decline from childhood to midlife ($\beta = -.07$, $p = .002$).
Conclusions: This suggests that WMH may index risk for dementia already measurable in midlife, and that individuals with more WMH in midlife may be at increased risk for further brain degradation leading to small vessel disease and dementia.
Supported By: The US-National Institute of Aging grant R01AG032282
the UK Medical Research Council grant MR/P005918/1.
US NIA 1R01AG049789: the brain imaging grant "Neural signatures of healthy and unhealthy aging"
The Jacob's Foundation
Keywords: White Matter Hyperintensities, Brain Aging, Cognition, Dementia

F3. Changes in Theta but not Alpha Modulation are Associated With Working Memory Impairments in Alzheimer's Dementia and Mild Cognitive Impairment

Michelle Goodman[1], Reza Zomorrodi[2], Sanjeev Kumar[2], Mera Barr[2], Zafiris Daskalakis[2], Daniel Blumberger[2], Corinne Fischer[3], Alastair Flint[4], Linda Mah[5], Nathan Herrmann[6], Bruce Pollock[2], Christopher Bowie[2], Benoit Mulsant[2], and Tarek Rajji[2]

[1]University of Toronto, [2]Centre for Addiction and Mental Health, [3]St. Michael's Hospital, [4]University Health Network, [5]Baycrest Health Sciences Centre, [6]Sunnybrook Health Sciences Centre

Background: Several studies have identified that neural oscillations play a key role in the functioning of working memory. However, the nature of aberrant oscillatory activity underlying working memory impairments in Alzheimer's dementia (AD) and mild cognitive impairment (MCI) remains largely unexplored. Individuals with AD and MCI display structural alterations in brain regions and pathways involved in working memory processes. Thus, we hypothesized that these individuals would also display altered oscillatory activity during memory activation.
Methods: We recorded electroencephalographic (EEG) activity during the N-back working memory task in three groups:

individuals with AD (n = 29) or MCI (n = 100), and healthy controls (HCs; n = 40). The modulation of theta (4-7 Hz) and alpha (7.5-12 Hz) EEG activity was measured as a ratio of post stimulus power to pre-stimulus power, during correct and incorrect responses. We also assessed the relationship between change in oscillatory power and working memory performance.
Results: Compared to HCs, the AD group demonstrated lower working memory accuracy and a smaller increase in theta power during correct responses on the 2-back condition; the MCI group demonstrated a smaller increase in theta power for correct responses on the 3-back condition. Theta modulation, but not alpha modulation, predicted working memory performance in the three groups for all conditions.
Conclusions: Taken together, these behavioral and electrophysiological results suggest that, in addition to impairments in working memory performance, the modulation of theta, but not alpha power, is impaired in AD and MCI.
Supported By: Brain Canada through the Canada Brain Research Fund, Health Canada and the Chagnon Family as well as the W. Garfield Weston Foundation (#RR120070)
Keywords: Alzheimer's Disease, Mild Cognitive Impairment, Electroencephalography (EEG), Working Memory

F4. Accelerated Brain Aging in Non-Demented Patients With End-Stage Renal Disease

Yi-Fang Chuang[1], Hsiu-Hui Tsai[2], Yen-Jun Lai[2], and Yen-Ling Chiu[2]

[1]National Yang-Ming University, [2]Far Eastern Memorial Hospital

Background: Chronic kidney disease exhibits a premature aging phenotype in many different organ systems, including the brain. Nevertheless, a comprehensive characterization of brain aging in non-demented patients with end-stage renal disease (ESRD) is lacking and it remains unclear if the collective changes of cognitive function and brain structures in ESRD is compatible with premature aging.
Methods: We compared 56 non-demented, independently living dialysis patients (mean age 59.4 ± 11.0 years; mean dialysis vintage of 5.9 years) and 60 non-dialysis controls on a battery of neuropsychological tests, brain MRI T1 imaging and diffusion tensor imaging. Participants with diagnosis of dementia, Mini-Mental State Examination < 24, medical history of stroke, or recent hospitalization within 1 month were excluded.
Results: Dialysis patients showed significantly worse performance in attention/information processing speed and executive function adjusted for age, sex, education, diabetes and depression. Reduced total brain volume and subcortical volume including hippocampus were found in dialysis patients. Vertex-wise analysis showed cortical thinning in middle frontal, lateral occipital and precuneus region. Furthermore, decreased white matter integrity was found primarily in bilateral anterior thalamic tract, fronto-occipital fasciculus, forceps minor and uncinate tract after correction for multiple comparisons.
Conclusions: Overall, differences in cognitive function, cortical volumes/thickness and white matter integrity associated with dialysis are also cognitive domains and brain structure changes associated with normal aging. In other words, non-demented, independently living dialysis patients present an accelerated brain aging phenotype even after taking into account effects of age, diabetes and depression.
Keywords: Neuroimaging, Neurocognition, Brain Aging

F5. Klotho, PTSD, and Advanced Cellular Age: Spinning the Thread of Life

Erika Wolf[1], Filomene Morrison[2], Danielle Sullivan[3], Mark Logue[3], Rachel Guetta[1], Annjanette Stone[4], Steven Schichman[4], Regina McGlinchey[5], William Milberg[5], Traumatic Stress Brain Study Group[6], Bertrand Huber[2], and Mark Miller[7]

[1]National Center for PTSD at VA Boston Healthcare System, [2]Boston University & VA Boston Healthcare System, [3]National Center for PTSD at VA Boston Healthcare System & Boston University School of Medicine, [4]Central Arkansas Veterans Healthcare System, [5]Harvard Medical School & VA Boston Healthcare System, [6]National Center for PTSD, [7]Boston University & VA Boston Healthcare System, National Center for PTSD

Background: Longevity gene klotho (KL) is named for the Greek goddess who spins the thread of time; it predicts lifespan, cognition, and cardiovascular health. We examined if KL influenced the association between PTSD and multiple biomarkers of cellular aging (epigenetic age, neural integrity, metabolic/inflammatory markers, KL expression).
Methods: The cohorts included 309 veterans and 83 postmortem cortical samples. Subjects underwent psychodiagnostic interviews, blood draw, and diffusion tensor imaging. Brain bank data were determined via medical records, next-of-kin interviews, and medical examiner and neuropathological exams. DNA was extracted from ventromedial and dorsolateral (DLPFC) prefrontal cortex and motor cortex; KL expression was derived from DLPFC via qPCR.
Results: After multiple testing correction, two SNPs interacted with PTSD in the veteran sample to predict advanced epigenetic age (peak p-corrected = .044). The peak SNP (rs9315202) interacted with PTSD to predict C-reactive protein (p = .049), and integrity of white matter tracts (right cingulum bundle/cingulate gyrus: pcorrected = .005; right fornix/stria terminalis: p-corrected = .035). The SNP predicted metabolic pathology (p = .015). Effects were accentuated in older subjects. In the brain, the SNP interacted with PTSD to predict advanced epigenetic age in older subjects in motor cortex (p = .004); a distinct SNP (rs495392) was nominally associated with DLPFC KL expression (p-corrected = .044).
Conclusions: The risk KL variant accentuated the pathological effects of PTSD on cellular aging across multiple peripheral and central biomarkers, with effects strengthening with age. Results carry implications for determining risk for accelerated aging and identifying new molecular targets for reducing its pace.
Supported By: This work was supported by the National Institute on Aging [grant number R03AG051877 (EJW)], United States (U.S.) Department of Veterans Affairs Clinical

Sciences R&D (CSRD) Service Merit Review Award [grant number I01 CX-001276-01 (EJW)], National Institute of Mental Health [grant number 5T32MH019836-17 (FGM)]; VA CSR&D Career Development Award [grant number 1 IK2 CX001772-01 (DRS)]; VA BLR&D Merit Award [grant number 1I01BX003477-01 (MWL)]; CSR&D Merit Award [I01-CX001038 (TDS)]; Alzheimer's Association Research Fellowship [AARF-17-529888 (JDC)]; Veterans Affairs Biorepository (BX002466); NIH/NINDS [grant number P30AG13846 (BRH)]; NIH/NIA [RF1AG054156, R56AG057768 (TDS)]; the National Center for PTSD. The contents of this abstract do not represent the views of the U.S. Department of Veterans Affairs, the National Institutes of Health, or the United States Government.
Keywords: Epigenetics, Genetics, Imaging genetics, Accelerated Aging, PTSD - Posttraumatic Stress Disorder

F6. Longitudinal Mid-Life Stroke Risk Predicts Brain Structure in the Aging Whitehall II Cohort

Eniko Zsoldos[1], Abda Mahmood[1], Sana Suri[1], Nicola Filippini[1], Archana Singh-Manoux[2], Mika Kivimaki[2], Clare Mackay[1], and Klaus P. Ebmeier[1]

[1]University of Oxford, [2]University College London

Background: Multi-measure cardiovascular and stroke risk scores predict gray matter volume reduction and white matter changes. We aimed to establish whether: 1) there is an association between Framingham stroke risk (FSRS) in mid-life across five phases (P) and reduced structural brain integrity beyond the effects of chronological or biological age, and 2) the predicted effects on brain structure reduction in older age are the same 5 (P9), 10 (P7), 15 (P5) and 22 (P3) years before as at the time of scan (P11).
Methods: We analysed T1 and dMRI scans from 566 Whitehall II participants (age 69.9±5.2yrs, Male=450). Negative correlation between FSRS and gray matter density (GMD) and fractional anisotropy (FA) at each phase was assessed using FSL-VBM and TBSS. Correlations with FSRS at P11 including P3−P9 as regressors were also run (multiple comparisons corrected, significance level TFCE $p<.05$).
Results: Each FSRS predicted widespread GMD and FA reduction. Smaller GMD was present in right medial temporal lobe (MTL) and gyrus after removing confounders. FSRS at P11, controlling for P9 didn't predict GMD reduction. Controlling for FSRS at P3-P7 predicted GMD reduction in MTL. FSRS at P11 controlling for P3-P9 predicted widespread FA reduction.
Conclusions: FSRS predicts reduced brain integrity 22yrs before the scan, beyond chronological and biological age. Additional GMD reduction is predicted in later life compared to 10-22yrs before the scan in the hippocampus, due to its plasticity, but not in posterior/cortical areas. FA associations are significantly different in four phases compared to in later life. They become more widespread the earlier the FSRS is.
Supported By: UK Medical Research Council, HDH Wills 1965 Charitable Trust
Keywords: Biological Aging, Brain Imaging, Stroke, Prospective Cohort, Brain Aging

F7. Externalizing Behaviors in Posttraumatic Stress Disorder (PTSD) are Related to the Severity of Sleep-Related Breathing Disorder (SRBD) and Indices of Hyperarousal

Madhulika Gupta[1] and Angelica Sheridan[1]

[1]University of Western Ontario

Background: Externalizing behaviors (EB) such as irritable behavior and angry outbursts (DSM-5 criterionE.1) are one of the indices of alterations of arousal in PTSD. Sleep disturbances have been reported to be a mediating factor between PTSD severity and EB. To our knowledge there are no reported studies of polysomnographic correlates of daytime EB in PTSD.
Methods: 40 consenting civilian PTSD patients (38 female; mean±SD age: 44.60±12.73 years) underwent ≥1 nights of Level 3 polysomnography (WatchPAT200; Itamar Medical, Israel) and completed a battery of instruments as part of a larger study of psychosomatic factors in PTSD. Participants completed the Hostility subscale of the Brief Symptom Inventory (Derogatis 1975)[Hostility(BSI)](which addresses 5 EB-related items including easy irritability, uncontrollable temper outbursts, urges to beat or harm someone, urges to break or smash things, and frequent arguments), the Insomnia Severity Index (ISI), Beck Suicide Scale (BSS) and PTSD Checklist for DSM-5 (PCL-5).
Results: Hostility (BSI) correlated directly ($r=0.677$, $p<0.001$) with PCL-5 scores, ISI ($r= 0.443$, $p<0.001$) and BSS ($r=0.515$, $p<0.001$), and the respiratory disturbance index (RDI)($r=0.619$, $p<0.001$), and negatively with sleep efficiency ($r=-0.395$,$p=0.012$). Multiple regression analysis using Hostility(BSI) as dependent variable and age, ISI, BSS, PCL-5 clusters and RDI as independent variables revealed age ($\beta=-0.23$, $t=-2.237$, $p=0.032$),PCL-5 ClusterE (measuring hyperarousal) ($\beta=0.385$, $t=3.394$, $p=0.002$) and RDI ($\beta=0.506$, $t=4.451$, $p<0.001$) remained significant predictors of Hostility(BSI).
Conclusions: EB in PTSD was directly related to severity of sleep-related breathing disorder, a relationship that has not been previously reported. EB was also directly related to both daytime and sleep-related indices of hyperarousal.
Keywords: PTSD - Posttraumatic Stress Disorder, Obstructive Sleep Apnea, Hostility, Aggression, Hyperarousal

F8. Closed-Loop Phase-Locked Electrical Stimulation Alters Low Frequency Coherence in a Fear Regulation Circuit

Meng-chen Lo[1], Ethan Blackwood[1], and Alik S. Widge[1]

[1]University of Minnesota

Background: Brain connectivity may depend on the oscillatory synchrony of local field potential (LFP) between regions. However, clinical exploitation of this knowledge is limited by the lack of established paradigms to manipulate brain synchrony. For fear-related disorders, fronto-amygdalar connections are particularly important. This work describes a method

to alter oscillatory synchrony (coherence) in fronto-amygdalar circuits in rodents.
Methods: Electrodes were implanted into the infralimbic cortex (IL) and the basolateral amygdala (BLA) of Long-Evans rats (n=3). We monitored IL theta-band (4-8 Hz) phase real-time for 30 minutes and delivered phase-locked single electrical pulses (100 μA and 90 μs pulse width) to BLA when IL phase was at 180°. LFPs were recorded from both IL and BLA 5 minutes before (baseline) and after the stimulation session. The coherence change over baseline was calculated.
Results: The stimulation method achieved a mean error of -0.42° from the targeted 180° phase, with a circular error variance of 0.6796 for stimulation phase accuracy (n=7). We outperformed the best published algorithm with a 10-fold improvement on mean error and 25% reduction on circular variance. The coherence between IL and BLA increased immediately post-stimulation (z-score =3) in the theta frequency band and lasted long for up to 90 minutes post-stimulation with an averaged z-score of 1 over baseline.
Conclusions: We demonstrated a method to alter brain oscillatory synchrony. This may provide a new technique to study brain networks. We intend to apply this to alter anxiety-related behaviors, which would provide evidence that brain synchrony is a key communicative mechanism.
Supported By: R21
Keywords: Brain Stimulation, Neural Oscillations, Fear And Anxiety, Mental Disorders, Neuromodulation

F9. A Novel Orally Active Triple Reuptake Inhibitor for the Treatment of Post-Traumatic Stress Disorder (PTSD): D-578 Attenuates Abnormal Fear Behavior in a Rodent Model of Traumatic Stress

Michael Lisieski[1], Arman Harutyunyan[1], Banibrata Das[2], Israel Liberzon[3], Frank Bymaster[4], **Timothy Hsu**[4], Maarten Reith[5], Shane. Perrine[1], and Aloke Dutta[2]

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Background: Post-traumatic stress disorder (PTSD) is a common disorder which causes marked functional impairment. Currently, the approved drugs for the pharmacotherapy of PTSD are two moderately effective SSRIs. Studies of traumatic stress exposure have shown that serotonin (5-HT), norepinephrine (NE) and dopamine (DA) systems are dysfunctional in PTSD and modulation of these monoamines could result in improved PTSD pharmacotherapy. Therefore, we have investigated the triple reuptake inhibitor D-578 in a model of traumatic stress. D-578 inhibits NE, 5-HT, and DA transporters with Ki values of 6, 21, and 30 nM, respectively, and has low affinity for CNS receptors.
Methods: The effects of D-578 and paroxetine were evaluated in the single prolonged stress (SPS) model of PTSD by exposing rats serially to SPS (restraint, forced swim, ether). Eight days later, rats began a cued fear conditioning procedure, which consisted of acquisition (day 8), extinction (day 9), and extinction retention (day 10). Rats were treated with vehicle, paroxetine, (5 mg/kg), or D-578 (10 mg/kg) 90 min prior to each session.
Results: SPS had no effect on the acquisition of conditioned fear or extinction behavior compared to sham treatment, but impaired the retention of extinction learning. D-578, but not paroxetine, attenuated the extinction-retention deficit induced by SPS. Neither drug altered acquisition or extinction learning.
Conclusions: These findings suggest that the D-578 has greater efficacy in normalizing traumatic-stress-induced extinction-retention learning in a model for PTSD compared to paroxetine and support testing of this agent for the pharmacotherapy of PTSD.
Supported By: Supported by NIH/ NIMH MH084888 (AKD)
Keywords: Stress Exposure, PTSD - Posttraumatic Stress Disorder, PTSD Treatment, Triple Reuptake Inhibitor, Rat Model

F10. Cue-Induced Conditioned Fear Learning Requires Orexin Receptor 1 Signaling in the Central Amygdala

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Background: Orexins (OX)/hypocretins are excitatory neuropeptides with canonical function in regulation of wakefulness. The neuropeptides have also been implicated in arousal, energy homeostasis, anxiety, and most recently in modulation of fear learning. OX neurons that originate in the perifornical hypothalamus (PeF) send projections to the amygdala, a region critical in fear learning and fear expression, but the specific functions of OX neurotransmission within the amygdala are not well understood.
Methods: We utilized rat brain slice electrophysiology, chemogenetic, confocal microscopy, pharmacology and behavior to elucidate functional connectivity between PeF OX projections and central amygdala (CeA) neurons and to explore specific mechanisms underlying OX neurotransmission in the CeA.
Results: Within the amygdala, the highest density of OX-positive fibers was detected in the CeA. We show that OX induces postsynaptic depolarization of medial CeA neurons that is mediated by OX receptor 1 (OXR1) but not OX receptor 2 (OXR2). We further characterized the mechanism of CeA depolarization by OX as phospholipase C (PLC)- and sodium-calcium exchanger (NCX)- dependent. Selective chemogenetic stimulation of OX PeF fibers recapitulated OXR1 dependent depolarization of CeA neurons. We also observed that OXR1 activity modified presynaptic release of glutamate within the CeA. Finally, either systemic or intra-CeA perfusion of OXR1 antagonist reduced the expression of cue-induced conditioned fear.
Conclusions: Our results suggest that the PeF-CeA orexinergic pathway can modulate cue-induced conditioned fear

through a signal transduction mechanism involving PLC and NCX activity and that selective OXR1 antagonism may be a putative treatment for fear-related disorders.
Supported By: NIMH R01 MH065702, MH052619, K01 AG044466
Keywords: Orexin, Central Nucleus of the Amygdala, Glutamate, Fear And Anxiety, Lateral Hypothalamus

F11. Molecular Markers of Fear Learning in Brain and Blood: Focus on Doublecortin (DCX)

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Background: Although considerable evidence implicates doublecortin (DCX) in neurogenesis and neural development, little is known about its function in non-neurogenic adult brain regions. The current study seeks first to explore whether fear learning is associated with altered amygdala (AMY) DCX expression and, second, to assess the utility of any such changes as predictive markers of fear learning.
Methods: C57BL/6 mice underwent associative fear conditioning in which tones were paired with foot shock, followed by fear expression, extinction, and/or generalization testing. AMY tissue and blood collected after sacrifice was employed for immunoblotting ($n \geq 8$), qRT-PCR ($n \geq 8$), or RNA sequencing ($n \geq 4$).
Results: Fear learning was found to modulate AMY DCX protein levels; by 24hrs after acquisition ($p = 0.0066$) or expression testing ($p = 0.012$) animals that displayed more freezing to tones had higher DCX than low-freezing animals. High-DCX animals also displayed a greater tendency to associate unpaired tones with shocks ($p = 0.003$) and to generalize freezing to novel tones ($p < 0.0001$). Analyses of RNA from brain and blood further revealed multiple genes whose expression in blood 2hrs post-fear learning were correlated with both AMY DCX RNA and with the extent of freezing displayed during fear acquisition ($p < 0.005$) and expression testing ($p < 0.01$).
Conclusions: Individual differences in fear acquisition, expression, and generalization are reflected in subsequent changes in the expression of amygdala DCX. Candidate biomarkers in blood whose expression profiles mirror DCX's may prove useful for predicting individual responses to fear learning.
Supported By: NIH, NARSAD, CIHR
Keywords: Fear Learning, Individual Differences, Molecular Biomarkers, Amygdala, Doublecortin

F12. TBS-Modulated Anger in Veterans With PTSD

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Background: Anger is recognized as an important clinical feature of posttraumatic stress disorder (PTSD) that can hamper recovery. Disruptions in brain regions associated with explicit emotion regulation, including the dorsolateral prefrontal cortex (dlPFC), are observed in PTSD. Transcranial magnetic stimulation (TMS) aims to improve PTSD-associated symptoms through non-invasive neural modulation. Here we examine whether intermittent theta-burst stimulation (iTBS), a novel TMS protocol, reduces self-reported anger in Veterans with PTSD.
Methods: Fifty Veterans with chronic PTSD received 10 daily sessions of sham-controlled, double-blind iTBS (1800 pulses/session) targeting the right dlPFC (intent-to-treat sample = 25 per group). All participants who completed the double-blind phase, were offered the option to receive another 10 sessions of unblinded iTBS. Participants completed the Dimensions of Anger Reactions Scale at baseline, midpoint and endpoint of both double-blind and open-label phases, and at one-month follow-up.
Results: Analyses revealed a significant main effect of self-reported anger across all six time points ($p=0.001$). During the double-blind phase only, participants randomized to active iTBS reported less anger at midpoint ($p=0.01$) and a trend towards less anger at endpoint ($p=0.06$) compared to participants randomized to sham. Participants initially randomized to sham showed a significant reduction in self-report anger once they received active iTBS during the open-label phase ($p=0.002$). Mediation analyses suggest that the reduction in anger occur in tandem with reductions in depression due to iTBS.
Conclusions: These results suggest that iTBS −through reductions in depression− reduces anger in Veterans with PTSD. Future studies focused on granular level anger outcomes are needed.
Supported By: VA RR&D SPiRE Award
Keywords: PTSD - Posttraumatic Stress Disorder, Noninvasive Brain Stimulation, Anger, Depression, Clinical Trials

F13. Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of the Selective Orexin-1 Receptor Antagonist JNJ-61393215: Results From the First-In-Human and Multiple Ascending Dose Studies

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Background: The role of orexin and orexin-1 receptors (OX1R) in the pathophysiology of several psychiatric disorders such as panic, anxiety and substance abuse is emerging. Here we report the safety, tolerability, pharmacokinetic and pharmacodynamic properties of the OX1R antagonist JNJ-61393215 in first-in-human single ascending dose (SAD) and multiple ascending dose (MAD) studies.

Methods: In the SAD study the pharmacokinetics and pharmacodynamics of JNJ 61393215 was evaluated in 8 cohorts of healthy male subjects after administration of single oral doses of JNJ 61393215 from 1 to 90 mg. In the MAD study, 32 healthy subjects in 4 cohorts received daily dosing of JNJ-61393215 up to 7 days, from 5 to 90 mg.
Results: JNJ-61393215 was safe and well tolerated both in the SAD and the MAD studies. The most common adverse events observed were somnolence (18.6%) and headache (18.6%). The compound did not produce any pharmacodynamic effects, consistent with preclinical data that show no significant behavioral effects in naïve/unchallenged animals. The Cmax and AUC of JNJ-61393215 increased proportionally with doses up to a single dose of 30 mg and less than proportionally with dose above 45 mg. Upon repeated dosing the accumulation (AUC) was low and decreased with dose from 136% at 5 mg QD to 103% at 90 mg. CSF levels confirmed central penetration.
Conclusions: These results support the safety and tolerability of the selective OX1R antagonist JNJ-61393215 in humans. The efficacy of JNJ-61393215 as a potential treatment for mood and anxiety disorders will be evaluated in future studies in patients.
Supported By: Janssen R&D
Keywords: Orexin Receptor, Anxiety Disorder, Pharmaceutical Industry, Pharmacokinetics

F14. Neurostimulation Enhanced Cognitive Restructuring: A Proof of Concept Study

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Background: Despite an explosion of research on the neurobiological underpinnings of emotion and psychopathology, there have been few attempts to advance behavioral treatments with neuroscience. Adults with several different psychiatric disorders have difficulty managing negative emotions, a problem traced back to impairments in the fronto-limbic brain circuitry. Therefore, I will present how repetitive transcranial magnetic stimulation(rTMS) and cognitive restructuring (CR) can be combined in a one-session intervention for emotional dysregulation (ED).
Methods: Fourty five transdiagnostic adults were enrolled in a pilot randomized double-blind controlled trial assessing neuromodulation-enhanced CR. Participants underwent real or sham high frequency rTMS administered over the dlPFC while practicing reducing negative emotions with CR. Multi-method data collection occurred during the intervention, at 1-week and 1-month.
Results: Included participants were primarily white (61.7%), heterosexual (66%), and female (76.6%), with mixed clinical characteristics. Preliminary analyses show a trend for significance for right-rTMS to enhance heart rate variability (HRV), a marker of emotion regulation($p=.08$). Controlling for baseline HRV, regulation HRV predicts changes in ED at 1-week follow-up($p=.04$) which in turn predicts changes in psychopathology at 1-month follow-up ($p=.0001$). All participants improved significantly in their ED and psychopathology following the intervention. Participants rated the intervention as moderately acceptable (average=5.04, SD=3.2), and 65% would recommend the therapy to a friend.
Conclusions: This study highlights that combining TMS and psychotherapy is feasible and acceptable. Participants improve over time and there is some preliminary evidence that stimulation may enhance the effectiveness of psychotherapy. There were no differences between active and sham stimulation suggesting that additional work is needed to refine the intervention.
Supported By: NARSAD
Keywords: HF-rTMS, DLPFC, Cognitive Reappraisal, Transdiagnostic, Emotional Dysregulation

F15. mOFC Volume Associated With Sub-Syndrome PTSD in US Veterans

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Background: PTSD is associated with both intensity and frequency of traumatic events. Previous investigations reported brain-based changes associated with PTSD sub-syndromes. Regions of interest examined in participants diagnosed with PTSD have included the orbitofrontal cortex (OFC), which is involved in emotional and behavioral inhibition. The present pilot study examined how PTSD criterion (Re-experiencing, Avoidance, Negative Thinking, and Arousal) related to orbitofrontal cortex (OFC) volume.
Methods: Participants included 47 trauma-exposed veterans between ages 18-54. PTSD was diagnosed based on a structured clinical interview (SCID). Trauma scores were summed from a derived scale measuring intensity and frequency of each symptom. Structural imaging data were collected on a 3T Siemens Verio scanner and analyzed using Freesurfer.
Results: Decreased volume in the Left Medial OFC was associated with Negative Thinking ($r=.31$, $p<.05$) and Arousal ($r=.32$, $p<.05$). In contrast, there was no relationship between the Left Medial OFC and Avoidance ($r=-.09$, $p>.05$), or Left Medial OCF and Re-experiencing ($r=.26$, $p>.05$). There were no correlations between trauma scores and the Right Medial OFC.
Conclusions: When both intensity and frequency of symptoms are considered, veterans with PTSD showed a significant association between negative thinking and arousal and left medial OFC volume. Given the high incidence of OFC damage with TBI, it would be important to consider changes in this region as they relate to PTSD symptomology.

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Keywords: PTSD - Posttraumatic Stress Disorder, US Veterans, Volumetric Neuroimaging

F16. Aberrant Causal Reasoning in Obsessive-Compulsive Disorder (OCD)

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Background: OCD entails maladaptive repetitive behaviors suggesting erroneous causal beliefs. Causal reasoning is complex and relies on specific contingency learning (SCL) and the ability to represent abstract outcomes (outcome representation; OR), among other processes. The orbitofrontal cortex (OFC) has been consistently implicated in both OCD and causal reasoning. However, its specific role remains unclear. We hypothesize that SCL is impaired in OCD, but OR is intact.
Methods: We have developed a paradigm that disambiguates SCL and OR. Subjects make a series of binary choices between abstract cues. Valued cues result in rewards that vary across three blocks: specific in block 1, random in block 2, and uniform in block 3. SCL and OR deficits lead to dissociable predictions in probe trials, which pair previously rewarded cues from different blocks without feedback. In initial studies, 8 patients with OCD and 5 controls completed this behavioral task, and 3 healthy controls completed the task with neuroimaging. Behavioral and neuroimaging data collection are ongoing.
Results: These initial behavioral data support our hypothesis that SCL is specifically impaired in OCD, while OR is intact. Preliminary neuroimaging data demonstrate lOFC activation during SCL, consistent with recent findings. Behavioral and neuroimaging data collection are ongoing.
Conclusions: We dissociate discrete component processes of causal learning in OCD; initial data suggest a specific deficit in SCL. Confirmation that SCL and corresponding lOFC recruitment are deficient in OCD would represent an important advance and may provide the foundation for the future development of novel, targeted remediation strategies.
Supported By: 1 K23 MH115206
Keywords: Obsessive Compulsive Disorder (OCD), Causal Reasoning, Orbital Frontal Cortex, Cognitive Neuroscience, Functional Neuroimaging

F17. Failure to Extinguish Fear in Trauma-Exposed Children With a Common Variant in the Cannabinoid Receptor 1 Gene

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Background: Deficits in fear extinction are implicated in the pathophysiology of anxiety disorders such as posttraumatic stress disorder. Recent studies suggest that signaling via the cannabinoid receptor 1 (CB1R) is essential for fear extinction. A common variant in the gene encoding the CB1R (CNR1) has been linked to poor extinction learning in adults. However, anxiety disorders typically begin in childhood. The present study examines the effect of CNR1 on fear extinction learning and its later recall in children.
Methods: 37 children (6-11 years) underwent a novel two-day fear extinction learning and memory recall experiment in virtual reality. Skin conductance responses (SCRs) were collected and genotyping was performed for CNR1 (rs2180619). Of note, a subset of children reported previous exposure to trauma (e.g., violence, medical).
Results: Overall, there were no group differences in extinction learning or subsequent memory recall (p's $>$ 0.05). However, within the trauma-exposed group, children with the AA genotype showed poorer extinction learning and extinction recall compared to C allele carriers, evidenced by higher SCRs to an extinguished cue ($p = 0.05$).
Conclusions: Genetic differences in the endocannabinoid system may contribute to a reduced ability of to extinguish learned fear among trauma-exposed children. Failure to extinguish may increase risk of anxiety.
Keywords: Fear Conditioning, Endocannabinoid, Anxiety

F18. Sex Differences in Stress-Induced Reward Processing in Major Depressive Disorder (MDD)

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Background: Women are at higher risk to develop Major Depressive Disorder (MDD) than men. This has been associated with sex differences in stress reactivity and reward processing, with further investigations of the underlying neurobiological mechanisms still ongoing.
Methods: Thirty-five healthy controls (HC; 17F/18M) and 33 individuals with MDD (16F/17M) completed two visits: one including a stress version and the other including a no-stress version of the Maastricht Acute Stress Test (MAST). Post-MAST, participants were scanned during a Monetary Incentive Delay (MID) task, from which reaction time (RT) and brain activity in VTA, hypothalamus, striatum, amygdala, OFC, and ventral ACC during anticipation and receipt of monetary gains were derived. Plasma cortisol levels were collected pre- and post-MAST.
Results: Reaction time (RT) during gain vs. neutral trials did not differ between men and women in either group. Analysis of cortisol data yielded a Visit x Sex interaction ($p<0.01$), with men exhibiting higher cortisol than women in response to stress. Region of interest analyses showed that when anticipating monetary gains during stress, HC men exhibited higher activity than women in the amygdala [p(FWE)=0.05], while women showed trend-level higher activity compared to men in

ventral ACC [p(FWE)=0.06]. There was a trend towards higher activity in amygdala [p(FWE)=0.09] during receipt of monetary gains in MDD women vs. men.
Conclusions: These preliminary results suggest sex-related patterns of stress reactivity and reward processing at physiological and neurobiological levels. Results from the larger study will examine potential differences in neural circuitry that may mediate sex differences in MDD.
Supported By: NIH
Keywords: Major Depressive Disorder (MDD), Sex Differences, Reward, Cortisol, Stress

F19. Motor Preparation in Obsessive-Compulsive Disorder: An LRP Study

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Background: Obsessive-Compulsive Disorder (OCD) patients are known to have various functional impairments in prefrontal and motor areas. For instance, larger readiness potential has been previously found among OCD patients. Here, we propose to use lateralized readiness potentials (LRP) to assess motor preparation in OCD patients. In a stimulus-response compatibility task, LRPs are used to evaluate the motor preparation processes when the compatibility between a stimulus and the expected response varies. Consistent with the literature, we hypothesized that OCD patients would show larger Gratton dip (activation of the incompatible response) and LRP peak, as well as a delayed LRP onset.
Methods: Nineteen OCD patients were matched on age and sex to 19 healthy controls. Continuous EEG was recorded in all participants during a stimulus-response compatibility task. EEG from electrodes C3 and C4 was then averaged into stimulus-locked LRPs. We compared both groups on various LRP measures, such as the LRP onset, the Gratton dip, and the maximum LRP peak.
Results: OCD patients showed significantly larger LRP peak than healthy controls [$F(1,36) = 8.60$, $p = .006$, $d = .95$], as well as larger Gratton [$t(27.90) = 2.08$, $p = .047$, $d = .68$]. However, there was no group difference regarding LRP onset.
Conclusions: Among OCD patients, it seems that motor regions are overactive during motor preparation. This is true for incorrect responses that are aborted before execution and responses that are truly executed. These results suggest that regulation of sensorimotor activity should be addressed in the treatment of OCD.
Supported By: Canadian Institutes of Health Research (#93556)
Fonds de Recherche du Québec - Santé (#20573)
Keywords: Obsessive-Compulsive Disorder, Electrophysiology, Event-Related Potentials, Lateralized Readiness Potentials, Motor Preparation

F20. Global Functional Network Modularity Facilitates Responding in Threat-Valenced Spatial Cueing

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Background: Preferential orienting to threatening stimuli is a common phenotype of posttraumatic stress disorder (PTSD) and is potentially mediated by functional brain organization. In fact, research suggests that increased brain network modularity (Q), a metric of brain network integration and segregation, may facilitate orienting to basic cues, which may be disadvantageous in PTSD.
Methods: This study investigated the interaction of neural network organization with spatial orienting in the context of threatening images. Here, 72 subjects (61 with PTSD, 11 healthy controls) underwent resting-state functional MRI (rs-fMRI) and completed a version of the Posner spatial cueing task (SCT) where the target was preceded by a threatening- or neutral-valenced image. rs-fMRI data were analyzed using a graph-network approach, where modularity was maximized using Louvain community detection. SCT data were modeled using a mixed linear effects model to gauge the effects of Q, PTSD diagnosis, validity and valence of the cue on reaction times during the task.
Results: We found a validity x Q x group interaction, which indicated quicker reaction times on incongruent trials for women with more globally modular brains. Interestingly, this effect appears to be driven by the control group, indicating a facilitating effect of modularity in healthy women that is not present in the PTSD group.
Conclusions: These results suggest a mechanism for facilitation of spatial orienting that is present in healthy adults but with a less clear function in PTSD. This finding suggests a need for further exploration of the effect of brain network modularity in PTSD populations.
Supported By: NIMH R21/R33
Keywords: PTSD - Posttraumatic Stress Disorder, Modularity, Spatial Cueing

F21. Increased Error-Related Brain Activity in Pediatric Anxiety Disorders

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Background: The error-related negativity (ERN) is a negative deflection in the event-related potential following an incorrect response that has been proposed as a neural biomarker of anxiety across the lifespan. This study examined the relationship of the ERN to anxiety disorders (AD) in older children and adolescents.
Methods: The ERN, correct response negativity (CRN), and accuracy were measured during a flanker task to assess performance monitoring in 96 youth with a lifetime diagnosis of an anxiety disorder and 96 age- and sex-matched matched healthy controls (HC) ages 8 to 18 years. Forty cases had a lifetime diagnosis of 2 or more AD; 39 cases had a lifetime diagnosis of a depressive disorder (DD).
Results: The ERN was significantly increased in cases with AD compared to HC ($p = .002$, Cohen's $d = .43$). Compared to

HC, the ERN was significantly increased in cases with generalized anxiety disorder (GAD) (p = .008, Cohen's d = .60) and cases with AD other than GAD (p = .02, Cohen's d = .32). Compared to HC, the ERN was significantly increased in cases with a DD (p = .02, Cohen's d = .63) and cases without a DD (p = .01, Cohen's d = .31).
Conclusions: The results provide further evidence of increased error-related brain activity in youth with AD, including those with AD other than GAD and those with a comorbid DD. An enlarged ERN may represent a transdiagnostic liability index for GAD and other AD in late childhood and adolescence.
Supported By: NIMH R01MH101493
Keywords: Event-Related Potentials, Anxiety Disorders, Children, Biomarkers, Adolescents

F22. Regulation of Fear Expression by Activity-Dependent BDNF in Direct Hippocampal-To-Prelimbic Projections

To see this abstract, please see Oral Abstract #O4.

F23. Sexual Assault Characteristics Predict Peritraumatic Pain and Posttraumatic Stress Responses

Heather Swain[1], Benjamin McLean[2], Carol Tran[2], Alexa Vitale[2], Jenyth Sullivan[1], Carissa Novak[2], Teresa D'Anza[3], Kathy Bell[4], Megan Lechner[5], Jennie Buchanan[6], Jenny Black[7], Rhiannon Reese[8], Jeffrey Ho[9], Gordon Reed[10], Ralph Riviello[11], Elizabeth Datner[12], Melissa Platt[13], Catherine Rossi[14], Patricia Nouhan[15], Ronald Kessler[16], Israel Liberzon[17], and Samuel McLean[1]

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Background: The association between sexual assault (SA) characteristics on acute pain and psychological responses following SA is unknown.
Methods: Women SA survivors ≥18 years of age who presented for emergency care within 72 hours of SA are enrolled into a large ongoing multisite study. Acute pain (0-10 scale) is assessed at the time of presentation for emergency care, posttraumatic stress (PTS) symptoms (DSM-IV PCL) and pain outcomes are assessed at one week. Characteristics significantly associated with pain at presentation(*) and pain(¥) and PTS(#) at one week were assessed.
Results: Among women SA survivors enrolled to date (n=656), SA characteristics associated with acute pain and PTS outcomes included explicit life threat*¥, use of a weapon*¥, > 1 assailant¥#, unknown assailant#, strangulation during assault*¥, absence of drugs or alcohol*¥#, and multiple forms of assault. Many of these associations persisted after adjustment for age, income, and education (e.g., association between explicit life threat and initial pain b = 1.23, p = 0.0053; association between strangulation during assault and pain severity at one week b = 1.16, p = 0.0003; association between absence of drugs or alcohol and PTS severity at one week b = -2.17, p = 0.0145). Complete and updated bivariate and multivariate associations will be presented at the conference.
Conclusions: SA characteristics influence acute pain and PTS severity after SA. Better understanding of these predictive relationships may help provide pathogenic insights and identify individuals for early intervention.
Supported By: R01AR064700
Keywords: Sexual Assault, Pain, Posttraumatic Stress Disorder

F24. Is Tic-Related OCD a Familial Subtype of the Disorder? A Swedish Population Cohort Study

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Background: DSM-5 introduced a new tic-related subtype specifier to obsessive-compulsive disorder (OCD). This subtype is thought to constitute a particularly familiar variant of the disorder, but data are limited. We investigated whether the familial aggregation of OCD differs based on the presence of a lifetime history of tics (T+OCD) at the population level.
Methods: Among all Swedish-born individuals (1973-2007; n=4,092,078), we identified all OCD cases (n=22,232), along with their monozygotic/dizygotic twin, other full siblings, maternal/paternal half siblings, and cousins. Hazard Ratios (HR) were used to estimate the risk of OCD in all biological relatives of individuals with T+OCD versus OCD only.
Results: Relatives of individuals with T+OCD had a higher risk of OCD, with HRs decreasing by degree of relatedness: 35.47 (95% CI 4.24-296.73) in monozygotic twins, 10.63 (95% CI 7.92-14.27) in full siblings, 3.72 (95% CI 1.92-7.20) and 0.30 (95% CI 0.04-2.12) in maternal and paternal half siblings, respectively, and 1.58 (95% CI 1.17-2.13) in cousins. The corresponding HR in relatives of OCD-only individuals were: 21.54 (95% CI 8.79-52.79), 4.52 (95% CI 4.06-5.02), 1.87 (95% CI 1.39-2.52), 1.80 (95% CI 1.31-2.49), and 1.43 (95% CI 1.29-1.59). The results were largely unchanged when taking age at first OCD diagnosis into account.
Conclusions: T+OCD is a strongly familial subtype of OCD. Identification of more homogeneous subgroups of OCD patients may inform future gene-searching efforts.
Keywords: Obsessive-Compulsive Disorder, Family Study, Tourette's Syndrome, Prospective Cohort

F25. Increased Adverse Childhood Experiences Predict Worse Acute Pain and Psychological Symptoms After Sexual Assault

Carissa Novak[1], Heather Swain[2], Benjamin McLean[1], Carol Tran[1], Alexa Vitale[1], Kristen Witkemper[1], Teresa D'Anza[3], Kathy Bell[4], Megan Lechner[5], Jennie Buchanan[6], Jenny Black[7], Rhiannon Reese[8], Jeffrey Ho[9], Gordon Reed[10], Ralph Riviello[11], Elizabeth Datner[12], Melissa Platt[13], Catherine Rossi[14], Patricia Nouhan[15], Ronald Kessler[16], Israel Liberzon[17], and Samuel McLean[1]

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Background: Increasing evidence suggests that adverse childhood experiences (ACEs) can result in enduring neurobiological changes that increase pain and psychological vulnerability. To date, the influence of ACEs on acute pain and psychological responses following sexual assault (SA) is unknown.
Methods: Women SA survivors ≥18 years of age who presented for emergency care within 72 hours of SA are enrolled into this ongoing study. Acute pain (0-10 scale) is assessed at the time of presentation for emergency care; ACEs (ACE questionnaire) are assessed six weeks after SA, pain, and posttraumatic stress (PTS) symptoms (DSM-IV PCL) are assessed one week after SA.
Results: Women presenting for emergency care after SA (n=538) reported substantially and significantly higher ACEs than the general population (mean (SD) 3.87 (2.87)). Number of reported ACEs predicted acute pain severity at the time of presentation for emergency care ($r = .155$ ($p < .001$)) and at one week ($r = .175$ ($p < .001$)), and predicted PTS symptoms at 1 week ($r = .216$ ($p < .001$)). This influence of past ACEs on acute pain and psychological responses persisted after adjustment for age, income, and education (pain at presentation b= b=.105, ($p < .015$)), (pain at one week b=.110 ($p < .014$)), (PTS symptoms at one week b=1.24 ($p < .001$)).
Conclusions: Among adult women SA survivors, reported adverse childhood experiences are associated with increased pain and psychological symptoms after SA.
Supported By: R01AR064700
Keywords: Adverse Childhood Experiences, Sexual Assault, PTSD - Posttraumatic Stress Disorder, Pain

F26. Exploring Post-Zygotic Variants in Obsessive-Compulsive Disorder

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Background: Obsessive-Compulsive Disorder (OCD) is a debilitating neuropsychiatric disorder that is known to be moderately heritable but has poorly understood pathogenesis, limiting development of novel pharmacologic treatments. Previous studies suggest a significant contribution to OCD risk from de novo germline variants, which arise spontaneously in the parental germ cells or zygote. Recent studies of autism spectrum disorder and intellectual disability suggest a risk contribution from post-zygotic variants (PZVs) arising de novo in multicellular stages of embryogenesis, suggesting these mosaic variants can be used to examine the genetic underpinnings of other neuropsychiatric disorders such as OCD.
Methods: We examined whole-exome sequencing (WES) data from peripheral blood of 184 OCD parent-proband trios and 777 control parent-child trios that passed quality control measures. We used the bioinformatics tool MosaicHunter to identify low−allele frequency, potentially mosaic single nucleotide variants (SNVs) in probands and control children, only considering variants with the alternate allele not present in parents and with frequency <0.05 in the dbSNP database to collect SNVs most likely to be true PZVs.
Results: The rate of all single-nucleotide PZVs per base pair is not significantly different between OCD probands (5.88 x 10^-9) and controls (5.80 x 10^-9), rate ratio = 1.01 (95% confidence interval = 0.654-1.53), one-sided p = 0.5.
Conclusions: We did not detect a higher burden of PZVs in blood in individuals with OCD. However, further studies may benefit from examining a larger sample of families or from looking for PZVs in other tissues.
Supported By: Howard Hughes Medical Institute Medical Research Fellowship; R01MH114927-02; Brain and Behavior Research Foundation Young Investigator Award
Keywords: Obsessive Compulsive Disorder (OCD), Genetic Variants, Psychiatric Genetics

F27. Heritability of Gamma Butyric Acid: A Mega-Press With Macromolecule Suppression Study

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Background: Gamma-butyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian brain. It plays a role in plasticity, learning, and memory as well as sensory processing, and is strongly implicated in cognition, normal brain functions, and in multiple neuropsychiatric illnesses. GABA in the brain is emerging as a biomarker for brain health, cognition, and diseases
Methods: To evaluate factors influencing this trait, we measured GABA metabolite in the mediofrontal cortex in a large homogeneous population and estimated the heritability (h2). Our sample included 352 individuals (237 controls, 20 with bipolar disorder,

83 with major depression, 8 with schizophrenia spectrum disorder, 1 subject with OCD, 2 with ADHD, and 1 with intermittent explosive disorder) from large Amish families that underwent magnetic resonance spectroscopy (MRS) using a macromolecule-suppressed MEGA-PRESS sequence. We calculated an empiric kinship and used SOLAR-Eclipse to determine heritability.
Results: We found that the heritability of GABA is 0.42 ($p<0.0001$) in the full sample. Removing all individuals with any current or past psychiatric illnesses, the heritability of GABA is 0.58 ($p<0.0001$).
Conclusions: This is the largest MRS study of GABA without macromolecule contamination thus far and also the first heritability estimate of GABA concentration in the brain. This study suggests that a proportion of GABA variance is attributed to genetic causes, supporting future genetic studies of GABA levels in cognition and brain illnesses.
Supported By: R01MH094520, U01 MH108148
Keywords: GABA, Imaging Genetics, MRS, Old Order Amish, OCD

F28. Whole-Exome Sequencing Study of Trichotillomania

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Background: Trichotillomania is an understudied, common, difficult-to-treat, chronic psychiatric condition characterized by repetitive hair pulling with onset typically at 11-13 years old. Previous research suggests that genetic factors are important, but progress has been slow in identifying reproducible risk genes associated with trichotillomania. In contrast, studies of de novo genetic variants have identified risk genes in related childhood-onset neuropsychiatric conditions, including autism, Tourette syndrome, and OCD. Here, we present results from the first whole-exome sequencing study of trichotillomania.
Methods: We performed whole-exome sequencing on 27 parent-child trios (81 individuals total) where the child had a diagnosis of trichotillomania. After quality control, we analyzed 25 trios for de novo single nucleotide variants and indels. We focused on variants with a frequency of <0.01 in the ExAC database that were likely gene disrupting (including stop codons, splice sites, frameshift indels) or missense variants predicted to be damaging. Rates of de novo variants are compared to 225 previously sequenced control trios from the Simons Simplex Collection.
Results: De novo variant analysis identified 5 likely gene disrupting and 9 predicted damaging missense variants in the 25 parent-child trios. These de novo variants occur in genes expressed in the brain, and overlap with gene sets of other psychiatric conditions. Preliminary pathway analyses suggest the importance of glutamate signaling.
Conclusions: Whole-exome sequencing can identify de novo genetic variants associated with trichotillomania. We are currently in the process of collecting and sequencing 100 parent-child-trios, with the hope of identifying specific risk genes and relevant biologic pathways.
Supported By: AACAP Pilot Research Award; Alan B. Slifka Foundation through the Riva Ariella Ritvo endowment Pilot Research Award;
Keywords: Trichotillomania, Exome Sequencing, De Novo Mutation, Genetic Variants

F29. Thalamus Volumes and Structural Connectivity are Associated With Trauma Re-Experiencing and Fear Extinction Recall

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Background: Sensory information flow through the thalamus is involved in fear learning and recall, processes implicated in posttraumatic stress disorder. Re-experiencing symptoms are a clinical expression of fear memory recall and are often dominated by the recollection of sensory-perceptual elements of the trauma. This study examined re-experiencing symptoms and fear extinction recall in relation to thalamus phenotypes in trauma-exposed adults.
Methods: Eighty trauma-exposed adults (43 with DSM-IV PTSD, and 37 non-PTSD trauma-exposed adults) underwent imaging on a 3T Tim Trio Siemens MR scanner. They completed the Clinician Administered PTSD Scale for DSM-IV, and a fear conditioning paradigm involving conditioning and extinction on the first day and extinction recall on the second day. Volumes of left and right thalamus and intracranial volume (ICV) were estimated using Freesurfer. Fractional anisotropy (FA) of the left and right anterior thalamic radiation (ATR) was obtained using TRACULA. Extinction recall measured persistence of extinction memory on the second day, normalized for maximum skin conductance response during conditioning on day one. Analyses controlled for age and sex.
Results: Greater re-experiencing symptoms were associated with larger left and right thalamus/ICV volumes ($F(1,76)=5.80$, $p=.018$), and with lower FA in the left and right ATR ($F(1,64)=8.65$, $p=.005$). Better extinction recall was associated with larger left and right thalamus/ICV volumes ($F(1,61)=6.06$, $p=.017$).
Conclusions: These findings implicate thalamus anatomy and structural connectivity in trauma intrusions and fear extinction memory, and they encourage further examination of multimodal thalamus metrics (e.g., sub-territory volume, shape, and function) in posttraumatic stress.
Supported By: NIMH R01 MH096987
Keywords: Posttraumatic Stress Symptoms, Thalamus, Fear Extinction, Magnetic Resonance Imaging, Probabilistic Tractography

F30. Neural Activation During Emotion Modulation Associated With Early PTSD Symptoms Severity

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Background: Neurobiological processes that take place following a traumatic event may determine who will develop posttraumatic stress disorder (PTSD) and who will not. Such processes can be probed by examining neural activation patterns during emotion modulation, which were found to be altered in PTSD. In this project, we study the progression of these alterations as trauma survivors either recover from early PTSD symptoms or develop sustained PTSD symptomathology. This report focuses on the association between these alterations and early PTSD symptoms severity.
Methods: Data were collected from N=37 adult civilians (n=24 male; mean age (SD)= 33.39 (12.91) years) within 30 days of admission to an emergency department following a potentially traumatic event. Functional magnetic resonance imaging (fMRI) was used to assess brain activation during the Shifted Attention Emotion Appraisal Task (SEAT) and CAPS-5 was used to assess symptoms severity.
Results: Brain activation patterns during emotion processing and modulation followed expected patterns. Specifically, we found activation of the insula, dACC and fusiform gyrus during implicit emotion processing; activation of precuneus and dlPFC during attention shifting; and activation of vmPFC and MFG during appraisal. Importantly, activation in Insula during attention shifting was stronger in subjects with higher PTSD symptoms (all results $p<.001$ uncorrected).
Conclusions: These findings suggest that within 30 days after trauma exposure, activation of regions underlying emotion processing correlate with initial PTSD symptom severity. Next, we will investigate whether brain activation during emotion processing and modulation can be used to predict PTSD symptom development over a 14-month period post-trauma.
Supported By: 1R01MH103287-01
Keywords: PTSD - Posttraumatic Stress Disorder, Functional MRI, Emotion Processing

F31. Intrinsic Brain Network Implicated in the Behavioral Inhibition System of Adolescents With Depression/Anxiety

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Background: The Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scales are thought to reflect individual's tendency to withdraw oneself from stress-inducing stimuli or to activate behavior towards reward, respectively. Previous studies have reported higher BIS and lower BAS scores in patients with MDD or SAD compared to healthy controls. However, their underlying neural mechanisms are still unknown.
Methods: 37 adolescents from the Boston Adolescent Neuroimaging of Depression and Anxiety study and 28 matched healthy controls completed 5 minutes of resting-state fMRI scan and the BIS/BAS scales. Three seed regions were selected based on the functional gradients of the cerebellum (Guell et al., 2018) to explore the main effect of BIS. The ROIs corresponded to the peaks of the default mode network, motor network, and task-positive regions. Correlation analyses were performed using the CONN toolbox (Whitfield-Gabrieli et al., 2012).
Results: BIS scores were significantly higher in-patient group ($p<0.001$), but there was no group difference in BAS scores. At a whole-brain height threshold of $p<0.005$, regarding the main effect of BIS score in the patient group, two regions were inversely correlated with the motor gradient ROI - right anterior supramarginal gyrus (SMG) and right dorsal anterior insula (dAI) (FDR cluster-corrected at $p<0.05$).
Conclusions: SMG has been implicated in response inhibition, and dAI in anxiety proneness during anticipation of threat. Negative connectivity between motor gradient ROI and SMG/dAI may be the driving force behind higher BIS scores in adolescents with depression/anxiety, as reflected in their inclination not to take actions in response to anxiety-inducing events.
Supported By: U01
Keywords: Depression And Anxiety, Adolescents, Resting State fMRI, BIS/BAS Scales

F32. Neural Markers of Successful In-Scanner Worry Reappraisal in Older Adults

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Background: Severe worry is a transdiagnostic symptom that is associated with increased risk of conversion to Alzheimer's disease and increased risk of cardiovascular events. There is a need to develop treatments that are effective in reducing worry in older adults. We investigated the neural basis of worry induction and reappraisal using a personalized worry task.
Methods: We recruited 36 individuals (age >50), with varying worry severity. Participants viewed individualized worry sentences (one/block) during functional magnetic resonance imaging followed by neutral (factual sentences) or reappraisal sentences. Participants rated their worry severity (1-5) per block. After preprocessing, we modeled worry induction, reappraisal, and neutral blocks, and parametrically modulated each with in-scanner worry. Using statistical non-parametric mapping, we performed a paired t-test to identify regions that were more active with greater in-scanner worry rating during induction compared to reappraisal.
Results: The dorsal anterior cingulate and the bilateral temporoparietal junction (TPJ) had greater activation associated with higher in-scanner worry rating during induction. They had greater activation associated with lower in-scanner worry rating during reappraisal.
Conclusions: Greater dACC/TPJ activation was exhibited when participants reported higher worry during induction, which may indicate increased affective mentalizing (SMG) coupled with a sustained effort toward implicit regulation

(dACC). In contrast, greater activation during reappraisal was exhibited if participants reported lower worry during reappraisal and may indicate reappraisal. These results indicate potential targets for future interventions designed to alleviate severe worry in older adults.
Supported By: NIH MH108509 and MH019986
Keywords: Anxiety, Worry, Brain Imaging, fMRI, Cognitive Reappraisal

F33. In Vivo Brain Imaging of 11beta-Hydroxysteroid Dehydrogenase, a Marker of Cortisol Production, in PTSD

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Background: In Post-traumatic Stress Disorder (PTSD), loss symptoms of anhedonia, numbing, and dysphoric arousal correlate with lower peripheral cortisol levels, but are less effectively treated. This is the first study assessing a putative marker of brain cortisol regulation in PTSD with in vivo imaging of 11beta-hydroxysteroid dehydrogenase (11beta-HSD1), an enzyme that generates cortisol in the brain.
Methods: Seven (2 female; 27.4+/-1.3 years) individuals with DSM-5 PTSD and eleven (5 female; 25.2+/-1.1 years) healthy, trauma-exposed controls (TC) underwent a positron emission tomography (PET) scan with [18F]-AS2471907, a radioligand for 11beta-HSD1. Participants received 95+/-13 MBq [18F]-AS2471907 as a bolus injection and were imaged for 180-240 minutes on the High-Resolution Research Tomograph. 11beta-HSD1 availability was estimated as [18F]-AS2471907 volume of distribution (VT), with nearly all radioactivity uptake thought to represent specific binding, as demonstrated by previous blocking studies. Effect sizes of global and a priori regional [18F]-AS2471907 VT were compared between PTSD and TC groups. Pearson's correlations were performed between global VT and a Montgomery-Asberg Depression Rating Scale loss subscore.
Results: Preliminary analyses suggest that the PTSD group has higher corticolimbic [18F]-AS2471907 VT than the TC group, ranging from 10% (d=0.18) in hippocampus to 33% (d=0.52) in anterior cingulum. Within the PTSD group, higher global [18F]-AS2471907 VT was associated with lower loss subscore ($R2=0.640$, $p<0.05$).
Conclusions: These preliminary results suggest an elevation of 11beta-HSD1 in corticolimbic regions in PTSD. In the PTSD group, higher 11beta-HSD1 availability may be linked to lower loss symptoms. Exploration of regional relationships may further elucidate the role of 11beta-HSD1 in PTSD pathophysiology.
Supported By: Brain and Behavior Foundation NARSAD Young Investigator Grant (Cosgrove), Veterans Affairs National Center for PTSD, Pfeiffer Foundation Fellowship, NIH Grants: P50DA033945; K02DA03175; K01AA024788; T32GM007205; F30MH116607; R56MH116941.
Keywords: PET Imaging, PTSD - Posttraumatic Stress Disorder, Cortisol, HPA Axis, Posttraumatic Stress Symptoms

F34. Neural Fear Response Generalizes Across Conceptual Categories in Posttraumatic Stress Disorder

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Background: Posttraumatic Stress Disorder (PTSD) may develop when mechanisms for making accurate distinctions about threat relevance have gone awry. The generalization across conceptually related objects within a category has been observed clinically in PTSD, but its neural signature remains unexplored.
Methods: Recent trauma exposed military veterans (n=48) were grouped into PTSD (n=24) and non-PTSD (n=24). The response elicited when learning generalize fear across conceptual categories (animals or tools) of semantically related items was assessed with functional magnetic resonance imaging, skin conductance measurements, and expectancy ratings.
Results: Significant fear conditioning was observed through increased responding to CS+ relative to CS− presentations [$F(1, 16)=8.829$, $p=.009$], but did not differ significantly between groups. PTSD participants were less confident of safety on new items from the unreinforced category than trauma-exposed controls [$F(1, 43)=4.249$, $p=.045$]. Learning to generalize fear associations to reinforced object categories, based on expectation of shock, was significantly slower in the PTSD group as compared to the trauma-exposed control group [$F(1, 44)=3.776$, $p=.058$]. Patients with PTSD had a stronger neural response than trauma-exposed control veterans that was associated with generalization to reinforced object categories in the amygdala, ventral striatum, ventral frontolimbic cortex, and insula ($Z>2.3$; $p<0.05$; whole brain corrected).
Conclusions: Fear in PTSD is associated with an enhanced neural response to a learned representation of threat that is based on an established conceptual knowledge of the relationship between basic-level exemplars within a semantic category. Learning to generalize fear associations to conceptual object categories is slower in PTSD.
Keywords: Fear Generalization, Veterans, PTSD - Posttraumatic Stress Disorder, Amygdala

F35. Estradiol Administration Modulates Functional Activation of the Fear Extinction Network in Women Using Oral Contraceptives: An fMRI Study

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Background: Fluctuations of estradiol (E2) in women influence fear extinction. High levels of E2 engage the ventromedial

prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC) and the amygdala. We explored the effect of E2 administration on the fear extinction network in healthy women on oral contraceptives using fMRI.
Methods: 48 participants were fear conditioned on day 1. On day 2, participants were randomized to take either E2 or placebo pill ~5 hours prior to extinction learning. Extinction memory recall was assessed on day 3. Outcome measure was BOLD signal. Blood samples were ascertained from all participants to measure estradiol. Variance in estradiol levels across all subjects was correlated with brain activations during extinction learning and during extinction recall.
Results: We observed a significant positive correlation between E2 levels and vmPFC ($t=4.16$, $pFWE<0.05$ [$r=0.51$ $p<0.001$]) activation during extinction learning and with dACC ($t=4.9$, $pFWE<0.05$ [$r=0.52$ $p<0.001$]) during recall. In an exploratory between group analyses (E2 vs. placebo groups), we found that women in the E2 group exhibited significantly less activation in the amygdala ($t=3.02$, $pFWE=0.05$) during renewal of fear. During extinction learning, we observed a trend towards significance within activations in the E2 group in the dACC and the amygdala ($t=3.55$, $pFWE=0.07$; $t=3.55$, $pFWE=0.07$, respectively).
Conclusions: Exogenous E2 engages regions involved in fear regulation, supporting the role of estradiol administration as enhancer of extinction-induced activations and reducing amygdala reactivity during renewal. We provide further support to the possibility of using estradiol as an adjunct to behavioral therapies aimed at fear and anxiety-based disorders.
Supported By: NIMH R61
Keywords: Estradiol, BOLD fMRI, Women, PTSD - Posttraumatic Stress Disorder

F36. Obsessive-Compulsive symptoms, Polygenic Risk Score and Thalamic Development in Children From the Brazilian High-Risk Cohort Study

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Background: Cortico-striato-thalamo-cortical circuitry has been consistently implicated in the pathobiology of Obsessive-Compulsive Disorder (OCD) with altered thalamic volumes reported. The aim of this study was to evaluate the relationship between thalamic volume, obsessive-compulsive symptoms (OCS), and genetic risk for OCD in a 3-year follow-up study of a community cohort.
Methods: 812 children (6-14 years-old) underwent two structural MRI scans; at baseline and 3-years later. A polygenic risk score (PRS) was also calculated for the participants using the most recent OCD GWAS summary statistics (p-threshold = 0.2). Linear mixed models were run with the participant's ID entered as random factor and thalamic volume as dependent variable. OCS and PRS were investigated independently as variables of interest. Models included an interaction term between the effect of interest and age. Sex, site, and intracranial volume were included as co-variates. In the OCS model, any non-OCD diagnosis was included as a covariate while in the PRS model the 4 principal components from genotyping were included.
Results: An inverse relationship between thalamic volume and OCS was observed ($p = 0.027$) as well as a positive interaction association between OCS and advancing age ($p = 0.015$). No direct relationship between thalamic volume and PRS was observed, but the PRS-age interaction was significant ($p = 0.031$).
Conclusions: Smaller thalamic volumes were associated with higher levels of OCS in children and adolescents. PRS for OCD was not related to thalamic volume but there was a positive PRS-age interaction suggesting an increasing effect with advancing age.
Supported By: Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP (São Paulo Research Foundation)
Keywords: Obsessive Compulsive Disorder (OCD), Cortico-Striatal-Thalamic-Cortical Circuit, Neuroimaging, Child and Adolescent Psychiatry, Community Sample

F37. Is There Astrocyte Pathology in PTSD? Preliminary Findings of a PET Study With the Monoamine Oxidase B Radioligand [11C]SL25.1188

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Background: Posttraumatic stress disorder (PTSD) is a debilitating mental condition that results from exposure to traumatic event(s), such as military combat, assault, or disaster. Pre-clinical models of PTSD and related conditions (depression and anxiety) suggest a decrease in astrocyte-related proteins (e.g. GFAP). There is a lack of in vivo studies of astrocyte pathology in patients with PTSD. Our specific aim was to use positron emission tomography (PET) of the monoamine oxidase B (MAO-B) probe [11C]SL25.1188 (an index of astroglial cell levels), to test the hypothesis that MAO-B in the brain is decreased in PTSD.

Methods: MAO-B binding ([11C]SL25.1188 distribution volume) was measured with PET and arterial sampling in 10 participants who fulfilled DSM-V criteria for PTSD and 16 healthy trauma-unexposed controls (HC). A magnetic resonance image was acquired for delineation of regions of interest on the PET images.
Results: HC and PTSD groups were matched with respect to age and sex (HC ~ 30.9 years, 9F vs PTSD ~ 38.6 years, 3F). We found that PTSD was associated with a wide-spread decrease (11-21%) in [11C]SL25.1188 binding across 10 regions ($F(1,24) = 4.677$; $p = 0.041$) implicating the limbic striatum ($p = 0.006$) and medial prefrontal cortex (0.024) (Group * region interaction ($F(9, 216) = 3.285$; $p = 0.016$).[11C]SL25.1188 binding was not associated with symptom severity in PTSD.
Conclusions: Our preliminary findings are partly in line with preclinical literature suggesting loss/dysfunction of astrocytes in PTSD, however, may also suggest an independent down-regulation of MAO-B. Replication of these early findings in a larger cohort is warranted.
Supported By: Funded by the Department of National Defence and Canadian Institute for Military and Veteran Health Research (CIMVHR) through a sub-award to Isabelle Boileau
Keywords: Positron Emission Tomography, PTSD - Posttraumatic Stress Disorder, Astrocytes

F38. Altered Resting-State Functional Connectivity in Fear and Reward Processing Among Patients With Comorbid PTSD-MDD

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Background: Individuals with comorbid posttraumatic stress disorder and major depressive disorder (PTSD-MDD) often exhibit greater functional impairment and poorer treatment response than individuals with PTSD-alone. Although previous research shows promising results demonstrating different neural abnormalities in fear and reward pathways for PTSD-MDD vs. PTSD alone, the findings were based on a small sample size and did not include a comparison with patients with MDD only. The present study was designed to explore potentially different neural abnormalities in these three groups: PTSD only, MDD only, and PTSD-MDD.
Methods: Functional magnetic resonance imaging (fMRI) was used to measure resting state functional connectivity (rs-FC) patterns of brain regions involved in fear and reward processing in four groups: patients with MDD (n=79), PTSD-alone (n=22), PTSD-MDD (n=31), and trauma-exposed healthy controls (TEHCs, n=40).
Results: Our findings indicated that, regardless of MDD comorbidity, compared to TEHC, PTSD was associated with decreased connectivity of the BLA-OFC and HIP-OFC pathways, which are key to fear processing and fear memory, respectively. The PTSD-MDD group exhibited greater decrease in both fear-processing pathway (BLA-OFC; HIP-OFC), and the reward-related striatal-subcortical pathway (NAcc-THA), than did the MDD-alone, PTSD-alone, and TEHC groups. Lastly, the MDD group, compared with TEHC, showed intact connectivity in the fear pathway (BLA-OFC) but reduced connectivity in the reward pathway (NAcc-THA).
Conclusions: Our findings suggest that comorbid PTSD-MDD may be associated with multifaceted functional connectivity alterations in both fear and reward systems. Clinical implications are discussed.
Supported By: R01MH072833; R01MH105355
Keywords: MDD, PTSD, Brain Imaging, fMRI, Resting State, Brain Connectivity, Reward

F39. Stress Speeds Arousal Fluctuations In mPFC Neurons and Pupillary Diameter

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Background: Although pupillary responses to threat have been studied as a biomarker in PTSD, the fluctuations of the resting pupil have not. Across the cortex, neurons increase their firing when the pupil dilates, likely in response to locus coeruleus. We hypothesized that cortical dynamics would be altered after stress, and the pupil might serve as a potential biomarker for stress-induced hyperarousal.
Methods: We measured pupillary fluctuations in mice before and after stress (n=8 stressed, n=7 unstressed). Pupillary fluctuations were quantified via spectral analysis and a Hidden Markov Model (HMM) describing arousal transitions. We also recorded from neurons in the mPFC using calcium imaging while monitoring pupillary fluctuations (n=458 stressed, n=372 unstressed neurons). We estimated the relationship between neural activity and transitions in pupillary arousal (using the HMM and spectral analysis).
Results: Acute traumatic stress causes more rapid transitions between pupillary states ($p<0.05$). These rapid transitions in the pupil reflect shifts in cortical arousal. Population (average) mPFC activity is highly correlated to pupil ($r2 = 0.56$), but neuron-pupil correlation is reduced by stress ($p<0.001$). mPFC neuron-pupil coupling is particularly reduced at low frequency (<0.5 Hz) after stress ($p<0.05$). mPFC arousal transitions precedes pupillary arousal transitions into the high arousal state by 0.5 seconds ($p<0.01$).
Conclusions: Rapid cortical arousal switching after stress can be inferred from an easily accessible external measurement. Slow fluctuations in pupillary diameter define epochs of high and low activity of mPFC neurons. A novel method of analyzing the resting pupil is presented, which could be used in translational studies of human PTSD.
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NARSAD YI (Kwan), Inscopix DECODE (Kwan)
Keywords: PTSD - Posttraumatic Stress Disorder, Calcium Imaging, Pupil Dilatation, Hyperarousal, mPFC

F40. Stressful Life Events in the Second Half of Pregnancy Predict Visual Network Connectivity in Young Adult Offspring Decades Later

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Background: Maternal stress during pregnancy can impact brain development and increase offspring psychopathology risk. Using a prospective longitudinal cohort, we aimed to determine whether stressful life events experienced during pregnancy might have detectable effects on brain function in young adult offspring decades later.
Methods: Resting-state fMRI was conducted in 130 young adults (47% male, age 23-24) from the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ). A subset of these individuals had assessments of maternal stressful life events collected prospectively during the first (n=91) and second (n=121) half of pregnancy. Cortical-cortical resting-state functional connectivity was calculated for 10 networks based on the Cole-Anticevic Atlas. Relationships between maternal stress and connectivity were assessed using a general linear model with network as within-subject factor.
Results: A network-by-stress interaction emerged ($F(9,1062)=2.51$, $p=0.008$), wherein maternal stressful life events during the second half of pregnancy predicted higher connectivity within the primary visual network (beta=0.20, p=0.03), but not the remaining networks (auditory, cingulo-opercular, default, dorsal-attention, frontoparietal, language, posterior-multimodal, somatomotor and secondary visual). Follow-up exploratory analyses further associated prenatal stress with greater connectivity between the primary visual and the dorsal-attention network (beta=0.19, p=0.04). No significant associations emerged for stress experienced during the first half of pregnancy.
Conclusions: We demonstrate that stressful life events during the second half of pregnancy predict increased visual network connectivity in young adult offspring. These findings are broadly consistent with temporal trajectories of functional network development and recent work (Elliott et al., 2018) linking similar connectivity profiles to transdiagnostic risk for mental illness.
Supported By: FP7-PEOPLE-IEF-2013
Keywords: Prenatal Maternal Stress, Resting State Functional Connectivity, Developmental Psychopathology, Visual Cortex

F41. Genetic Variation in the Oxytocin System Impacts Infants' Prefrontal Brain Asymmetry Responses to Emotional Faces

To see this abstract, please see Oral Abstract #O3.

F42. Childhood Internalizing Symptoms and Epigenetic Aging

Marieke Tollenaar[1], Roseriet Beijers[2], Elika Garg[3], Thao Nguyen[3], David Lin[4], Julia MacIsaac[4], Idan Shalev[5], Michael Kobor[4], Michael Meaney[3], Kieran O'Donnell[6], and Carolina de Weerth[2]

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Background: Epigenetic age acceleration (EAA) is an indicator of biological aging and has been associated with a range of physical and psychological health problems in adulthood. Early life stress may impact upon EAA, but few studies have examined associations between psychological distress and EAA in childhood. In the current longitudinal study, we examined whether childhood EAA is associated with internalizing or externalizing symptoms throughout childhood.
Methods: Internalizing and externalizing symptoms were examined in 148 children (69 girls) at ages 2.5, 4, 6, 7 and 10 by maternal report. At age 6 buccal epithelial cells were collected and genome-wide DNA variation and methylation were measured. EAA was estimated using the Horvath clock. Associations between internalizing and externalizing symptoms and EAA were examined with regression and mixed model analyses. Genetic propensities for EAA and psychopathology were considered as covariates.
Results: Higher levels of internalizing symptoms at ages 2.5 and 4 significantly predicted higher EAA at age 6. In turn, EAA at age 6 significantly predicted internalizing symptoms from ages 6-10 in addition to childhood symptoms. Polygenic risk scores for EAA or psychopathology did not affect these results. Associations between EAA and externalizing symptoms did not reach significance.
Conclusions: We show for the first time that EAA measured in childhood is associated with internalizing symptoms across childhood. This may indicate EAA as a possible biomarker of childhood stress and emphasizes the importance of early identification of childhood psychiatric symptoms. Early interventions may prevent possible negative health effects of early childhood psychiatric problems.
Supported By: NWO; Jacobs Foundation; Royal Netherlands Academy of Arts and Sciences; National Institutes of Health; Eunice Kennedy Shriver National Institute of Child Health and Human Development
Keywords: Childhood Psychiatry, Child Internalizing Symptoms, Externalizing, Epigenetic Aging, Stress

F43. Heritability Estimates on Arterial-Spin Labeling and Resting State MRI Data on Amish Connectome Project

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Background: We collected 3D arterial-spin labeling (ASL) and resting state fMRI (rsfMRI) data in a sample of Amish connectome project participants. We aimed to a) compute and identify the significant additive genetic contribution to the inter-subject variance in gray and white matter regions using the

cerebral blood flow (CBF) signals, b) use the genetic analysis to resting state networks (RSNs) ROIs for functional connectivity measures as accessed by regional homogeneity (ReHo) methods. This is the first study that evaluated heritability of CBF and ReHo of RSNs in Amish sample.
Methods: Participants underwent for ASL (N=200) and rsfMRI (N=386) data acquisition, using a 3 T Siemens Prisma scanner. CBF signals were extracted from gray and white matter regions and were used in the heritability estimation. A single-modality ENIGMA rsfMRI workflow was used for rsfMRI data processing and Kendall coefficients of concordance (KCC) scores from ReHo maps were extracted from 24 RSNs ROIs to perform heritability calculation.
Results: Average CBF signals were found significantly heritable (global brain CBF: h2=65%, p=2.8×10-4, average gray matter CBF (gmCBF): h2=64%, p=3.6×10-4, and average white matter CBF (wmCBF): h2=36%, p=3.8×10-2). gmCBF signals (h2: 44%-79%, $p<0.05$, 41 out of 48 regions) and wmCBF signals (h2: 34%-68%, $p<0.05$, 17 out of 38 regions) were heritable. KCC scores from all 24 ROIs from major RSNs were found heritable (h2: 48%-83%, p<5.0×10-3).
Conclusions: Both CBF and rsfMRI signals are significantly heritable in Amish participants. CBF and ReHo measures, obtained following the ENIGMA rsfMRI workflow are found to be promising endophenotypes for future studies.
Supported By: NIH grants U54EB020403, U01MH108148, 2R01EB015611, R01MH112180, R01DA027680, R01MH085646, and T32MH067533
Keywords: Heritability, Regional Homogeneity, ENIGMA rsfMRI Workflow

F44. Simultaneous EEG-fMRI-Eye Tracker Measurements for Determining Subject's Vigilance During Resting-State fMRI

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Background: Resting-state fMRI (rsfMRI) is widely used for studying the human brain. Vigilance drift during rsfMRI influences brain activity and functional connectivity. However, measures of subjects' vigilance during rsfMRI are still not readily available. We aim to determine the EEG measure of the subject's vigilance state and to validate this measure using simultaneous eye tracker recording data obtained during EEG-fMRI. In addition, eye tracker data and fMRI activities correlations were examined.
Methods: Simultaneous EEG-fMRI-Eye Tracker data during three 12-min rsfMRI scans (eyes open) was collected from 4 healthy volunteers (12 runs). Four runs, each missing more than 25% of pupil diameter data were excluded. The pupil size fluctuation is an indirect index of activity of the locus coeruleus, involved in the regulation of vigilance. We investigated the correlation between the lower EEG beta band global field power (GFP-β) and pupil size. We used pupil size, pupil change and pupil unrest index (PUI) as regressors to find the correlations between the fMRI BOLD signal and those eye tracker measures.
Results: The average correlation between pupil size and GFP-β is 0.23, with a significant correlation for 5 rsfMRI runs ($p<0.05$), and is marginally significant for the rest of 3 runs (p-values: 0.05, 0.07 and 0.09). We found a correlation between pupil dimension, pupil size, and PUI change with fMRI data, including several brain regions in salience and default mode networks.
Conclusions: We propose that GFP-β could account for EEG vigilance measure during rsfMRI, as verified with simultaneous eye tracker recording.
Supported By: The study was supported by the Laureate Institute for Brain Research and William K. Warren foundation, and in part by the P20 GM121312 award from National Institute of General Medical
Sciences, National Institutes of Health.
Keywords: rsfMRI, Concurrent EEG/fMRI, Eye Tracking, Vigilance, Arousal

F45. Feature Learning of the Developing Amygdala: Predicting Age, Maltreatment, and Psychopathology Using Multimodal Connectomics in Youth

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Background: Adolescence is a period of extensive neural circuit reorganization, creating windows of vulnerability to adverse experiences. Unfortunately, little is known about the developmental connectomics of the amygdala during adolescence, a set of important circuits with respect to emotional salience and the effects of early-life adversity (ELA) and subsequent psychopathology.
Methods: We implement a feature learning approach to biomarker discovery based on magnetic resonance imaging (MRI) in 41 non-traumatized typically-developing (TD) youth (ages 8-18 years) and 40 youth with trauma-related affective psychopathology (TRAP). All youth underwent a trauma and psychiatric screen and MRI at rest, during emotional face processing, and diffusion tensor imaging (DTI). Amygdala connectome biomarkers were identified based on five cross-validated prediction algorithms common to feature selection, each predicting age-at-scan, degree of maltreatment, and presence/absence of TRAP.
Results: Rest- and task-based MRI results showed considerable network-level overlap. In predicting maltreatment, amygdala functional connectivity (FC) with regions in the cingulo-opercular (salience) network (anterior cingulate cortex, middle cingulate cortex, insular cortex) were informative. In predicting presence/absence of TRAP, amygdala FC with regions in the dorsal attention and frontoparietal networks (dorsolateral prefrontal cortex, inferior parietal lobule) were informative. Amygdala FC with the default-mode network (parahippocampal gyrus, orbitofrontal gyrus) were informative for both predictions.

Conclusions: This study highlights the emerging importance of feature learning in biomarker discovery in contrast to traditional "group-level" statistics. Moreover, multimodal imaging produced unique, network-level correlates of ELA and TRAP in a developing sample, indicating the amygdala connectome may be an efficient probe in making differential predictions.
Supported By: National Institute of Mental Health Career Development Award (RJH), American Academy of Child and Adolescent Psychiatry Junior Investigator Award (RJH), NARSAD Young Investigator Grant (RJH), University of Wisconsin Institute for Clinical and Translational Research Translational Pilot Grant Award (RJH), National Science Foundation Graduate Research Fellowship Program (TJK), University of Wisconsin Institute of Clinical and Translational TL1 Training Award (SAH), the University of Wisconsin School of Medicine and Public Health
Keywords: Child And Adolescent Psychiatry, Neurodevelopmental Trajectories, Brain Networks, Machine Learning

F46. Increased Extra-Axial Cerebrospinal Fluid is Associated With Decreased Cortical Thickness and Delayed Motor Development in Early Childhood

Veronica Murphy[1], Mark Shen[1], Sun Hyung Kim[1], Emil Cornea[1], Martin Styner[1], and John Gilmore[1]

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Background: Increased extra-axial cerebrospinal fluid (EA-CSF) is associated with autism spectrum disorder diagnosis in young children. However, little is known about EA-CSF development in normal children or in children at risk for schizophrenia. We examined EA-CSF in a cohort of typically developing children (N=104) and in children at risk for schizophrenia (N=38).
Methods: Brain structure, including global tissue volumes, cortical thickness (CT), and surface area (SA), was assessed using 3T MRI at ages 1 and 2 years. Cognitive development was assessed using the Mullen Early Learning Scales of Learning. Mixed models were used to analyze the relationship between EA-CSF and brain tissue and cognitive measures. Results were corrected for multiple comparisons using Hochberg's false discovery rate method.
Results: EA-CSF was positively associated with overall brain size, including total brain volume ($p=2.4E-4$ $R^2=0.16$; $p=6.3E-4$ $R^2=0.22$), grey ($p=3.1E-4$ $R^2=0.16$;: $p=4.6E-4$ $R^2=0.23$) and white matter ($p=8.8E-4$ $R^2=0.14$; $p=0.002$ $R^2=0.18$) volumes, and total SA ($p=1.8E-4$ $R^2=0.19$; $p=0.004$ $R^2=0.17$) at ages 1 and 2 years respectively. Average CT was negatively associated with EA-CSF ($p=0.004$ $R^2=0.12$). Delayed motor abilities were associated with larger EA-CSF volume similar to studies of children at risk for autism ($p=0.02$ $R^2=0.12$). EA-CSF was not significantly increased in children at risk for schizophrenia.
Conclusions: Increased EA-CSF is associated with decreased CT and delayed motor development suggesting that it may be a biomarker of abnormal brain development. Further studies are needed to determine the usefulness of EA-CSF as an imaging biomarker of risk for neurodevelopmental disorders.
Supported By: NIH; RO1; NIMH; R36
Keywords: MRI Brain Imaging, Brain Development, Schizophrenia, Cerebrospinal Fluid, High Risk

F47. Longitudinal Development of Social-Cognition Regions Covaries With Amygdala Volume in Children With Williams Syndrome

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Background: Williams syndrome (WS), typically characterized by hypersociability and non-social anxiety, is caused by hemideletion of ~25 genes at chromosomal location 7q11.23. Previous evidence suggests alterations in the development of amygdala volume in children with WS compared to typically developing children. Here, we longitudinally studied the structural covariance of amygdala size with changes in gray-matter volume across the rest of the brain to explore development of networks from childhood/adolescence through early adulthood in WS.
Methods: MEMPRAGE structural scans were acquired longitudinally, every two years, for 18 children with WS (mean age=13.7+4.1 years, range=5-20; 13 females). Scans were spatially normalized into a common group space using SPM12 and ANTS, and penalized-spline models of relative changes in gray-matter volume over time were created for each voxel using R's gamm4 package. These voxelwise trajectories were then correlated with a group trajectory of right amygdala volume, computed using Freesurfer's longitudinal amygdala/hippocampus segmentation tool. Voxel trajectories that were highly correlated (positively or negatively) with changes in amygdala volume over time were identified.
Results: Across the modeled age range, we found significant negative correlations ($p<0.01$ Bonferroni corrected) between the right amygdala and the ipsilateral inferior parietal lobule (IPL), superior temporal sulcus (STS), and temporo-parietal junction (TPJ): as relative right amygdalar volume increased, gray-matter in IPL, STS, and TPJ decreased.
Conclusions: These findings of a structural network involving the amygdala and areas associated with social cognition that develops across childhood through early adulthood may provide a developmental perspective on the neural basis for the hypersociability and social/emotional characteristics observed in WS.
Supported By: NIMH Intramural Program
Keywords: Longitudinal Brain Imaging, Neurodevelopment, Genetics, Spatiotemporal Structural Covariance, 7q11.23 Copy-Number Variation

F48. Frontoparietal Cortical Thickness Predicts Response to Cognitive Behavioral Therapy in Children and Adolescents With Obsessive-Compulsive Disorder

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Background: Obsessive-Compulsive Disorder (OCD) is characterized by the presence of obsessions (i.e. intrusive thoughts/images/impulses) and compulsions (i.e. repetitive actions to prevent/mitigate distress). Cognitive Behavioral Therapy (CBT) with exposure and ritual prevention is a first-line treatment for pediatric OCD, yet personalized medicine could improvement response rates. Herein, we identify brain structural markers of CBT response in pediatric OCD, representing stable and easily-measured metrics to help precision medicine efforts in youth.
Methods: Twenty-eight unmedicated youths with OCD and 27 demographically-matched healthy participants (5-18 years) completed MRI scans (0.8mm isotropic voxels). Patients completed 16 weeks of CBT. Linear mixed-effects models were used to identify regions where cortical thickness moderated the slope of change in OCD severity across pre-, mid-, and post-treatment assessments, allowing for missing data and controlling for age, sex, and IQ. False discovery rate (FDR) was used for multiple comparisons correction.
Results: Thinner cortex in nine regions significantly predicted improvement in symptom severity (all $t>3.4$, FDR-corrected $p<.05$), including the middle and superior frontal, angular, lingual, precentral, superior temporal, and supramarginal gyri. These regions also showed normative negative associations between thickness and age or pubertal development. Further analyses examining structural connectivity using diffusion-weighted imaging are underway.
Conclusions: While most youths benefited from CBT, responses varied. Our high-resolution MRI data suggest robust associations of frontoparietal thinness with better treatment improvement. Thus, accelerated maturation of the frontoparietal circuit might predict and facilitate CBT response in pediatric OCD, pointing to a potential target for novel treatments and early prevention strategies.
Supported By: R01MH115024
Keywords: Structural MRI, Obsessive Compulsive Disorder (OCD), Children and Adolescents, CBT, Prediction of Treatment Outcome

F49. In Vivo Examination of Gray Matter Microstructure Integrity in Autism Spectrum Disorder

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Background: Prior histological post-mortem studies have shown gray matter (GM) microstructural abnormalities in autism spectrum disorder (ASD) but in-vivo evaluation of GM microstructure in ASD remains limited. In this study we employ diffusion kurtosis imaging (DKI) to non-invasively study GM microstructure in-vivo in ASD compared to typically developing participants (TD).
Methods: DKI and T1-weighted data were acquired in 16 ASD patients and 17 age-matched TD young adults (males, 18-25 years old). Mean (MK), radial (RK) and axial (AK) kurtosis and mean diffusivity (MD) metrics were calculated for the four cortical lobes and 68 cortical regions of interest (ROI) obtained using FreeSurfer's Desikan-Killiany atlas. Between-group comparisons were conducted for all regions. Multiple comparisons were corrected using Benjamini-Hochberg approach.
Results: We found significant decreased MK, RK, and MD in the GM of the ASD group. Significantly decreases were found primarily in the temporal lobe (MK $p = .006$*, RK $p= .000$*, MD $p= .044$) and functionally relevant GM ROIs previously associated with ASD neuropathology, including left (MK $p= .001$, RK $p= .001$*) and right (MK $p= .009$, RK $p= .001$*, MD $p= .006$) superior temporal gyri and left insula (MK $p=.008$, RK $p= .005$). Decreased diffusion metrics in GM were correlated to increased disease severity measured by the Adult Diagnostic Interview-Revised.
Conclusions: A novel imaging technique highlights microstructural alterations in the GM of young adults with ASD. Incorporating these microscopic GM markers into a comprehensive model of ASD may address diagnostic heterogeneity.
Supported By: NIMH R03-MH076180
Keywords: Diffusional Kurtosis Imaging (DKI) , Autism Spectrum Disorder, Gray Matter Microstructure, Brain Cortex

F50. Individual Variation of Cortical Morphology at Age 6 is Established in the First Year of Life

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Background: Variation in cortical morphology contributes to individual differences in cognition, behavior, and risk for neuropsychiatric illness. While cortical morphology develops rapidly in early childhood, it is not known when in development individual variation is established.
Methods: 277 typically developing children, part of the UNC Early Brain Development Study, were longitudinally scanned with 3T MRI after birth and at ages 1, 2, 4, and 6 years. Development trajectories of cortical gray and white matter volume, cortical thickness and surface area development were analyzed. The proportion of variance at 6 years explained by measures at at earlier ages was determined.
Results: Cortical thickness was relatively stable from 1 to 6 years, while total surface area increased about 19% from 1 to 6 years. 91% of the variance of cortical gray matter volume at age 6 years was explained by gray matter volume at age 1 year. Regional variation in cortical thickness was stable from 1 to 6 years; and 93% of regional variability at 6 years explained by cortical thickness at age 1. Finally, 85% of average surface area variation at age 6 years was explained by surface area at age 1 year.
Conclusions: A large proportion of the individual differences in cortical morphology apparent at age 6 years is already present at age 1 year. This indicates that individual differences in cortical morphology are largely established by age 1 year and suggests that alterations of cortical morphology associated with disorders of cognition and behavior later in life arise before age 1 year.
Supported By: HD053000, MH064065, MH111944, MH070890

Keywords: Brain Magnetic Resonance Imaging (MRI), Brain Development, Cortical Thickness, Cortical Surface Area, Gray Matter Volume

F51. Putative Causal Relationship Among Polygenic Scores, Cortical Surfaces, and General Intelligence

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Background: There is likely a shared mechanism among genetics, variation in brain structure, and general intelligence (g). Recent large-scale genome wide association studies (GWAS) have identified hundreds of genetic loci associated with intelligence, including many that may be functionally relevant in brain expression genes. However, the cumulative influence of these loci on brain structure is not known, particularly its intermediary influence on g performance scores.
Methods: Here, we examined the putative causal relationship in which cortical morphology mediates the relationship between GWAS-derived polygenic scores and general intelligence. In two relatively large imaging-genetics samples (IMAGEN, N=1651; IntegraMoods, N=742), polygenic scores for intelligence across ten thresholds were assessed for their association with g performance as well as vertex-wise measures for cortical thickness and surface area. Vertex-wise mediation was used to assess the indirect effect of cortical structure.
Results: The association between polygenic scores and general intelligence was mediated by surface area and cortical thickness in the prefrontal cortex, anterior cingulate, insula, and medial temporal cortices. This relationship survived stringent correction for multiple comparisons among all polygenic thresholds, cortical vertices, and neuroimaging modalities, independently in both samples (IMAGEN: PFWER-corrected< 0.0025; IntegraMoods: PFWER-corrected< 0.0025).
Conclusions: Our results provide evidence for a mechanism in which cumulative genetic load for intelligence predicts general intelligence via surface area and cortical thickness. The consistency of our data across samples, sites, and diagnostic groups also suggests that cortex morphology could be a novel potential biomarker for neurocognitive dysfunction that are among the most intractable psychiatric symptoms.
Supported By: NARSAD
Keywords: Brain Imaging, Imaging Genetics, Genetics, Intelligence, Cortical Surface Area

F52. Cognitive, Psychosocial, and Environmental Correlates of Adolescent Brain Structure

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Background: Adolescence presents a unique window of vulnerability to mental illness but also a window of opportunity for neuroscience-informed interventions to mitigate the risk of psychiatric disorders. Although previous studies have found correlates of adolescent brain, a study that takes a multifaceted approach to the individual is missing.
Methods: We used data from the IMAGEN longitudinal study of adolescence in eight European centers to determine the demographic, psychosocial, cognitive, and environmental correlates of brain structure in adolescents (residualized for age, sex and study center). We used sparse canonical correlation analysis (SCCA) to investigate the correlates of regional cortical and subcortical volumes, cortical thickness, and cortical surface area. Best sparsity parameters were determined using resistant sparse canonical correlation analysis with 5-fold cross validation. P values were calculated using random permutations.
Results: At baseline, there was a significant association between non-neuroimaging variables and subcortical volumes (n=977, r=0.31, p<0.001), cortical volumes (n=953, r=0.34, p<0.001), and cortical surface areas (n=962, r =0.37, p<0.001), and cortical thickness (n=983, r =0.21, p=0.001). Neuroimaging variables with the highest loading were global brain measures followed by frontal, temporal, and thalamic areas. On the non-neuroimaging side, largest coefficients were observed for IQ subscales, parental education, openness to experience, birth weight, height, weight, average grades, and parental smoking during pregnancy. Similar patterns of association were observed at second follow up.
Conclusions: Intelligence, perinatal variables, and anthropometric measures correlated the highest with MRI measures of brain structure in adolescents. Most of the observed correlation was driven by global brain volume and total surface area.
Supported By: This work received support from the following sources: the European Union-funded FP6 Integrated Project

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Keywords: Neurodevelopmental Trajectories, Adolescence, Structural MRI, Neuroimaging, Neural Correlates

F53. Atypical Cerebral Lateralization in Children With Autism Spectrum Disorder

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Background: Recent research has suggested that Autism Spectrum Disorder is characterized by abnormal network connectivity across development. Previous work has identified abnormal lateralization of functional connectivity at rest in prematurely born individuals, with greater lateralization associated with poorer language ability. This study utilized resting-state fMRI to investigate cerebral lateralization in children with ASD to elucidate potential mechanisms of aberrant neurodevelopment.

Methods: Using resting-state fMRI data from the Autism Brain Imaging Data Exchange, examined connectivity lateralization in 309 children with ASD and 434 typically-developing (TD) peers aged 6-14 years. Functional connectivity was performed using linear regression while controlling for sex, age, site, and motion. Significance was assessed at $p<0.05$, corrected for multiple comparisons. Preliminary analysis investigated connectivity lateralization in 40 neonates (mean gestational age=39.9 weeks) to examine effects of development on cerebral lateralization.

Results: Children with ASD exhibited increased connectivity lateralization in right BA-22, right BA-19, and right BA-23/31, and decreased connectivity lateralization in right BA-10. Neonates showed bilateral ipsilateral lateralization in both hemispheres across similar regions seen in children with ASD.

Conclusions: Findings suggest that children with ASD demonstrate increased right-hemisphere lateralization in temporal and parietal regions and reduced right-hemisphere lateralization in a frontal region relative to TD peers. This atypical lateralization is associated with multiple resting-state brain networks including the default mode (PCC, mPFC), fronto-parietal (fusiform), ventral-attention (middle temporal gyrus), cingular-oppercular (insula), and subcortical networks (putamen). These findings, in concert with preliminary findings in neonates, suggest altered cerebral network development in ASD.

Supported By: Vernon W. Lippard, M.D., Student Summer Research Fellowship in Pediatrics

Keywords: Autism Spectrum Disorder, fMRI Resting State, Neurodevelopment, Infants

F54. Neuromarkers of Behaviour Regulation in 7-17 Year Old Children With ADHD, DCD and ADHD-DCD

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Background: Children with ADHD show elevated scores in behaviour regulation, which translates to daily-life challenges. ADHD often co-occurs with Developmental Coordination Disorder (DCD); however, behaviour regulation in DCD is not well understood. Here, we investigate differences in amygdala and dorsolateral prefrontal cortex (dlPFC) functional connectivity (FC) related to behaviour regulation, between children with ADHD, DCD, combined ADHD-DCD and typically developing (TD) children.

Methods: Resting-state fMRI data from 104 children (31 TD, 31 ADHD, 16 DCD, 26 ADHD-DCD; aged 7-17 years) were preprocessed and cleaned with ICA-AROMA. Emotional control, inhibition and shifting were assessed as aspects of behaviour regulation using the Behavior Rating Inventory of Executive Function. Amygdala and dlPFC FC maps were computed for each participant, and tested for group differences that related to aspects of behaviour regulation, at $p<0.01$ cluster correction.

Results: Children with DCD scored lowest in all domains, followed by TD children, and children with ADHD and ADHD-DCD, with a significant difference between DCD/TD and ADHD/ADHD-DCD. FC findings revealed several differences between groups. For example, stronger amygdala-ventromedial FC associated with emotional control was found in TD/DCD compared to ADHD; stronger amygdala-caudate FC associated with shifting was found in DCD vs. all other groups;

and stronger dlPFC-vmPFC FC related to inhibition was found in ADHD vs. TD.
Conclusions: Our findings suggest that behaviour regulation problems in ADHD-DCD are likely attributable to ADHD, and that an intricate balance of FC strength in amygdala and prefrontal networks supports varying behaviour regulation in TD children, and children with DCD, ADHD and ADHD-DCD.
Supported By: Alberta Innovates; NSERC; NSERC CREATE I3T (Canada); CIHR (Canada)
Keywords: Emotion Regulation, ADHD, Inhibition, Set-Shifting, Self-Regulation

F55. An Image-Based Meta-Analysis of Successful and Failed Stopping in Attention Deficit/Hyperactivity Disorder Using Statistical Parametric Maps

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Background: Patients with Attention Deficit/Hyperactivity Disorder (ADHD) often demonstrate abnormal brain functioning during the stop signal task, although previous work has typically used small samples thereby limiting conclusions.
Methods: A preliminary image-based meta-analysis (n=834) comparing patients with ADHD (n=379; age range= 8-50 years, 269 males) and controls (n=455; age range=8-50 years, 273 males) on the stop signal task was performed using Seed-based d Mapping. The protocol was registered with Prospero (CRD42018095365).
Results: Groups did not differ according to mean stop-signal reaction time (d=0.24 p=.11). During successful stopping, patients with ADHD showed underactivation in left orbitofrontal cortex (OFC) and left amygdala as well as in bilateral thalamus and inferior frontal gyrus. Reduced deactivation was observed in precuneus/posterior cingulate cortex (PCC). During failed stopping, patients showed underactivation in dorsomedial prefrontal cortex and left IFG/OFC/anterior insula as well as reduced deactivation in precuneus/PCC and bilateral putamen (SDM-Z >2, p<.005).
Conclusions: A lack of performance differences may be due to pre-scan practice sessions and the removal from some studies of poorly performing subjects. During successful and failed stopping, patients with ADHD showed reduced activation in predominantly left-sided salience network in conjunction with reduced deactivation in bilateral basal ganglia and posterior default mode network. Underactivation in the left amygdala aligns with recent mega-analysis findings of relatively reduced amygdala gray matter volume in ADHD, and suggests that abnormalities in this region may underlie deficits in task-related salience. Overall, findings suggest a deficit in performing dynamic adjustments between DMN and task positive networks in ADHD.
Supported By: NIMH ROI1
Keywords: ADHD, Attention Deficit Hyperactivity Disorder, Adolescence, Meta-Analysis, Brain Imaging

F56. Task-Evoked Effective Connectivity in Salience and Central Executive Networks Predicts Cognitive Control Ability and Inattention Symptoms in Children With ADHD

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is associated with pervasive impairments in attention and cognitive control. Although these impairments have been extensively investigating with resting-state fMRI little is known about task-evoked functional brain circuits and their relation to inattention symptoms and cognitive control deficits in children with ADHD.
Methods: We used a task fMRI dataset with 27 children with ADHD and 30 matched typically-developing (TD) children, and dimensional analyses, to investigate the relation between inattention symptoms, Go/NoGo task performance, and task-evoked functional brain circuits. We examined effective connectivity using psychophysiological interactions in two core cognitive control systems: (i) cingulo-opercular "salience" (SN) and (ii) fronto-parietal "central executive" (CEN) networks.
Results: We found that multivariate patterns of effective connectivity between brain regions in SN and CEN predicted children's performance on the Go/NoGo task. Specifically, the strength of task-evoked effective connectivity between right dorsal anterior cingulate cortex (rdACC) and right ventrolateral prefrontal cortex (rVLPFC) was significantly and positively correlated with NoGo accuracy. Furthermore, the strength of task-evoked connectivity in rdACC-rVLPFC was significantly and negatively correlated with the severity of inattention symptoms in children with ADHD. Brain-behavior relationships were robust against potential age, gender and head motion confounds.
Conclusions: Our findings highlight aberrations of task-evoked connectivity in SN and CEN in children with ADHD, its relation to inattention symptoms and cognitive control deficits, and suggest potential biomarkers for predicting clinical symptoms and treatment outcomes in childhood ADHD.
Supported By: National Institutes of Health grants EB022907, NS086085 and MH105625, and Children Health Research Institute grant.

Keywords: Human,fMRI, iSPOT-A, Response Inhibition, Psychophysiological Interaction Analysis

F57. Children With ADHD Have Deficit in Reproducing the Rey-Osterrieth Complex Figure in Delayed Recall Condition

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Background: It was shown that children with ADHD have cognitive deficit, particularly deficit in working memory (Martinussen et al., 2012). In our previous research we have revealed that ADHD children have deficit in visual and verbal memory in delayed recall condition in comparison to immediate condition (Kiselev & Lvova, 2016; Kiselev, 2018). The goal of this research was to examine the hypothesis that children with ADHD have deficit in reproducing the Rey-Osterrieth Complex Figure in delayed recall condition.
Methods: The experimental group included 16 children with ADHD at the age of 7-8 years. The control group included 16 typically developing children. The children from groups were matched for IQ, gender and age.

Children from both groups were assessed with Rey–Osterrieth complex figure test (ROCF). This test is designed to assess reproducing the complex figure in immediate and delayed recall conditions. ANOVA with repeated measures was used to reveal group differences in reproducing the figure in two conditions.
Results: We have not revealed significant differences between children from experimental and control group in reproducing the figure in immediate condition. However, the interaction of condition type and group was significant [F(1,30)=10,58; p=0,003)]. Children with ADHD had deficit in the accurate reproduction and placement of specific design elements of Rey-Osterieth Complex Figure in Delayed Recall condition.
Conclusions: In view of our previously received results in children with ADHD, we can propose that deficit in memory in delayed recall condition can be one of the key symptoms in this disorder.
Supported By: Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.
Keywords: ADHD, The Rey-Osterrieth Complex Figure, Memory Deficit

F58. An Astrocyte-Specific Molecular Mechanism of Interaction Between a Genetic Risk Factor and Cannabis to Produce Long-Term Cognitive Dysfunction After Adolescent Exposure

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Background: Adolescent cannabis use has been associated with long-term cognitive dysfunction attributed to action of the main cannabis ingredient, delta-9-tetrahydrocannabinol (Δ9-THC), on the cannabinoid receptor 1 (CNR1). However, not all marijuana users develop cognitive impairment, suggesting a genetic vulnerability to adverse effects of cannabis. As both neurons and glial cells express CNR1, genetic vulnerability could influence Δ9-THC-induced signaling in a cell type-specific manner.
Methods: In this work we use mouse models of cell-specific expression of dominant-negative Disrupted-In-Schizophrenia-1 (DN-DISC1) selectively in astrocytes to evaluate the molecular mechanisms, whereby an adolescent Δ9-THC exposure could interact with genetically predisposed astrocytes to produce recognition memory impairment in adulthood.
Results: Our results showed that astrocyte-specific, but not neuronal-specific, expression of DN-DISC1 and Δ9-THC-treatment during adolescence synergistically impairs recognition memory in adult mice. Similar results were observed following adolescent Δ9-THC treatment of animals combined with knockdown of endogenous Disc1 in hippocampal astrocytes. We found that DN-DISC1 and Δ9-THC synergistically activated the inflammatory NF-kB-COX-2 pathway in astrocytes resulting in increased release of glutamate and decreased immunoreactivity of parvalbumin-positive pre-synaptic inhibitory boutons around pyramidal neurons in the CA3 area of the hippocampus. The cognitive abnormalities were prevented in DN-DISC1 mice exposed to Δ9-THC by simultaneous adolescent treatment with the COX-2 inhibitor, NS389.
Conclusions: Our results suggest that memory impairments within vulnerable individuals following adolescent cannabis use can be exclusively mediated by astrocytes via synergistic activation of the inflammatory cascade in these brain cells and this may be prevented by anti-inflammatory treatment.
Supported By: R01; NIDA
Keywords: Marijuana, Astrocytes, NF-kB, Gene-Environment Interaction, Genetic Predisposition

F59. Trauma Exposure in Adolescence and Clinical Outcomes in Young Adulthood

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Background: Adolescent traumatic experiences are associated with clinical outcomes in adulthood, including but not limited to, PTSD. Statistical approaches which address the range of traumatic experiences and potential outcomes can provide insight into the neurobiology and phenomenology of traumatic experiences. The analysis aimed to identify classes of adolescent trauma exposure in a longitudinal sample to evaluate potential outcomes in young adulthood.
Methods: The sample consisted of 2311 participants followed longitudinally from childhood through young adulthood. Adolescent trauma experiences between 13 and 18 years of age were included in a latent class analysis (LCA) to determine classes of exposure. These classes were then used to predict clinical outcomes in young adulthood.
Results: Three classes were identified by the LCA. The Low Trauma Exposure class (61%) experienced low probabilities of trauma exposure. The Violence Exposure class (23%), which was predominately male, reported high rates of physical assault, injury and witnessing a death. The Sexual Assault class

(16%), predominately female, reported high rates of rape and sexual assault, witnessing a death, and assault of a friend/family member. The Violence Exposure class was most likely to be diagnosed with Alcohol or Marijuana Use disorder, while the Sexual Assault class was most likely to be diagnosed with PTSD or MDD in young adulthood.
Conclusions: Trauma is associated with a range of outcomes, which may depend on trauma type. One critical factor in evaluating trauma exposure and outcome is sex, which will have implications for both identification and treatment of patients who have experienced trauma.
Supported By: NIMHR01
Keywords: Age At Trauma Exposure, Childhood Trauma, Post Traumatic Stress Disorder

F60. Relationship Between Problematic Internet Use (PIU) and Marijuana Use in Adolescents

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Background: As marijuana is being decriminalized/legalized, its use is anticipated to increase. Problematic Internet use (PIU) has been associated with substance use in adolescents. Thus, the relationship between PIU and marijuana is of interest.
Methods: PubMed, PsycINFO and Web of Science were searched from inception through June, 2018. Search terms PIU, Internet addiction, pathological Internet use, and excessive Internet use were combined with key words marijuana, cannabis, substance use, and drug use. References from identified articles were reviewed for additional studies. Inclusion criteria included studies in English, sample size greater than 1000 subjects, mean subject age $\leq$ 18 years, and studies that statistically examined the relationship between PIU and current (any use in past year) or lifetime marijuana use.
Results: 8 cross-sectional studies with 39,781 unique subjects met inclusion criteria. Seven studies were from Europe and one from the United States. Both PIU and marijuana use were assessed by self-report. PIU was assessed by 8 different measures. There were 5 studies on current marijuana use and three studies on lifetime use. PIU was significantly associated with current marijuana use in 5 studies (100%) and lifetime use in 2 studies (67%). Effect sizes were small to moderate.
Conclusions: Most studies found a positive relationship between PIU and either current or lifetime marijuana use. Studies with standardized methodology in measuring PIU and more precise assessment of quantity and frequency of marijuana use are needed. Given the potential risks of early marijuana use, longitudinal studies to determine direction of causality are also warranted.
Keywords: Problematic Internet Use, Marijuana, Adolescence

F61. dACC Dysfunction During Inhibitory But Not Excitatory Motor Control in OCD: Glutamate Dysmodulation Estimated Using ^{1}H fMRS

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Background: Dysfunction of the dorsal anterior cingulate cortex (dACC) has been documented during motor control in OCD (Friedman et al., 2017). However, fMRI cannot distinguish if this dysfunction relates to impaired excitatory or inhibitory functions of the dACC. Using a combination of a specifically developed motor paradigm with distinct excitatory or inhibitory modes for responding, and ^{1}H functional MRS (fMRS) that is uncoupled from hemodynamics, we investigated functional imbalances in the excitatory and inhibitory (E/I) synaptic drive of the dACC in OCD.
Methods: ^{1}H fMRS data from the dorsal anterior cingulate (dACC; 4.1cm3) youth with OCD (4M+1F; 15.7$\pm$2.1 yrs.) and HC (4M+2F; 15.3$\pm$1.7 yrs.) were acquired (3T Siemens Verio). In the excitatory mode, participants tapped their right forefinger to either a green or red flashing square (.1 s stimulus duration, 32 s task epochs, 16 s rest epochs). In the inhibitory mode, responses were elicited only to green squares (80%, requiring inhibition on the remaining 20% of the trials). Differences in glutamate modulation (expressed as a % change relative to visual fixation) during the excitation and inhibition epochs were contrasted between groups (t-tests).
Results: The mean dACC glutamate modulation during the excitation mode was higher for both groups but not significantly different from each other ($p=0.74$). During the inhibition mode, however, dACC glutamate modulation was significantly lower in OCD youth (-2.4%$\pm$2.6% vs 6.0%$\pm$2.7%; $p=0.027$).
Conclusions: These results while preliminary, provide a compelling approach toward in vivo characterization of the relative contributions of excitatory vs. inhibitory signaling in the pathophysiology of OCD.
Supported By: R01 MH59299 (DRR), Children's Hospital of Michigan Foundation, Miriam Hamburger Endowed Chair, Paul and Anita Strauss Endowment and by the Lycaki-Young Funds from the State of Michigan.
Keywords: Glutamate, Functional MRS, OCD, Obsessive Compulsive Disorder (OCD), Excitation/Inhibition Balance

F62. Gene Expression Change With Weight Restoration Treatment for Anorexia Nervosa: Modeling the Impact of Weight Gain on Expression Change

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Background: Anorexia nervosa (AN), characterized by extreme food restriction and resulting in a significantly low body weight, is associated with genetic factors. However, little is known about how genomic factors change with weight gain, the essential first step in treatment. Thus, we examined how gene expression levels change with nutritional rehabilitation in AN.
Methods: 55 females receiving inpatient treatment for AN provided blood samples for RNA sequencing at admission (T1) and discharge (T2). For each gene, differential expression was evaluated using a method similar to computing a paired t-test

but adapted for count data. Covariates (e.g., RIN number) were included in analyses. To identify differentially expressed genes that may be specific to weight gain vs AN disease-state, weight change from T1 to T2 was included as a covariate.
Results: 551 genes were differentially expressed from T1 to T2 (q-value<0.05). After correcting for multiple testing, only a pathway for Hemoglobin's Chaperone remained significant. 44 genes remained significantly differentially expressed when weight change was added to the model, several of which were related to iron production and regulation.
Conclusions: Differences were observed in gene expression levels with nutritional rehabilitation in AN—a majority of which may be due to weight gain. The 44 genes that remained significant after controlling for weight gain could provide additional targets for the genetic etiology of AN. Admittedly, blood may not be the ideal tissue to explore gene regulatory mechanisms in psychiatric illness; still, results provide insight into the transcriptomic changes that occur as a result of nutritional rehabilitation in AN.
Supported By: K01MH106675
Keywords: Eating Disorders, Anorexia Nervosa, Gene Expression, mRNA, Weight Gain

F63. Abnormal Spontaneous Regional Brain Activity in Acutely Underweight Patients With Anorexia Nervosa

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Background: Task-based as well as resting-state functional MRI studies have repeatedly shown alterations in patients with anorexia nervosa (AN). These alterations might be driven by baseline signal characteristics such as (fractional) amplitude of low frequency fluctuations (fALFF/ALFF), as well as regional signal consistency [i.e. regional homogeneity (ReHo)] within circumscribed brain regions. To our knowledge, no study has yet reported on ALFF and ReHo measures in patients with AN. Another goal of the current study was to relate the aforementioned measures to grey matter (pseudo)atrophy – a well-known finding in AN (King et al.,2017).
Methods: Resting-state functional as well as structural MRI data were acquired in 74 acutely underweight AN patients and 74 pairwise age-matched female healthy controls (HC). ALFF/fALFF and ReHo values were calculated using DPARSF toolbox. Structural MRI data were processed using FreeSurfer.
Results: Group-level analyses showed differences for both measures in several brain regions relevant in AN (ventral visual stream, networks related to cognitive control and habit formation). The findings were independent of the different preprocessing streams (in-/excluding global signal regression). Grey matter volumes/thickness were reduced in patients. Furthermore, the magnitude of correlation between grey matter volume/thickness and fALFF and ReHo were reduced in AN compared to HC.
Conclusions: Abnormal local resting-state characteristics in AN-related brain-networks (Nunn, 2008) as well as reduced structure-function relationships may help to explain previously reported task-related and classical resting-state neural alterations in AN. AN may thus serve as a model-disorder to further investigate dynamic changes in the regional relationships between brain structure and function.
Supported By: DFG research grant: EH 367/7-1
Keywords: Resting State Functional Connectivity MRI (fcMRI), Cortical Thickness, Anorexia Nervosa, ALFF, ReHo

F64. Fronto-Striatial Circuits in Adolescent Anorexia Nervosa Before and After Symptom and Weight Improvement: A Cross-Sectional and Follow-Up Resting-State fMRI Study

Esther Via[1], Anna Calvo[2], Elena de la Serna[3], Anna Blázquez[3], Jaime Moya[3], Luisa Lázaro[3], Susana Andrés-Perpiñá[3], María Teresa Plana[3], Itziar Flamarique[3], Esteve Martínez[3], Jose Pariente[2], Elena Moreno[3], Nuria Bargallo[4], and Josefina Castro-Fornieles[3]

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Background: Low cognitive flexibility (CF) is considered a putative trait marker of anorexia nervosa (AN), independent of body mass index (BMI). CF has been linked to the fronto-striatal circuit, but literature in adolescent samples is conflicting.
Methods: 57 adolescent females (37 AN, 20 healthy control-HC-) were scanned twice during the resting-state in a 3T scanner. Between sessions, the AN group received a 6-month multidisciplinary outpatient treatment. Baseline and baseline-to-follow-up between-group differences in the fronto-striatal system (seed-based analysis) were evaluated by T-test and ANOVA analyses, cluster-level PFWE<.05. At significant regions, extracted connectivity values were included in a multiple linear regression analysis, with eating symptoms (EAT40 scores) and BMI (baseline, change) as dependent variables.
Results: The AN group significantly improved in BMI/EAT40, with no differences in CF neuropsychological assessment. At baseline, the left dorsal putamen to precuneus connectivity was significantly lower in AN compared to HC. There was a time x group interaction in the right dorsal caudate to right anterior insular cortex connectivity, driven by lower connectivity measures in AN (compared to HC) that normalized at follow-up. Greater baseline EAT40 scores explained lower changes in the caudate to insular connectivity in the AN group.
Conclusions: Connectivity alterations between striatal regions and relevant areas to AN such as the precuneus (self-body consciousness) and the mid-anterior insula (link between interoception and emotions) seem associated with the acute state in AN but tend to improve with recovery. Severity before treatment predicts smaller improvement at 6-months follow-up. These alterations are not associated with low CF in adolescent AN.
Supported By: Alicia Koplowitz Foundation (FAK) (DN040546)
Generalitat de Catalunya (Child Psychiatry and Psychology Group 2017SGR4881 and CERCA programme).

Keywords: Anorexia Nervosa, Longitudinal Brain Imaging, Resting-State Functional Connectivity, Cognitive Flexibility

F65. Altered Network Connectivity in Individuals Prone to Obesity

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Background: Understanding how the propensity to obesity affects intrinsic brain network connectivity may provide important insight into mechanisms of food intake. This study used a novel whole-brain, data-driven approach to examine differences in large-scale network connectivity between obesity-prone and obesity-resistant individuals.
Methods: Fifty-six adults completed the study, half of whom had a propensity to be resistant to weight-gain and obesity (obesity-resistant [OR]) and half of whom were prone to weight gain and obesity (obesity-prone [OP]). The final analysis included 25 OR participants (11 women, 14 men) and 28 OP participants (14 women, 14 men). Following a four-day run-in diet, participants underwent functional magnetic resonance imaging (fMRI) during a 10-minute resting-state scan, in the fasted state. Networks were identified using independent component analysis (ICA). Between-network connectivity (BNC) analysis then assessed correlations between ICA component time series' and individual voxel time series. Finally, SPM t-tests were used to determine group effects on BNC.
Results: A significant group difference was observed in basal ganglia BNC, bilaterally ($p < 0.05$, FWE-corrected), with greater connectivity in the OP compared to OR group. This finding was driven by increased negative connectivity between basal ganglia voxels and a lateral sensorimotor network (lateral SM) in the OP group.
Conclusions: Increased between-network connectivity was observed in the basal ganglia in OP compared to OR individuals, an effect driven by a more strongly negative association between basal ganglia and lateral SM, potentially reflecting a dissociation between the neural representation of the body (lateral SM) and habitual food-seeking behaviors (basal ganglia).
Supported By: NIH/NIDDK: R01DK103691, R01DK089095, K01DK100445
Keywords: Obesity, Resting State fMRI, Intrinsic Connectivity Networks

F66. Longitudinal Associations Between Neuro-Psychiatric Symptoms and Dopamine Transporter Imaging in Parkinson's Disease

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Background: Non-motor or neuropsychiatric symptoms (NPS) of Parkinson's disease (PD) have major impact on disease outcome and quality of life in Parkinson's disease. An understanding of the neurobiology of NPS is critical for the development of more effective intervention strategies.
Methods: The Parkinson's Progression marker initiative (PPMI) is a multicenter, international, longitudinal study evaluating clinical, biochemical, and imaging measures of Parkinson's disease (PD) progression. Data from dopamine transporter (DAT) SPECT were centrally reconstructed, attenuation corrected, and analyzed with a standardized volume of interest template for extraction of regional count densities in the left and right caudate and putamen. Striatal binding ratios (SBR) from all 4 regions at baseline, year 1, 2 & 4, and neuropsychiatric symptoms measured by part 1 of Unified Parkinson's Disease Rating Scale (UPDRS) at baseline, year 1,2,3 & 4 were analyzed with latent growth curve models.
Results: NPS gradually worsened over the course of PD. Baseline SBR as well as change in SBR significantly predicted trajectory (slope) of NPS (p values < 0.005) but not the baseline NPS. These findings were significant after adjusting for age.
Conclusions: Quantitative DAT SPECT imaging data in PD provide insight into role of dopaminergic system in etiology of NPS.
Keywords: Neuropsychiatric Symptoms, Parkinson's Disease, A Functional Near-Infrared Spectroscopy, Latent Class Analysis, Predictor

F67. Exploring the Role of the Habenular-Interpeduncular Circuit in Affective States in Diabetes

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Background: Epidemiological data demonstrates that diabetics are twice as likely as healthy individuals to suffer from depression and animal models confirm that diabetic states disrupt cholinergic and nitrergic signaling in the brain. The cholinergic Habenula-Interpeduncular circuit (Hb-IPN) has been implicated in depression as a regulator of serotonergic and dopaminergic tone, however, to date no one has examined the Hb-IPN in diabetics. Here we examine the molecular response of specific cell types as well as the contribution of dysregulated nitrergic signaling in the IPN to affective states in diabetes.
Methods: C57Bl6J mice were injected with STZ to induce diabetes or with NOS1 shRNA or M3 DREADD viruses in the IPN. Hyperglycemia was confirmed by blood glucose measurements from tail vein. Animals underwent behavioral battery to assess baseline anxiety and motivation. To determine changes in gene expression, ChAT-EGFPL10a mice were given 2% sucrose or 0.2% saccharin in drinking water for 6 weeks. Brain regions were microdissected and translational profiling performed, followed by RNA-Seq.
Results: Activation of the IPN, either by chemogenetics or knock-down of NOS1, increases blood glucose and anxiety-related behaviors. TRAP data from ChAT Hb cells reveal that sucrose upregulates 3500 genes, including Nos1, while saccharin only upregulates 19.
Conclusions: Activation of the IPN increases blood glucose and anxiety-related behaviors, suggesting a novel role for this

circuit in regulation of affective states in response to changing metabolic demands. Understand the molecular mechanisms by which hyperglycemia contributes to neuronal dysfunction and resulting depressed mood may provide a novel treatment for depression in diabetic patients.
Supported By: Leon Levy Foundation
Keywords: Nitric Oxide Synthase, Diabetes, Acetylcholine, Medial Habenula

F68. Presenting Clinical Features of Anti-NMDA Receptor Encephalitis in Children and Adolescents

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Background: Anti-NMDA receptor (NMDAr) encephalitis is caused by IgG antibodies against the GluN1 subunit of NMDA receptors, which produce effects that make misdiagnosis as a psychiatric disorder likely. This study examines the temporal progression of anti-NMDArE clinical features in children and adolescents who are likely to be referred for psychiatric evaluation.
Methods: PubMed and EMBASE databases were searched systematically to identify all published reports of anti-NMDAr encephalitis with prominent behavioral or psychiatric symptoms. Frequencies of clinical features from 7 major symptom domains were tabulated, and temporal ranks were assigned based on their relative order of first appearance in each patient. Median ranks were computed to establish the temporal sequence in which individual features or domains were first observed.
Results: 167 unique cases (121 female) age 18 years or younger met inclusion criteria. After behavioral/psychiatric symptoms, the most commonly observed features were seizures (72.5%), other dyskinesias (62.9%), orofacial dyskinesias (49.1%), mutism or staring (40.7%), and insomnia (39.5%). Behavioral signs and symptoms were observed very early, but seizures and fever were presenting symptoms in only 31 (18.6%) and 16 (9.6%) cases, respectively. Insomnia was among the earliest features to be observed, with dyskinesias peaking with or immediately after insomnia. Motor dysfunction peaked after insomnia, followed by cognitive dysfunction. Catatonic features and autonomic dysfunction peaked relatively late.
Conclusions: Every psychiatrist is likely to encounter these patients and should have a high index of suspicion when new psychiatric symptoms arise in the context of a recent viral prodrome, seizures, unexplained fever or insomnia.
Keywords: NMDA Receptor, Autoimmune Disorder, Encephalitis, Diagnosis, Recent Onset of Psychosis

F69. Developing Methods to Achieve Large-Scale Neuroimaging of Trauma Survivors: Lessons From the Aurora Study

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Background: Large-scale prospective neuroimaging of trauma survivors is urgently needed to better understand brain structural and functional changes during the development of adverse posttraumatic neuropsychiatric sequelae. Sharing of methods that achieve successful neuroimaging of trauma survivors will allow the field to most rapidly gain new insights into disease pathogenesis and identify potential therapeutic targets.
Methods: The AURORA Study enrolls 5,000 trauma survivors at dozens of emergency departments across the US. A subset of AURORA participants undergo neuroimaging 2 weeks and 6 months after trauma at four neuroimaging sites. Participants are contacted via phone/email/text to gauge interest, and an extensive MRI safety screening is performed to assess participant eligibility.
Results: Important methodologic changes that have improved data collection to date include providing transportation (required for 39/62 (63%) of sessions), improving individual neuroimaging site communication with participants (e.g. reduction of time from first contact to scheduling from 5 days to 3 days, $p=0.0618$), and streamlining the MRI eligibility assessment. Because the scheduling window occurs before low adherence participants are dropped from the study, we implemented a prediction tool to only recruit participants who were likely to demonstrate continued adherence to the study. The current survey follow-up rate for all participants is 71%. After using 3 days of data to assess likelihood of adherence and excluding those less likely to follow-up, the new predicted survey follow-up rate will be 76%.
Conclusions: Large-scale prospective neuroimaging of trauma survivors is feasible. Optimizing methods to recruit trauma survivors for neuroimaging is critical to obtaining high quality data.
Supported By: This project was supported by NIMH U01MH110925 and the US Army Medical Research and Material Command.
Keywords: Trauma, Neuroimaging, Methods

F70. Evaluating Posttraumatic Neuropsychiatric Sequelae Trajectories During the First Eight Weeks After Trauma Exposure Across RDoC Constructs Using Brief Serial Smartphone-Based Self-Report Survey

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Background: Nearly 80% of the US population owns a smartphone; this percentage continues to rapidly increase. Brief Smartphone-based surveys provide the opportunity to perform frequent serial assessments of common, morbid posttraumatic symptoms and gain better understanding of trauma survivor experiences during the early post-traumatic period.
Methods: The AURORA Study enrolls 5,000 trauma survivors at dozens of emergency departments (EDs) across the US. The Discovery by Mindstrong™ App is installed on participant's smartphone in the ED. Symptoms indicating key RDoC constructs, including hyperarousal, pain, loss, sleep, and threat are assessed frequently (range 4-6 times) during the initial eight weeks after trauma. Based on a set of initial 616 participants, measurement models, latent growth curve (LGC), and growth mixture models/classes are developed for each construct, and class developmental relationships are assessed.
Results: The measurement models were created for each RDoC construct (e.g., pain CFI 0.98, hyperarousal CFI 0.96), and LGCs developed (e.g., pain CFI 0.97, hyperarousal CFI 0.95). Latent classes were identified/selected based on relative model fit (primarily) and clinical utility (secondarily)(e.g., pain − 3 classes identified, hyperarousal − 3 classes identified). Multidimensional outcome groups, and relationships between latent classes across RDoC constructs from this ongoing study will be presented.
Conclusions: Serial smartphone-based assessments have the potential to provide better understanding of posttraumatic mental health trajectories, co-morbidities, and developmental relationships, and can identify individuals for early interventions.
Supported By: This project was supported by NIMH U01MH110925 and the US Army MRMC.
Keywords: Growth Mixture Modelling, Trajectories, Smartphone-Based Self-Report Survey, Measurement Model

F71. Neuroendocrine Determinants of Structural Brain Parameters and Treatment Outcome in Major Depression

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Background: Increased aldosterone (aldo) levels and central mineralocorticoid-receptors (MR) activation are linked to therapy resistance to antidepressants. Apart from regulating of slow wave sleep, heart rate variability, and salt preference; aldosterone affects the secretion of cerebrospinal fluid.
Methods: 17 patients with major depression, were examined 3 times during 6 weeks. 13 patients completed the study. Central and peripheral MR related biomarkers (saliva aldo and cortisol; plasma vasopressin and oxytocin; slow wave sleep, heart rate variability, salt taste preference) and psychometrics were determined as well as magnetic resonance imaging measures (3 tesla) of the volume of specific anatomical areas, using Freesurfer 6 software for automatic volume detection.
Results: Superior response and outcome, as characterized by the HDRS-21 and CGI-S, respectively, is correlated to lower volume of the lateral ventricles, total ventricular volume and the size of the choroid plexus (all $p<0.05$), and by trend correlated to higher volume of the central (CCC) and mid anterior corpus callosum (MACC) ($p<0.1$). The volume of the CC is inversely correlated to that of the ventricular system. The volume of the ventricular system is positively correlated to plasma vasopressin and body mass index (BMI), whereas the total volume of the CC is negatively correlated to the saliva concentration ratio of aldo/cortisol.
Conclusions: Neuroendocrine (aldo/cortisol ratio; vasopressin) and metabolic (BMI) parameters determine the ventricular volume and the volume of the corpus callosum. This may link these markers to the pathophysiology of therapy refractoriness in depression.
Supported By: The hormonal analyses were supported by a grant of APVV-0028-10 and VEGA 2/0057/15
Keywords: Depression, Neuroendocrinology, Hydrocephalus, Aldosterone

F72. Relationship Between Decision Making and Brain Activity in Participants With High and Low Levels of Depressive Symptoms

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Background: Impairments in decision making in depressive episodes destroy everyday functioning. Decision-making deficits may relate to hyposensitivity to reward and anhedonia, or hypersensitivity to negative information in depressed subjects. The aim of the current study was to investigate brain activity during performance of a decision-making task with negative and positive feedback in two groups of participants, one with higher and one with lower levels of depressive symptoms.
Methods: The Inventory of Depressive Symptoms (Rush et al., 1986) was used for assigning 30 female volunteers to control (C, IDS score<20, average age 19.8, SD=6.7) or depressive (D) groups (IDS score>30, average age 21.5, SD=1.05) who performed a decision-making task (Kustubayeva et al., 2010). The task required assessment of the hazards and benefits of different possible routes in an exploration scenario. Participants received manipulated feedback each time they chose a route. EEG was recorded by using a Neuron-Spectrum_4. EEG/ERP preprocessing and analysis of P300 parameters (hazards, benefits, choice, and feedback) were done with the EEG/ERPlab toolbox (Lopez-Calderon& Luck, 2014).
Results: Decreased P3 amplitude (Cz) for benefits and hazards ($p<0.05$) in the D group in comparison with control were

observed only in the negative feedback condition; there were no significant differences in the positive feedback condition. There was a significant feedback*group*condition effect ($p<0.005$) for P3 amplitude. P3 wave response to hazards showed a larger amplitude in comparison to response to benefits in the depressed group.
Conclusions: Female participants with higher depressive symptoms tend to have higher brain activation in response to hazards in comparison to benefits.
Supported By: grant AP05135266 Ministry of Education and Science of Kazakhstan to AMK
Keywords: Decision Making, Electroencephalography (EEG), Depression, ERPs, Emotion

F73. Efficacy of Brexanolone Injection in Subjects With Postpartum Depression With and Without Baseline Antidepressant Therapy: Insights From an Integrated Analysis of Three Pivotal Trials

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Background: Postpartum Depression (PPD) is the most common complication of childbirth. Brexanolone injection (BRX), an investigational, intravenous formulation of allopregnanolone, was examined in three pivotal trials in women with PPD, and an integrated, three-trial dataset was analyzed.
Methods: Women $\leq$6 months postpartum, with PPD and Hamilton Rating Scale for Depression (HAM-D) total scores $\geq$26 (Studies A and B) or 20-25 (Study C) received BRX (90 or 60 μg/kg/hr; BRX90 or BRX60) or placebo as 60-hour infusions. Randomization was 1:1:1 to BRX90, BRX60, or placebo (Study B) and 1:1 to BRX90 or placebo (Studies A and C). Stable baseline antidepressants were permitted from 14 days before screening through at least Hour 72. Depressive symptoms were assessed by HAM-D. Safety was assessed by adverse event reporting.
Results: Subjects were dosed as follows: 102 BRX90, 38 BRX60, and 107 placebo. At the Hour 60 primary endpoint, BRX90 showed a significantly larger reduction from baseline HAM-D score versus placebo ($p<0.001$). Antidepressants were used by 22% and 23% of the BRX90 and placebo subjects, respectively. The most common antidepressants ($\geq$3 subjects) were sertraline and bupropion for BRX90 and sertraline, fluoxetine, and paroxetine for placebo. At Hour 60, significant HAM-D score improvements were observed for BRX90 subjects with ($p=0.028$) and without ($p<0.001$) antidepressant medication versus their respective placebo groups. The most common adverse events ($\geq$10%) across BRX subjects were headache, dizziness, and somnolence.
Conclusions: BRX90 achieved the primary endpoint of a significant reduction in depressive symptoms versus placebo at Hour 60 irrespective of baseline antidepressant use.
Supported By: Sage Therapeutics
Keywords: Postpartum Depression, Brexanolone, Antidepressant, Allopregnanolone, Depression

F74. Impaired Fear Extinction in Omega-3 Fatty Acid Deficient Rats is Attenuated by Chronic Amphetamine Treatment

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Background: Mood disorders are associated altered prefrontal cortex (PFC) and amygdala (AMY) structural and functional connectivity, and deficits in the omega-3 fatty acid docosahexaenoic acid (DHA). Reciprocal connections between the rat PFC and basolateral AMY mediate conditioned fear acquisition and extinction, and this circuit undergoes robust synaptic pruning during adolescence. DHA promotes synaptogenesis and synaptic pruning, and chronic amphetamine (AMPH) treatment induces synaptic reorganization in the rat PFC. The present study investigated whether developmental deficits in brain DHA accrual and/or chronic AMPH exposure impact fear conditioning in young adulthood.
Methods: In-house bred male rats were maintained on a diet with (control, CON, n=16) or without (deficient, DEF, n=22) the omega-3 fatty acid alpha linoleic acid (ALA) from gestation to adulthood. From P40-P80, rats received thirty injections of AMPH (1 mg/kg) or saline. A 3-day cued fear conditioning protocol was initiated after a 10-day washout on P90.
Results: AMPH treatment increased locomotor activity similarly in CON and DEF rats. During fear acquisition training, DEF rats exhibited faster acquisition compared with CON rats, and there was no effect of prior AMPH treatment. During fear extinction, DEF rats took significantly longer to achieve extinction compared with CON rats. Prior AMPH treatment significantly accelerated extinction in DEF rats but not CON rats. Neither diet nor AMPH altered extinction recall.
Conclusions: These findings suggest that deficits in brain DHA accrual during development negatively impact the functional maturation of the PFC-AMY circuit, and that this effect is attenuated by chronic AMPH treatment.
Supported By: NIMH R01 MH107378
Keywords: Amphetamine, N-3 Fatty Acids, Fear Conditioning, Developing Brain

F75. How Many Sessions Needed for fMRI Neurofeedback Training to Increase Amygdala Activity and to Influence Functional Connectivity?

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Background: We examined the effect of a number of real-time fMRI neurofeedback (rtfMRI-nf) training sessions on the abilities to increase left amygdala (LA) activity and to influence LA resting-state functional connectivity (rsFC).
Methods: Mood and/or anxiety disorder (MA) patients were trained to upregulate LA activity while recalling positive autobiographical memory. Five patients completed 5 rtfMRI-nf (90min) sessions. One subject was excluded from rsFC analysis because of missing physiological data. rsFC was evaluated by GLM analysis with the mean LA signal as a regressor, and then a paired t-test was performed to compare beta maps between rtfMRI-nf sessions (post-versus-pre-connectivity changes at each session).
Results: Increased LA activity and reduced self-reported depression and anxiety were evident in the first rtfMRI-nf session. The mean percent BOLD signal change for LA was the highest at the first session and gradually decreased over sessions. Changes of LA were observed through the first to fourth sessions but not for the fifth rtfMRI-nf session. LA rsFC increased [$p < 0.005$ (uncorrected)] with: left superior temporal gyrus and right middle frontal gyrus (rMFG) - 1st visit; left superior frontal gyrus (lSFG) and rMFG - 2nd visit; left precentral gyrus and bilateral posterior cingulate gyrus - 3rd visit; left paracentral gyrus and lSFG - 4th visit.
Conclusions: A single rtfMRI-nf session is sufficient for subjects to self-upregulate LA activity, with the effect on rsFC observed in later training sessions. This suggests that the training effect on intrinsic brain activation could persist after the first successful upregulation of LA activity.
Supported By: This study was supported by the Laureate Institute for Brain Research and William K. Warren Foundation, and in part by the P20 GM121312 award from National Institute of General Medical Sciences, National Institutes of Health. The funders were not involved in the study design, data collection and analysis, and interpretation of results.
Keywords: Real-Time fMRI Neurofeedback, Amygdala, Depression, Anxiety, Treatment Response

F76. Persistent Intrinsic Functional Network Connectivity Alterations in Middle-Aged and Older Women With Remitted Depression

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Background: In younger populations, residual functional neural network alterations persist in remitted depression, yet there are less data for older adults who are at high risk of recurrence. This study tested for differences in intrinsic network functional connectivity in midlife and older women with remitted depression.
Methods: 69 women (24 with a history of depression and 45 with no psychiatric history) over age 45 entered the study and completed 3T MRI with a resting state acquisition. Participants with past depression met DSM-IV-TR criteria for an episode in the last 10 years, but not in the prior year. Whole-brain seed-to-voxel analyses examined the default mode network (DMN), executive control network (ECN), and salience network (SN), plus bilateral hippocampal seeds. All analyses adjusted for age and were conducted with a cluster FDR correction of $p < 0.05$ and a height threshold of $p < 0.001$ uncorrected.
Results: Women with a history of depression exhibited decreased connectivity between the SN, using a right insula seed, and ECN regions, specifically the left superior frontal gyrus. They also exhibited increased connectivity between the left hippocampus and the left postcentral gyrus. We did not observe any differences in connectivity for DMN or ECN seeds.
Conclusions: Remitted depression in women is associated with connectivity differences between the SN and ECN, and between the hippocampus and the postcentral gyrus, a region involved in interoception. Further work is needed to determine whether these findings are related to functional alterations and whether they are related to recurrence.
Supported By: K24 MH110598
Keywords: Intrinsic Connectivity Networks, Remitted Major Depressive Disorder (RMD), Women, Resting state functional connectivity MRI (fcMRI)

F77. Ventromedial Prefrontal Functional Connectivity During Value-Based Decision Making in Impulsive vs. Non-Impulsive Older Suicide Attempters

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Background: Impulsivity and disruptions in value-based decision making are both components of the suicidal diathesis; however, how these components interact is unclear.
Methods: 118 adults ages 45+ with a history of suicide attempts ($n = 35$), suicidal ideation without attempts ($n = 25$), depression without suicidal ideation or attempt ($n = 26$), and non-depressed controls ($n = 32$) performed a three-armed bandit learning task during fMRI scanning. A psychophysiological interaction (PPI) assessed differential ventromedial prefrontal cortex (vmPFC) connectivity at the time of reward feedback. The interaction of impulsivity, group, and PPI connectivity in the patient groups was assessed in areas showing a significant interaction of impulsivity (Negative Urgency UPPS subscale) and PPI connectivity in the non-depressed control group. Effects on behavior were investigated by assessing the interaction of PPI connectivity and previous reinforcement on the value of the next trial's choice.
Results: In non-depressed controls, impulsivity moderated the PPI between vmPFC and lateral frontoparietal regions (FDR $p < .05$). In patient groups, suicide attempters (vs. non-suicidal depressed and ideators) lacked modulation of vmPFC to lateral-frontoparietal PPI by impulsivity ($F2,73 = 4.69$; $p = 0.01$). Attempters vs. depressed controls displayed a weaker modulation of reinforcement-guided behavior by vmPFC to lateral-frontoparietal connectivity ($t = -2.82$, $p < 0.005$).

Conclusions: Suicide attempters high in trait impulsivity display abnormal vmPFC-cognitive control region connectivity during value-based decision-making, which undermines their ability to utilize reinforcement history in their choices.
Supported By: NIMH
Keywords: Reinforcement Learning, Suicide, fMRI, Computational Modeling

F78. The Impact of Family History of Depression on the Relation Between Episodic Memory Encoding and Intrinsic Hippocampal Connectivity

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Background: Family history of major depression (FH-MDD) connotes significant risk for depression, although the processes that mediate risk are unknown. Episodic memory encoding is one potential process as depression is robustly associated with deficits in encoding. Encoding is dependent on the hippocampus, a region with structural and functional abnormalities in depression. This study examines whether the association between hippocampal connectivity and episodic memory encoding is abnormal in those with FH-MDD, potentially reflecting a key mechanism of MDD's familial transmission.
Methods: Resting-state fMRI data were collected from 10 subjects with no FH-MDD, 23 with one generation of FH-MDD (parent or grandparent), and 20 with two generations of FH-MDD. FH-MDD was defined via direct interview and blind to proband's clinical status. Brain regions that showed a significant relation between intrinsic hippocampal connectivity and encoding (Wechsler Memory Scale-III) were further examined to determine the impact of FH-MDD.
Results: Preliminary results suggest that encoding was negatively correlated with hippocampus connectivity with medial prefrontal cortex (mPFC), pre- and post-central gyrus, supramarginal gyrus, and temporal pole. There was a trending Encoding x FH-MDD interaction for hippocampal-mPFC connectivity, $F(2,47)=3.023$, $p=.058$, such that those with no FH-MDD had a more negative relation ($r=-0.766$) between hippocampal-mPFC connectivity and encoding compared to individuals with one ($r=-0.661$) or two ($r=-0.420$) generations of FH-MDD. No other regions showed significant interactions.
Conclusions: Our preliminary results suggest that FH-MDD moderates the relation between episodic memory encoding and hippocampal-mPFC connectivity. Thus, FH-MDD may change the way the brain supports this critical cognitive ability, thereby increasing risk for developing MDD.
Supported By: NIMH RO1 036197
Keywords: Resting State fMRI, Family History, Major Depressive Disorder (MDD), Hippocampus, Encoding Memory

F79. Confidence and Action in Trans-Diagnostic Psychiatric Symptom Dimensions

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Background: Previous work has shown success utilising trans-diagnostic dimensions to disambiguate confidence relationships in psychiatry; in a perceptual decision-making task, 'Anxious-Depression' manifested in low confidence while 'Compulsivity' was related to over-confidence (Rouault, Seow et al., 2018). It remains unclear if these differences in confidence affect behaviour control — a key issue for disorders of compulsivity.
Methods: A general population sample ($N = 439$) performed a predictive inference task via Amazon's Mechanical Turk. We tested how individuals used feedback in the environment to update behaviour and confidence estimates, and the extent to which this process goes awry in distinct trans-diagnostic dimensions of psychopathology.
Results: Consistent with our previous report, individuals high in 'Anxious-Depression' had lower overall confidence, while 'Compulsive' individuals showed higher confidence ($Ps < .001$). As one might expect, trial-by-trial confidence appropriately tracked participants' tendency to adjust their decisions. While this coupling was intact in individuals high in 'Anxious-Depression', we observed an evident breakdown in the link between confidence and action for those high in 'Compulsivity' ($P < .001$).
Conclusions: Although 'Anxious-Depression' was linked to low overall confidence, confidence was nonetheless tightly linked to behaviour. In contrast, 'Compulsivity' was associated with overestimated confidence and a deficit in their ability to update behaviour as their confidence changed. These data are consistent with models of compulsive disorders that highlight how behaviour becomes divorced from intention.
Supported By: ISSF
Keywords: Confidence, Action Selection, Transdiagnostic Traits, Compulsivity, Anxious Depression

F80. Poster Withdrawn

F81. Combining Dorsolateral Prefrontal Repetitive Transcranial Magnetic Stimulation and Attentional Bias Modification Does Not Attenuate Maladaptive Attentional Processing in Dysphoric Students

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Background: High frequency repetitive Transcranial Magnetic Stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) has been shown to reduce depressive symptoms and improve cognitive biases such as attention

bias. One promising technique that may complement rTMS treatment is attention bias modification (ABM) training, given the similarity in modulating attention bias and affecting neuronal activity.
Methods: We tested whether the combination of rTMS treatment and ABM training in a single session would attenuate maladaptive attentional processing and improve mood in participants with subclinical depressive symptoms. We included 72 dysphoric but otherwise healthy participants who showed a heightened BDI-II score (between 9 and 25) in our main analyses. Participants were randomly assigned to one of four groups, receiving either 1) a single ABM treatment, 2) a single rTMS treatment, 3) a combination of ABM and rTMS or 4) a sham treatment.
Results: Mixed ANOVAs and supporting Bayesian analyses revealed no significant changes in attentional bias, attentional control, or mood after a combination treatment of rTMS and ABM training in a single session ($p=.641$, $BF10=0.005$), nor did a single session of rTMS independent of ABM training affect attentional bias systematically ($p=.571$, $BF10=0.019$).
Conclusions: The combined effect of rTMS and ABM treatment did not yield any significant differences as compared to control conditions, which was supported by additional Bayesian analyses. The null findings will be discussed in the light of the sample size, dosage and task specifics. Lastly, we will relate our findings to the ongoing discussion on ABM training in depression.
Supported By: Other
Keywords: Attentional Bias Modification, Transcranial Magnetic Stimulation (TMS), Dysphoria, Depression

F82. Attention Impairments and the "Inattention Biotype" in Major Depressive Disorder

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Background: Attention impairment is an under-investigated feature and diagnostic criterion of Major Depressive Disorder (MDD) that predicts poorer prognoses. Despite the centrality of attention for a variety of critical cognitive functions, we lack a detailed characterization of attention impairments and their neural signatures in MDD patients.
Methods: We advance a deep multi-modal characterization of selective attention impairment in MDD, using data acquired from $n=1008$ MDD patients and $n=336$ age- and sex-matched healthy controls participating in the international Study to Predict Optimized Treatment for Depression. Our characterization is anchored in a behavioral marker of selective attention and validated by independent measures of large-scale network dysfunction (fMRI, 15% of sample), oscillatory neural activity (EEG), and clinical symptoms.
Results: Selective attention impairment in MDD, unlike other cognitive behavioral measures, is specifically associated with intrinsic hypo-connectivity of the fronto-parietal attention network ($r(97)=0.23$, $p=0.02$) and not other networks (p's>.05). This attention impairment is also associated with decreased alpha (8-13 Hz) power at rest ($r(678)=-0.154$, $p<.001$), demonstrating that intrinsic connectivity and resting-state synchrony are related to a specific attention behavior measured independently. Selective attention impairment is independent of insomnia, excessive worrying, or depression symptom severity (p's>.05), but may increase negative biases ($r(679)=0.234$, $p<.001$) potentially perpetuating sad mood.
Conclusions: Attention impairment in MDD patients represents a distinct biotype of depressed individuals that is specific, cohesive, and observable across multiple units of analysis. Our findings provide a target for development of precise therapeutics to address inattention and inform a novel theoretical framework for understanding the biological pathways underlying attention impairment in MDD.
Supported By: National Defense Science and Engineering Graduate Fellowship (NDSEG)
Keywords: Attention, Fronto-Parietal Network, Alpha, biotypes, Cognitive Impairment

F83. Differential Effects of Ketamine on Mood Symptoms and Cognitive Function in MDD and PTSD

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Background: Ketamine, a dissociative anesthetic, is effective in reducing psychiatric distress in individuals with major depression (MDD) and posttraumatic stress disorder (PTSD). However, the effect of ketamine administration on cognition in these disorders has not been directly investigated. The present study sought to address this area by exploring the effect of ketamine administration on a battery of cognitive tests in individuals with MDD, PTSD, and age and sex matched healthy controls.
Methods: Individuals with MDD ($N=14$), PTSD ($N=14$), and healthy matched controls (HC; $N=17$) were recruited from the community. An average dose of 0.5 mg/kg ketamine was delivered intravenously over 40 minutes. Measures of mood (MADRS, HAM-D, PCL), and cognition (Cogstate battery) were collected prior to ketamine administration and at 1 and 24 hours post-administration.
Results: In both MDD and PTSD groups symptom severity was reduced following ketamine administration (p's<.001). Performance on visual memory ($p=.015$; $\eta 2p=.19$), verbal learning ($p<.001$ $\eta 2p=.39$), and psychomotor speed ($p=.013$; $\eta 2p=.20$) tasks worsened immediately following ketamine administration (i.e., lower verbal recall, slowed reaction times), and then returned to baseline levels 24-hours later. No group x test interactions were observed, suggesting the observed pattern of change did not differ by diagnosis.
Conclusions: Ketamine administration resulted in improved psychiatric symptoms both immediately and 24-hours post-administration in individuals with MDD and PTSD. By contrast,

ketamine had an acute deleterious effect on cognition which resolved by 24-hours post administration. Result have meaningful implications for clinicians advising patients on the effects of ketamine administration.
Supported By: VA National Center for PTSD
Keywords: Ketamine, Cognition, Major Depressive Disorder, PTSD

F84. Subjective Responses to Amphetamine in Adolescents With a Bipolar Phenotype

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Background: Individuals vary in their acute subjective responses drugs in ways that influence future use and misuse. One source of variation is psychiatric symptomatology. There is epidemiological and laboratory-based evidence that adolescents who report high rates of hypomania are at risk for drug abuse. In the present study, we examined subjective and physiological responses to acute oral d-amphetamine in 18-19-year-olds self-reporting a bipolar phenotype (BPP).
Methods: Healthy 18-19-year-old male and female volunteers ($N = 30$) who scored low (< 4) or high (>4) rates on a measure of bipolar symptomatology attended three 4-hr laboratory sessions. At the beginning of the sessions, they received 0, 10 or 20mg of d-amphetamine under double-blind conditions in randomized order. Heart rate, blood pressure, self-reported mood and subjective drug effects were monitored.
Results: Participants with the high BPP reported lower subjective responses to the low dose of d-amphetamine. They reported less "feeling" ($p < .01$) and "liking" ($p < .05$) the drug as well as less stimulation ($p < .01$) and euphoria ($p < .05$). Interestingly, at the higher dose they and reported more stimulation ($p < .05$).
Conclusions: The primary finding was adolescents with high BPP were less sensitive to the subjective effects of lower doses of amphetamine. However, the effects of the drug on cardiovascular measures did not differ between groups. These results suggest that the subjective responses to a stimulant drug are affected by psychiatric symptomatology, but are dissociable from the physiological effects. How these altered subjective responses affect future drug use remains to be determined.
Supported By: NIDA R01DA02812, T32DA043469; NIH T32GM007019
Keywords: D-amphetamine, Bipolar Disorder, Adolescence, Subjective Experience, Addiction

F85. Reported Side-Effects, Weight and Blood Pressure After Repeated Sessions of Transcranial Photobiomodulation

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Background: Transcranial Photobiomodulation (t-PBM) with Near-Infrared Radiation (NIR) has emerged as a potential treatment for brain disorders. t-PBM NIR penetrates the skull, modulating the function of the subjacent cortical areas of the brain. This study assessed the side-effects emerging from repeated LED t-PBM for the treatment of MDD.
Methods: A secondary analysis was performed on a double-blind, randomized clinical trial in MDD individuals, who received NIR t-PBM or sham therapy twice a week for eight weeks. Side effects were tracked weekly using the Systematic Assessment for Treatment-Emergent Effects - Specific Inquiry (SAFTEE-SI), while body weight and systemic blood pressure were recorded at baseline and endpoint.
Results: The NIR t-PBM group experienced more side-effects compared to the sham group, but only a trend for statistical significance was observed ([n=9 vs. 9] $\chi 2 = 3.60$; $df = 1$; $p = 0.058$). The rate of side-effects described by participants as "severe" in intensity was low and similar between the treatment groups ([n=9 vs. 9] $\chi 2 = 0.4$; $df = 1$; $p = 0.53$). The NIR group had three times as much weight gain (kg), though not statistically significant (NIR [n=6] 1.89±.929 vs. sham [n= 8] .67±3.41; z=-1.56, p=.120). In the NIR t-PBM group, diastolic blood pressure increased (mmHg), reaching statistical −not clinical− significance (NIR[n=6] 5.67±7.26 vs. sham [n=8] -6.13±6.88; z=-2.40, p=.016).
Conclusions: This exploratory study with a small sample size indicates that repeated sessions of NIR t-PBM may be associated with treatment-emergent side-effects. The metabolic and hemodynamic profile after repeated t-PBM appeared benign.
Supported By: Brain and Behavioral Research Foundation (NARSAD - Dr. Cassano); Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, NIH Award UL1 TR001102), and financial contributions from Harvard University and its affiliated academic healthcare centers
Keywords: Transcranial Photobiomodulation, Near-infrared light (NIR), Depression, Blood Pressure, Side Effects

F86. Predictive Model of First-Onset Depressive Disorders in Adolescent Females

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Background: Depressive disorders (DD) are among the most prevalent and impairing conditions in females. While their onset escalates throughout adolescence and young adulthood, it is unclear what characteristics in early adolescence predict subsequent onset. We aimed to identify predictors of first-onset DD using the Adolescent

Development of Emotions and Personality (ADEPT) all-female longitudinal cohort.

Methods: 550 girls (aged 13-15 years) completed comprehensive in-person assessments on psychiatric diagnoses, life stressors, family history, personality, peer and family relationships, and event-related potentials (ERP) (wave 1). Four subsequent waves (waves 2-5) were carried out through to age 16-18 years, with >92% retention. Logistic regressions and Receiver Operating Characteristic (ROC) analyses examined wave 1 predictors of DD onsets over the next 3 years.

Results: 78 participants had a first onset of DD after wave 1. Significant ($p<.05$) wave 1 predictors of DD were family history (of DD, anxiety, substance use disorder), antecedent anxiety and behavioral disorders, depressive symptoms, irritability, neuroticism, ruminative response style, stressors (e.g. family conflicts, peer victimization), and blunted reward positivity ERP during reward processing. A predictive model retaining only non-redundant measures yielded 78% sensitivity, 60% specificity, and Area Under the Curve=.74.

Conclusions: An array of early risk factors encompassing psychiatric disorders and symptoms, personality traits, life stressors, psychiatric family history, and atypical brain activity are informative for predicting first-onset DD and show a good classification accuracy, despite somewhat limited specificity. These results will be discussed in the context of prevention strategies for DD and other ADEPT findings.

Supported By: R01 MH093479; R56 MH117116

Keywords: Mood Disorders, Developmental Trajectories, Prevention, Risk Factors

F87. Longitudinal Association Between Low-Grade Inflammation and Specific Symptoms of Depression

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Background: Although the association between low-grade inflammation and depression is well established, few studies have investigated this association at the symptom level. We studied the longitudinal association between serum interleukin 6 (IL-6) and C-reactive protein (CRP) levels and specific depressive symptoms.

Methods: In the ALSPAC birth cohort, serum IL-6 and CRP levels were measured at age 9 years, and 19 depressive symptoms were assessed at age 18 years. We used modified Poisson generalized linear regression to calculate the risk ratio (RR) for each depressive symptom. We used confirmatory factor analysis to create two continuous latent variables for somatic/neurovegetative and psychological dimension scores and used structural equation modeling to test the association between IL-6 and these dimension scores.

Results: Using data from 2,731 participants, we found that individuals in the top third of the serum IL-6 distribution were more likely to develop diurnal mood variation (adjusted RR, 1.75, 95% CI, 1.13-2.69), concentration difficulties (adjusted RR, 1.50, 95% CI, 1.11-2.02), fatigue (adjusted RR, 1.31, 95% CI, 1.12-1.54), and sleep disturbances (adjusted RR, 1.24, 95% CI, 1.01-1.52) than those in the bottom third. CRP was not associated with any depressive symptom after confounding adjustment. IL-6 was associated with both somatic/neurovegetative ($\beta = 0.059$, $SE = 0.024$, $P = 0.013$) and psychological ($\beta = 0.056$, $SE = 0.023$, $P = 0.016$) scores.

Conclusions: Low-grade inflammation is particularly associated with the so-called somatic/neurovegetative symptoms of depression. These symptoms could be useful markers for treatment response in anti-inflammatory drug trials for depression.

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Keywords: Inflammation, IL-6, Depression, Somatic/Neurovegetative Symptoms, ALSPAC

F88. Elevated Glutamate Transporter Expression in Females With Depression

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Background: Major depressive disorder (MDD) is a common mental illness that has a strong association with suicidality. Conventional antidepressant treatments target the monoamine system, but only one-third of patients substantially improve with treatment. Mounting evidence indicates that abnormal function of the glutamate system contributes to the pathophysiology of depression. We have previously shown increased glutamatergic gene expression in the dorsolateral prefrontal cortex (DLPFC) of depressed females. Here, we have tested the hypothesis that genes regulating the glutamate transporters, rather than the monoamine transporters, have abnormal expression in depression.

Methods: We extracted RNA from the gray matter of the DLPFC from three groups of subjects: MDD suicides (n=51), MDD patients who did not complete suicide (n=28), and controls (n=32). We measured the expression of genes encoding transporter proteins within the glutamate (EAAT1, EAAT2, VGLUT1, VGLUT2) and monoamine systems (SERT, NET, DAT, PMAT, VMAT) using QPCR, and performed multivariate analysis of covariance to investigate effects of diagnosis and sex using SPSS v. 24.

Results: We detected a significant increase in glutamate transporter gene expression [$F(4,48)=3.45$, $P=0.015$] in females with MDD, but these differences were not observed in

males. The monoaminergic genes had similar expression in all diagnostic groups.

Conclusions: Our analyses reveal altered expression of glutamate transporters in the DLPFC of depressed females. The results may indicate novel biomarkers for MDD, possibly representing targets for improved drug treatment. Further studies are planned to test if these gene expression markers predict antidepressant efficacy in depressed females.

This work was performed in collaboration with Joel Kleinman MD PhD.

Keywords: Major Depressive Disorder (MDD), Gene Expression, Glutamate, Dorsolateral Prefrontal Cortex

F89. Differential DNA Repair Gene Promoter Methylation in Anterior Temporopolar Area Gray Matter in Bipolar Disorder

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Background: Enzymes of the base excision repair (BER) pathway, the major DNA repair mechanism, were shown to be dysregulated in bipolar disorder (BD). The underlying mechanisms are yet to be elucidated. We examined epigenetic DNA methylation regulation of genes encoding for BER enzymes with potential influences of various clinical features in BD.

Methods: Methylation levels were examined by Illumina Infinium Methylation EPIC BeadChip in 274 CpGs in the promoter region of 23 BER enzyme genes in post-mortem gray matter from dorsolateral prefrontal cortex (BA9) and anterior temporopolar cortex (BA38) of 20 BD patients (17 males, mean age: 47.5 ± 14.1 years) and 10 age- and sex-matched controls (8 males, mean age: 48.4 ± 13.4 years). Among BD cases, associations between clinical variables (sex, suicide, current mood, history of lifetime psychosis, lithium, valproate, antipsychotic, alcohol use, smoking) and methylation in seven genes were also examined.

Results: Compared to controls, BER genes NEIL1 ($p=0.006$), APE1 ($p=0.003$), XRCC1 ($p=0.004$) and POLε ($p=0.003$) were hypomethylated and MPG ($p=0.005$), MUTYH ($p=0.011$) were hypermethylated in BD only in BA38; results were not significant after adjustment for multiple comparisons (FDR-Q=0.282). Among tested variables, only history of lifetime psychosis and antipsychotic drug exposure were significantly associated with methylation in POLε (FDR-Q=0.029) and MUTYH (FDR-Q=0.025), after controlling for age and post-mortem interval.

Conclusions: Our findings suggest an epigenetically influenced BER mechanism in BD. Further studies are warranted to investigate gene expression and protein levels of BER enzymes in brain and peripheral tissues in BD, particularly in relation to psychosis and medication use.

Supported By: P30 GM103328

Keywords: Bipolar Disorders, DNA Methylation, Oxidative Damage, Base Excision Repair

F90. Sex Differences in Predictors of Completed Suicide

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Background: The glutamate system is the major excitatory system in the brain and abnormalities of this system occur in major depression (MDD). We have previously reported higher expression of glutamate receptor genes in MDD subjects who died by suicide (MDD-S) relative to MDD non-suicides (MDD-NS).

Methods: We preformed QPCR to measure the expression of glutamatergic genes in the gray matter of postmortem dorsolateral prefrontal cortex taken from depressed male suicides (n=24) and depressed male patients who did not die by suicide (n=15). In parallel, glutamatergic gene expression was tested in depressed female suicides (n=27) and depressed female patients who did not die by suicide (n=13). Gene interaction terms were generated as potential predictors of completed suicide. We tested the sensitivity and specificity of these potential predictors using receiver operator characteristic (ROC) analysis. ROC analysis illustrates the diagnostic ability of this potential biomarker as its discrimination threshold is varied.

Results: ROC analysis of the male groups shows that expression of GRIK3 and GRIA2 isoforms produced a good prediction of completed suicide. The area under the curve (AUC) is 0.81 (95% CI=0.67-0.95), $p=0.0011$. Analysis of the female groups shows that expression of GRIN2B, GRIK3 and SLC1A2 produced a good prediction of completed suicide. The area under the curve (AUC) is 0.81 (95% CI=0.68-0.94) $p=0.002$.

Conclusions: These results show that glutamatergic gene expression markers produce a good prediction of completed suicide when we tested males and females separately. Ongoing studies aim to replicate these data in a second cohort, and to identify additional markers to improve the accuracy of this prediction.

Keywords: Human Postmortem Brain, RNA Editing, Gene Expression, Glutamate Receptors, Dorsolateral Prefrontal Cortex

F91. Endocannabinoids and Risk for Depression in Traumatic-Injury Survivors

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Background: Biological mechanisms associated with response to trauma may impact risk for depression. One such mechanism is the endocannabinoid signaling (eCB) system, comprised of cannabinoid receptors (CB1), encoded by the CNR1 gene, and two major endogenous ligands, the endocannabinoids (eCBs) 2-arachidonoylglycerol (2-AG) and N-arachidonylethanolamine (AEA). Reduced serum 2-AG and a polymorphism in the CNR1 gene have been found to be associated with major depression. Posttraumatic stress disorder (PTSD) and major depression are often comorbid and we have found that circulating eCB concentrations at the time of traumatic injury and CNR1 genotype are predictors of PTSD 6 months later. The current investigation tests the hypothesis that these measures of the eCB system are also predictors of depression 6-months after trauma.
Methods: N=172 adults were recruited from the emergency department following traumatic injury and completed a blood draw for eCB assay and CNR1 genotyping; depression (Center for Epidemiologic Studies of Depression Scale-Revised [CESD-R]) and PTSD (Clinician Administered PTSD Scale) symptoms were assessed 6-months later. Multiple linear regression (outcome=CESD-R) was used to test 2-AG, AEA, and CNR1 snips as predictors of depression at 6-months.
Results: Controlling for age, gender, race/ethnicity, and PTSD, higher 2-AG predicted greater depression at 6-months (B=5.78, p=0.003); AEA was not significant (p>0.285). Carriers of the minor alleles for CNR1 snps rs806371 (B=6.11, p=0.009), rs1049353 (B=5.56, p=0.026), and rs2180619 (B=5.29, p=0.029) had greater depression at 6-months.
Conclusions: The eCB system may serve as a potential therapeutic mechanism for targeted remediation of depression after trauma.
Supported By: R21MH102838
Keywords: Endocannabinoids, Trauma, Depression, Genotype, Posttraumatic Stress Disorder

F92. Polygenic Risk Score from Schizophrenia Predicts PTSD and Depression Symptoms After Trauma Exposure

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Background: Posttraumatic stress disorder (PTSD) develops in about 10% of those exposed to trauma. Identifying those who develop early symptoms can be a powerful prognostic tool, as early intervention can be crucial for the disease course. Genetic susceptibility is an important risk-factor, but identifying single-nucleotide polymorphisms (SNPs) causal variants has been challenging, highlighting the polygenic architecture of PTSD and its symptoms. Many SNPs of small effect size may be more useful to capture such phenotypes. Polygenic risk score (PRS) from the largest genome-wide association study (GWAS) - the Psychiatric-Genomics Consortium for Schizophrenia (PGC-SCZ) – has shown shared vulnerability across psychiatric disorders, including Schizophrenia, MDD and BP. We aimed to evaluate whether the PRS from PGC-SCZ can predict PTSD, its symptoms, or comorbid depression in subjects assessed longitudinally after trauma-exposure.
Methods: Participants were recruited from the emergency department of a trauma-center and PTSD and depression assessed approximately 1 (n=267), 3 (n=238), 6 (n=197), and 12 (n=173) months after trauma. Genotyping from saliva-DNA collected at each data-point was performed with Psych-Array. Summary statistic from the PGC-SCZ was used to calculate PRS to predict PTSD or depression symptoms at different time points.
Results: SCZ-PGC was able to highly predict PTSD (r2=6.14% p=7.6x10-7) and depression symptoms (r2=3.96% p=7.6x10-5) at 1 month. Nominal predictions were observed at 3, 6 and 12 months for PTSD, and 6 and 12 months for depression symptoms.
Conclusions: Transdiagnostic psychiatric vulnerability assessed with PRS successfully predicts patients with distinct PTSD and depression risk and severity levels after trauma exposure and may facilitate early intervention.
Supported By: R01 MH094757 "Prospective Determination of Psychobiological Risk Factors for PTSD"
Keywords: MDD, PTSD, PRS, SCZ

F93. CYP2D6 Revisited in GENDEP, a Multicenter Clinical Trial of Nortriptyline and Escitalopram

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Background: The polymorphic CYP2D6 enzyme is estimated to be responsible for the oxidation of 20-25% of all drugs in clinical use. However, genotyping for its variants is not routinely clinically available. The gene is particularly complex, with different platforms analysing different subsets of variants. GENDEP (Genome-based therapeutic drugs for depression) is a multicentre clinical trial which found an association between CYP2D6 genotype and

nortriptyline concentration, but no association between CYP2D6 or CYP2C19 and response to nortriptyline. The CYP2D6 data were produced using the AmpliChip CYP450 Test, which had weaknesses, such as lack of coverage of hybrid alleles between CYP2D6 and its adjacent pseudogene (CYP2D7).
Methods: CYP2D6-specific TaqMan CNV probes (Hs04083572, intron 2 and Hs00010001, exon 9) were used to screen for gain or loss of copy including hybrid alleles. Specific long-PCR assays were used to follow up and characterize alleles.
Results: Of N=617, 14 had CNV probe patterns consistent with hybrid alleles, 42 had patterns consistent with only one copy of CYP2D6 (indicating the presence of a CYP2D6*5 deletion allele, of which 7 had not been previously detected), and 15 had patterns consistent with more than 2 copies of CYP2D6 (of which 5 had not been thus previously detected). Preliminary analysis of adjusted diplotypes versus log nortriptyline concentration and versus 10-hydroxynortriptyline:nortriptyline ratio shows an improvement in fit of the data.
Conclusions: We are providing updated, more comprehensive data for CYP2D6 in GENDEP. Preliminary analysis versus nortriptyline concentration phenotypes is promising and will be further analysed versus adverse drug reactions and indicators of antidepressant efficacy.
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Keywords: Antidepressant, SSRI, CYP2D6

F94. Human Brain Proteome-Wide Association Study of Longitudinally Assessed Late-Life Depression

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Background: Brain proteome can offer a valuable window into biological processes underlying late-life depression. Here we performed a proteome-wide association study of longitudinal measures of late-life depression.
Methods: Depression was assessed annually with the Center for Epidemiological Studies Depression scale in older adults recruited by the Rush Religious Order Study (ROS) and Memory Aging Project (MAP). An unbiased quantitative proteomic analysis of post-mortem brain tissue from the dorsolateral prefrontal cortex was performed using mass spectrometry and Tandem Mass Tag (TMT) isobaric labeling. A proteome-wide differential expression analysis as well as protein co-expression network analysis of longitudinal measures of depression were performed. Depression was the average of the depression scores assessed over the follow-up years for each subject.
Results: A total of 254 participants, followed annually for a mean of seven years, were included in the study. We detected 11,243 proteins after quality control. In the proteome-wide differential analysis, we found TMEM119 to have significantly lower abundance in subjects with higher depression scores after adjusting for sex, age, education, antidepressant use, cognitive diagnosis, and post-mortem interval at FDR < 0.05. The protein co-expression network analysis is in progress.
Conclusions: TMEM119 has been found to be highly and selectively expressed in microglia, the predominant immune cells of the brain. Furthermore, TMEM119 is a hub protein and marker of homeostatic microglia. Lower expression of TMEM119 is associated with neuroinflammation or activated microglia. Our findings suggest that late-life depression is associated with neuroinflammation.
Supported By: R01 AG056533; U01AG046161; U01 AG061357
Keywords: Proteome-Wide Association Study, Late-Life Depression, Longitudinal Study, Protein Co-Expression Network Analysis, Mass Spectrometry

F95. Effect of HLA Alleles on Suicide Attempts and Chronic Pain in Women

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Background: Women have higher rates of suicide attempts (SA). A prominent risk factor for SA is chronic pain (CP), which is also more common in women. Immune dysfunction is associated with both conditions. An individual's immune response is shaped, in part, by the polymorphic Human Leukocyte Antigen (HLA) locus, which has been implicated widely in major psychiatric disorders. The goal of this study was to identify common HLA genotypes associated with both SA and CP.

Methods: Genome-wide data (HumanOmni1-Quad) was used to impute 7 HLA genes in 504 SA cases and 3041 controls of African American females. HLA imputation was performed using HIBAG and multi-ethnic parameter estimates. HLA alleles with posterior probabilities <0.5 were excluded. Association with SA was evaluated using logistic regression. Association with CP rating was evaluated using linear regression in 834 subjects, controlling for age and ancestry (first two principal components). Bonferroni correction was used to adjust for multiple testing. Moderating effect of HLA alleles on the link between SA and CP was analyzed.
Results: SA is associated with CP in women (p=5e-8). HLA-DQA1*02:01 was more frequent in both SA cases (p=0.039) and individuals with chronic pain (p=0.046), but lost its significance after Bonferroni correction. Also, the association between SA and CP was not moderated by HLA-DQA1*02:01 (p>0.05). HLA-DQA1*02:01 have also been associated with other psychiatric disorders.
Conclusions: These results showed that HLA-DQA1*02:01 alleles are associated with SA and CP independently, and do not moderate the association between SA and CP.
Keywords: Suicide Attempts, Chronic Pain, HLA

F96. MicroRNA Dysregulation in Bipolar Manic and Euthymic Patients

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Background: Bipolar disorder (BPD) is a major psychiatric disorder with an unclear pathophysiology. Peripheral blood samples are easily drawn, making them are good candidates for diagnosing diseases. MicroRNAs are small non-coding RNA transcripts that regulate gene expression by binding to the 3'- UTR of mRNAs and directing their degradation. The aim of this study was to use blood plasma to investigate microRNA dysregulations in bipolar manic and euthymic patients.
Methods: Blood samples were collected from 58 patients with bipolar I disorder (19 manic, 39 euthymic) and 51 healthy controls. Total RNA was extracted from peripheral whole blood using Tri-Reagent (Sigma)
Results: Four microRNAs (miR-29a-3p, p=0.035; miR-106b-5p, p=0.014; miR-107, p=0.011; and miR-125a-3p, p=0.014) were upregulated in the entire bipolar group, compared to the healthy controls. Seven microRNAs (miR-9-5p, p=0.032; miR-29a-3p, p=0.001; miR-106a-5p, p=0.034; miR-106b-5p, p=0.003; miR-107, p<0.001; miR-125a-3p, p=0.016; and miR-125b-5p, p=0.004) were more upregulated in bipolar manic patients compared to the healthy controls, and two microRNAs (miR-106a-5p, p=0.013, and miR-107, p=0.021) showed statistically significant upregulation in the manic patients compared to the euthymic patients.
Conclusions: Our results showed greater miRNA dysregulation in the manic patients than in the euthymic patients. Two microRNAs could be more selective for bipolar manic episodes. Future studies should include depressive patients along with euthymic and manic patients
Supported By: Funded by HUBAK
Keywords: Bipolar Disorder, miRNAs, Mania, Euthymia

F97. Bipolar Depression: A Neuropsychological and MRI Brain Myo-Inositol Spectroscopy Controlled Study

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Background: Several published studies with proton magnetic resonance spectroscopy (1H-MRS) had shown myo-inositol (MI) concentrations changes in Bipolar Disorder (BD). Also, BD patients present cognitive impairment documented in specific areas such as attention, learning and memory and executive functioning. These impairments are present during the acute phases of illness and tend to persist into periods of relative wellness.
Methods: We studied 8 BD patients and 8 normal controls. The MI concentration by 1H-MRS in the medial and lateral prefrontal areas, fronto-orbital areas, insula, basal ganglia, thalamus and temporal and occipital cortex were measure. Also, a cognitive battery was administered and differences between the groups were analyzed. BD patients met criteria for a current depressed episode and were under treatment with lithium carbonate.
Results: No statistically significant differences were observed with 1H-MRS for MI concentration between PD patients and controls in any of brain areas studied. The group of depressive bipolar patients presented a significant difference in Executive Functions performance compared to healthy controls, primarily impairments in processing speed, inhibitory control, attention and cognitive flexibility.
Conclusions: Our finding with no differences between normal controls and depressive BD patients on lithium treatment on MI brain concentration are in agreement with previous published studies. The differences in performance in order execution and phonological fluency could be related to impulsivity, and differences in verbal memory associated with the executive component of free recall. Supporting the notion that specific cognitive functions are impaired during the depressive episode in subjects suffering from BD, even if they are under lithium treatment.
Supported By: PAYCID Mexico
Keywords: Myoinositol, MR Spectroscopy, Bipolar Disorder, Neurocognitive Tests

F98. Counts of Small Subgraphs Within the Resting Functional Connectome are Parsimonious, Stable and Individualized Features in Healthy as Well as Disordered Mood

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Background: Correlations of blood-oxygen level dependent signal time-series can define a connectome, in which brain regions represent edges and correlation coefficients edge weights. The large number of features of connectomes makes them hard to use in clinical studies. We tested if the counts of small topologically different subgraphs (graphlets) within connectomes would be sufficient to identify an individual over time and distinguish patients with depression from healthy controls.
Methods: Resting state functional MRI data for 23 healthy participants (age: 29.96 +-3.51, 15 F, 8 M) of the Human Connectome Project (HCP) from a test date and a follow-up retest was preprocessed with the Minimal Processing Pipeline developed by HCP. We kept the highest 20% edges across all participants to obtain undirected, unweighted graphs. We counted graphlets of size 5 or less and computed graphlet- and network-based distance metrics between scans from the same person to assess if they had minimal distance compared to all other scans. We compared the average counts of each graphlet between 37 healthy controls (age: 36.85+-12.74, 18 F, 19 M) and 47 depressed patients (age: 25.44+-4.75, 32 F, 13 M, 2 other) using t-tests, false discovery rate (FDR) corrected.
Results: Graphlet-based distance was sufficient to identify individuals' retest identities from their test scans. 11 graphlets demonstrated different mean counts between patients and controls at $p<0.05$, but did not survive FDR correction.
Conclusions: Graphlet counts uniquely identify individuals, suggesting that they are a parsimonious trait-like representation of the human connectome with potential use in clinical studies with relatively small sample sizes.
Supported By: NIH
Keywords: Resting State fMRI, Graph Analysis, Depression

F99. Higher Levels of Inflammatory Proteins are Associated With Reduced White Matter Integrity in Depressed Adolescents

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Background: Elevated inflammation has been linked with adult depression; few studies, however, have examined the relation between inflammatory proteins and depressive neurophenotypes in adolescents, specifically white matter integrity of the cingulum cingulate (CC), a key tract that underlies emotion regulation.
Methods: Twenty-nine adolescents diagnosed with Major Depressive Disorder (MDD) and forty-three controls recruited from the community ($N=72$; 24 males; 15.93 ± 1.10 years) completed a diffusion-weighted MRI scan, from which we computed mean fractional anisotropy (FA) across left and right CC. Concentrations of interleukin 1-beta (IL-1b), tumor necrosis factor-alpha (TNF-a), and resistin were assayed from dried blood spots using a Luminex multiplex bead array. Generalized linear models were used to test whether these inflammatory proteins were associated with CC FA across all participants.
Results: Accounting for age, sex, and BMI, depressed youth exhibited significantly higher levels of inflammatory proteins than did healthy controls (all $Bs>1.20\pm0.29$; all $ps<.001$) but did not differ in CC FA ($p=.250$). Further, higher levels of IL-1b and resistin were significantly associated with decreased CC FA across all participants (all $Bs<-0.40\pm0.18$; all $ps<.05$); higher levels of TNF-a had a trend-level association with reduced CC FA ($p=.065$).
Conclusions: Consistent with data from depressed adults, we found robust evidence of elevated inflammation in depressed adolescents and, further, that higher inflammation is associated with reduced white matter organization of the CC. Although depressed adolescents did not differ from healthy controls in white matter organization of the CC, we speculate that over time elevated inflammation among depressed adolescents will lead to reductions in fronto-cingulate-limbic white matter.
Supported By: K01(K01MH117442), R01(R37MH10149)
Keywords: Adolescent Depression, Diffusion Tensor Imaging (DTI), Inflammation, Inflammatory Cytokines, Fronto-limbic Connectivity

F100. Characterizing Grey Matter and White Matter in Pediatric Bipolar Disorder and Offspring

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Background: Due to the neurodevelopmental nature of bipolar disorder (BD), it is imperative to characterize the neurostructural signatures of pediatric BD in order to develop objective tools that assist in the diagnosis and treatment of mood disorders. Evaluating the development of unaffected offspring of BD parents, a genetically-high risk group, may also serve to identify makers of both susceptibility and protection.
Methods: Using magnetic resonance imaging and diffusion tensor imaging from a 3T Philips Intera scanner, the current study aims to evaluate cortical and subcortical grey matter (GM) differences as well as whole-brain white matter network alterations in 145 children between the ages of six and seventeen. Subject groups include children with BD, unaffected offspring of adults with BD, and healthy controls. GM segmentations were performed using Freesurfer 6.0 and whole-brain white matter networks were constructed using the FDT toolbox.
Results: Multiple One-Way ANOVAs examining the GM, which were bonferroni corrected for multiple comparisons and group, showed significant ($p<0.05$) volume differences in the bilateral caudate, cerebellum, and hippocampus, as well

as the left amygdala and right thalamus. Significant cortical areas included the bilateral paracentral, precentral, precuneus, superior temporal, and inferior parietal areas. In all significant areas, BD children had smaller volumes than healthy controls. White-matter networks are to be analyzed and BD children are hypothesized to have less efficiently connected networks.
Conclusions: Results show GM neurostructural differences in a large single simple study that are in accordance with current literature. Further investigations into whole-brain white matter networks will provide further insights into pediatric BD.
Supported By: Dunn Foundation
Keywords: Gray/White Matter Link, Pediatric Bipolar Disorder, Multimodal Neuroimaging

F101. Subcortical Volume and Suicidal Ideation in Treatment-Resistant Depression

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Background: Neuroimaging studies have revealed the involvement of subcortical regions in the aetiology of suicide and depression. Structural abnormalities in the amygdala have been associated with suicide attempts while reductions in hippocampal volume have been consistently associated with depression severity. This study explored the relationships between severity of suicidal ideation (SI) and depressive symptoms and amygdala and hippocampal volume in patients with treatment-resistant major depressive disorder (MDD).
Methods: Structural brain correlates associated with SI were assessed using magnetic resonance imaging (MRI) in 21 participants with treatment-resistant MDD. T1-weighted structural images were collected on a 3T Siemens MR-PET system using a multi-echo magnetization-prepared rapid gradient echo (MPRAGE) protocol. Cortical reconstruction and segmentation were performed using FreeSurfer-6.0.0. Severity of SI and depressive symptoms were assessed using the Columbia Suicide Severity Rating Scale and the Montgomery-Asberg Depression Rating Scale, respectively.
Results: Controlling for age and intracranial volume, a Pearson partial correlation revealed a negative association between lifetime SI severity and left amygdala volume ($p = 0.02$), which remains significant when adjusted for depression severity ($p=0.03$). In addition, depression severity was negatively correlated with left hippocampal ($p=0.006$) and amygdala ($p=0.05$) volumes.
Conclusions: These preliminary findings suggest that higher lifetime SI scores are associated with reduced amygdala volume. In addition, results showed agreement with previous findings reporting reduced hippocampal and amygdala volume with increased depression severity. Further research is required to confirm these findings and to investigate additional regions.
Supported By: University of Ottawa Medical Research Fund
Keywords: Suicidal Ideation, Treatment Resistant Depression, Major Depressive Disorder (MDD), Structural Magnetic Resonance Imaging

F102. Reduced Cingulate White Matter Volume and Increased Nonplanning Impulsivity in Veterans With a History of Suicide Attempts

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Background: Suicide is one of the leading causes of death for military personnel and veterans. Neuroimaging studies have revealed abnormalities in white matter tracts and brain connectivity in suicide behavior (SB); however, reports of alterations in white matter and their association with related behaviors are limited. The current study examined the relationship between cingulate white matter volume (WMV), impulsivity, and SB in veterans.
Methods: Seventy-eight veterans, ages 18 to 65, underwent magnetic resonance imaging on a 3T Siemens Verio scanner. Morphometric analysis of brain images was performed using FreeSurfer to evaluate differences in WMV in cingulate regions of interest. Participants completed the Columbia Suicide Severity Rating Scale (CSSRS) to assess lifetime suicide ideation and attempts and the Barratt Impulsivity Scale (BIS).
Results: Twenty-nine veterans had a history of suicidal ideation (SI), 23 had a history of suicide attempts (SA), and 26 had no SB. Controlling for age, sex, and total intracranial volume, reduced WMV was observed in the left rostral anterior cingulate cortex (rACC) in veterans with SA relative to veterans with SI, $p = .03$. Additionally, nonplanning on the BIS was negatively correlated with left rACC WMV for veterans with a history of SA, $p = .03$.
Conclusions: These data demonstrate a significant reduction in rACC WMV in veterans with SA that was negatively correlated with planning measures. These results are consistent with ACC involvement in inhibitory processes. These findings build on evidence that SB is associated neurobiological abnormalities and suggest that white matter changes may be related to actual attempts.
Supported By: Military Suicide Research Consortium (Yurgelun-Todd) W81XWH-10-2-0178
Keywords: Cingulate Cortex, White Matter, Impulsivity, Suicide Behavior, Veterans

F103. Using Multimodal Neuroimaging and Machine Learning to Determine Response to Subcallosal Cingulate Deep Brain Stimulation (SCC-DBS) for Depression

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Background: Deep brain stimulation (DBS) of subcallosal cingulate (SCC) has shown therapeutic promise for depression. However, patient selection is not ideal. While early SCC-DBS trials showed cerebral blood flow (CBF) changes, CBF has not been utilized for patient selection.

Here we aimed to learn whether multimodal neuroimaging provided better classification of response than single measures alone.
Methods: CBF and grey matter volume (GMV) were measured at baseline using arterial spin labelling and T1 MRI in 19 patients who received SCC-DBS, and 48 healthy controls (HCs). Parametric statistics were performed on CBF and GMV in the depression network to compare responders, non-responders and HCs. Then a multilayer perceptron machine learning (ML) algorithm was used to investigate whether CBF or GMV, or both were more accurate in classifying responders.
Results: Parametric statistics showed responders had significantly lower CBF in the depression network, whereas non-responders were no different from HCs. Including GMV as a covariate further improved classification. ML results showed CBF alone had a 63.2% classification accuracy, and VBM alone had a 63.2% classification accuracy, both considering age as a feature. The combination of CBF and VBM showed an 84.2% classification accuracy (80% sensitivity, 88.9% specificity).
Conclusions: Overall, the machine learning method that used a combination of CBF and GMV provided the best prediction results. Once validated prospectively, use of multimodal neuroimaging with machine learning may provide better patient selection in future SCC-DBS trials.
Supported By: AIHS CRIO grant
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Multimodal Neuroimaging

F104. Reduced White Matter Microstructure is Associated With Escalating Depressive Symptoms in Female Adolescents

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Background: Research has demonstrated associations between adolescent depression and alterations in white matter microstructure, particularly in regions implicated in emotion regulation. The present study explored sex-specific premorbid white matter microstructure correlates of escalating depressive symptoms during adolescence.
Methods: Adolescents from the National Consortium on Alcohol & Neurodevelopment in Adolescence (NCANDA) who were 14-16 years old at study entry and exhibited an increase in depressive symptoms, as measured by Center for Epidemiologic Studies Depression Scale (CES-D) scores, during three years of follow-up were selected for inclusion (N=177, n=81 females). Using diffusion tensor imaging, whole-brain regression analyses were used to examine relationships between baseline fractional anisotropy (FA) (voxel threshold $p<0.01$, cluster-forming threshold $p<0.05$) and peak increase in depressive symptoms during follow-up, as a function of sex. Participant age, alcohol use, and scanner platform, were statistically controlled for post-hoc.
Results: Among female adolescents, lower baseline FA in the right superior corona radiata and right external capsule was associated with greater increases in CES-D scores during follow-up (β=-0.0183, p=0.0024). In contrast, in male adolescents, greater baseline FA in the middle cerebellar peduncle was associated with greater increases in CES-D score during follow-up (β=0.0218, p=0.0012).
Conclusions: These findings suggest that, for female adolescents, less coherence and/or integrity in major integrative white matter pathways may represent a significant risk factor for subsequent escalation in depressive symptoms during adolescence, while male adolescents show a different pattern. Such results may serve as a neurobiological marker of risk and target for prevention of depression during adolescence, although replication will be necessary.
Supported By: This work was supported by the U.S. National Institute on Alcohol Abuse and Alcoholism with co-funding from the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Child Health and Human Development [NCANDA grant numbers: AA021697, AA021695, AA021692, AA021696, AA021681, AA021690, AA021691].
Keywords: Depression, Adolescence, Diffusion Tensor Imaging (DTI), White matter microstructure, Sex differences

F105. Neural Correlates of Risk and Resilience in Individuals With Family History of Mood Disorder

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Background: Family history of mood disorder increases risk for developing mood disorders, though not all individuals with such a history develop mood disorders. We examined risk and resilience factors in individuals with a family history of depression using MRI.
Methods: 3T T1-weighted MRI and diffusion tensor imaging scans were acquired in 26 healthy volunteers without family history of mood disorders (HV); 48 individuals with current/past mood disorder and a first- or second-degree relative with history of major depressive episode and suicide attempt (termed MOOD group); and 23 high-risk-resilient (HRR) individuals, with the same family history as MOOD group but no personal history of mood disorder (mean age 42). Grey matter volume (GMV) was analyzed in SPM12 using voxel-based morphometry. Fractional Anisotropy (FA) was quantified with Tract-based Spatial Statistics.
Results: HRR and MOOD groups showed lower GMV in cerebellum compared to HV (GMV contrasts threshold: voxel $p<0.001$, cluster-wise p(FWE-corrected)<0.05)). The HRR group also showed low GMV in frontal pole/insula compared to HV. Both HRR and MOOD groups showed lower FA in cingulate and parietal white matter than HV (FA contrasts threshold: p(tfce-corrected)<0.05). HRR additionally showed lower FA in prefrontal/temporal cortices compared to HV. No HRR vs. MOOD contrasts were significant.

Conclusions: Consistent with earlier studies, HRR and MOOD individuals exhibit overlapping structural brain differences compared to HV, including low GMV in cerebellum and low FA in cingulate and parietal white matter. Unique GMV and FA findings in HRR individuals may represent resilience factors, as most HRR individuals were through peak age of risk for MDD.
Supported By: NIMH R01MH108032
Keywords: Depression, Familiality, Gray Matter Volume, Diffusion Tensor Imaging (DTI)

F106. Structural Brain Characteristics in Treatment Resistant Depression: A Review of Magnetic Resonance Imaging Studies

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Background: Major depressive disorder (MDD) has been related to structural characteristics that are correlated with the severity of disease. However, the correlation of these structural changes is less clarified in treatment resistant depression (TRD). Our review summarizes the existing literature on structural characteristics in TRD to create an overview of known abnormalities of the brain in patients with MDD to form hypotheses about the absence or existence of a common pathophysiology of MDD and TRD.
Methods: Systematic research of Pubmed and Cochrane Library for studies published between 1998 and 2016 investigating structural brain changes in TRD patients compared to healthy controls or MDD subjects.
Results: Fourteen articles are included in this review. Lower gray matter volume (GMV) in the ACC, right cerebellum, caudate nucleus, superior/medial frontal gyrus and hippocampus does not seem to differentiate TRD from milder forms of MDD. Lower GMV in the putamen, inferior frontal gyrus, precentral gyrus, angular- and post central gyri together with specific mainly parietal white matter tract changes though seem to be more specific structural changes for TRD.
Conclusions: The currently available data on structural changes in TRD compared to milder forms of MDD and healthy controls cannot sufficiently distinguish between a 'shared continuum hypothesis' and a 'different entity hypothesis'. Our review clearly suggests that while there is quite some overlap in affected brain regions between milder forms of MDD and TRD, TRD also comes with specific alterations in mainly the putamen, and parietal white matter tracts.
Keywords: Structural Characteristics, Putamen, Therapy Resistant Depression, Neuro Imaging

F107. Cortical Thickness Features Differentiate 16-Week Antidepressant Response Profiles in Major Depressive Disorder

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Background: The heterogeneity of major depressive disorder (MDD) complicates the identification of reliable biomarkers for informing antidepressant treatment. In a large multi-site cohort of MDD patients and healthy controls (HC) as part of the CAN-BIND consortium, we assessed whether baseline cortical thickness features, measured on a vertex-wise basis, was related to antidepressant response at 16 weeks.
Methods: MDD subjects (n=181) were treated with escitalopram 10-20 mg/d for 8 weeks, and at this timepoint, responders continued on the same treatment, while those who had not achieved a >50% reduction in symptom severity received adjunctive aripiprazole 2-10 mg/d. FreeSurfer 6.0 was used to generate baseline vertex-wise cortical thickness values. MDD subjects were stratified into response profile groups at week 8 (escitalopram responders, non-responders) and week 16 (escitalopram continued responders, responders to escitalopram+aripiprazole and continued non-responders). We compared cortical thickness between each responder group and HC (n=95) using general linear model, controlling for age, sex and scanning site. Corrections for multiple comparisons were made using Monte Carlo simulation and cluster thresholding.
Results: All week 16 subgroups exhibited bilateral cortical thinning, as compared to HC, in bilateral medial frontal cortex, bilateral parietal cortex, left superior temporal gyrus and left insula. The greatest extent of thinning was seen in continued non-responders.
Conclusions: There are regions of significant cortical thinning associated to response profile at 16 weeks of pharmacological treatment in MDD, which may help to elucidate treatment subtypes based on cortical thickness as part of a biomarker profile that could inform early treatment decisions.
Supported By: Ontario Brain Institute
Keywords: Major Depressive Disorder (MDD), Cortical Thickness, Structural Neuroimaging, Antidepressant Response

F108. The Relationship Between the Habenula, Motivational Symptoms, and Ketamine Treatment

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Background: Ketamine causes rapid anti-anhedonic response in treatment-resistant depressed (TRD) patients, yet little is known about the brain regions underlying this effect. Theoretical and empirical accounts implicate the structure and function of the habenula as a key neural region driving symptoms of anhedonia. In this study, we examined the relationships among pre-treatment habenula volume, motivational symptoms and ketamine response.
Methods: Data were drawn from a randomized, double-blind, saline-controlled, crossover trial of ketamine (0.5mg/kg). The analysis included 20 TRD patients and 18 healthy controls with valid anticipatory and consummatory anhedonia measures (Temporal Experience Pleasure Scale) at baseline and several timepoints post-infusion. Habenula volumes were manually segmented, using an established geometric method, from high-resolution (0.7mm3 isotropic voxel) 7T structural magnetic resonance imaging scans acquired at baseline.
Results: Smaller habenula volume was associated with greater anticipatory, but not consummatory, anhedonia in patients at a trend level (p=0.058, r2=0.15), although this did not differ significantly from the correlation observed in controls (group*habenula, p=0.085). As expected, ketamine significantly improved both anticipatory (p=0.044) and consummatory (p=0.028) anhedonia. These effects were however not moderated by baseline habenula volume (anticipatory: p=0.68; consummatory: p=0.19).
Conclusions: These findings suggest that habenula gray-matter volume might be related to anticipatory, but not consummatory anhedonia. However, the habenula volume does not seem to be important for the anti-anhedonic effects of ketamine. Habenula activity has previously shown to drive negative motivation through interplay with midbrain neural circuits. Future studies should explore if the function, and not structure, of the habenula and connected reward-circuit underlies ketamine's anti-anhedonic effects.
Supported By: Intramural research program at National Institute of Mental Health
Keywords: Ketamine, Habenula, Anhedonia, Treatment-Resistant Depression, Gray Matter Volume

F109. Abnormal White Matter Connectivity Patterns Underlying the Tri-Level Symptoms of Depression and Anxiety

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Background: Depression has been linked to alterations in white matter integrity, including reduced fractional anisotropy (FA) in both cortico-amygdala and cortico-striatal tracts. Further research is needed to examine the relationships between these tracts and specific symptom profiles. Hierarchical models have shown a broad general factor underlying the shared features of anxiety and depression, referred to as general distress, and sub-factors that are specific to depression, referred to as anhedonia, and anxiety, referred to as fear. The present study examines the differential alterations of FA in uncinate fasciculus and accumbofrontal tract associated with hierarchically derived model symptoms; general distress, fear, and anhedonia.
Methods: Diffusion tensor imaging (DTI) and symptom data have been collected on a sample of 267 young adults ages 18-19 based on self-reported trait neuroticism and reward sensitivity. FSL's tract-based spatial statistics (TBSS) package was used to analyze and run correlations between FA and demeaned symptom factor scores.
Results: Preliminary analyses of 44 subjects did not yield significant relationships between FA and tri-level symptoms. However, correlations between accumbofrontal tract and anhedonia factor score approached significance (p=06). Also, exploratory analyses yielded trends at Anterior Thalamic Radiation (p=.055), Superior Longitudinal Fasciculus (p=.06), and Forceps Minor (p=.07). We are hoping to obtain more robust results with the entire sample.
Conclusions: This study contributes to the efforts for mapping the underlying neural mechanisms of depression and anxiety symptoms. For anhedonia, the trends found in accumbofrontal tract, CF Minor, and ATR are consistent with previous research and hold promise for further investigation.
Supported By: This research was supported by Grant R01-MH100117-01A1 from the National Institute of Mental Health to RN, REZ, SYB, and MGC
Keywords: Depression, Anxiety, Diffusion Tensor Imaging (DTI), Anhedonia

F110. Replicating the Effects of Ketamine on Global Brain Connectivity in Treatment Resistant Depression

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Background: Global brain connectivity (GBC) – a measure of hubs in resting-state functional magnetic resonance imaging (rsfMRI) – was found to be reduced in patients with treatment resistant depression (TRD). Furthermore, GBC values in responder returned to healthy controls (HC) levels after ketamine. However, GBC may be affected by preprocessing choices such as global signal regression, used to correct physiological noise and other non-neuronal signals. Here, we include physiological parameter regression prior to calculating GBC and aim to replicate reduced GBC in TRD.

Methods: We included 24 patients with TRD (mean MADRS 37.6 ± 5.1) and 22 healthy controls in a double-blind, placebo-controlled crossover study receiving either ketamine hydrochloride (0.5 mg/kg) or placebo. An 8-minute rsfMRI scan at 3T was conducted at baseline and at about 2 days after drug/placebo with simultaneously recorded cardiac and respiration data. We calculated whole-brain GBC maps from rsfMRI data preprocessed with physiological noise regression. We compared baseline to post-ketamine differences of GBC with a linear mixed effects model.
Results: In GBC maps between TRD patients and HC, we found no significant main effect or groupxdrug interaction in any brain region. Pairwise contrasts between drug, scan and group were not significant (all $p>0.05$, family wise error corrected). Additionally, no shift in GBC values was found between TRD and HC at baseline, or after treatment.
Conclusions: We do not find reduced GBC in TRD patients or changes in GBC 2 days after ketamine using physiological noise regression. Future work will investigate whether GBC is mediated by response to ketamine.
Supported By: Funding for this work was provided by the Intramural Research Program at the National Institute of Mental Health (NIMH), National Institutes of Health

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Disorders Research Award (to CAZ).
Keywords: Resting-State fMRI, Ketamine, Brain Connectivity, Treatment Resistant Depression

F111. Temporal and Parietal Morphometry Predicts Durable Antidepressant Response in Serial Ketamine Infusion

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Background: One-third of major depressive disorder (MDD) patients fail to respond to first-line interventions and symptoms become refractory with further failed treatments. Thus, more effective rapidly-acting interventions and treatment-response biomarkers are needed. Subanesthetic doses of serial ketamine infusion (SKI) can prolong initial antidepressant response, though effects typically diminish within weeks. We used machine learning to identify pre-treatment structural neuroimaging and demographic profiles predictive of sustained SKI response.
Methods: Thirty-one participants (age= 39.7+/- 11.1; 12 females) with treatment-resistant MDD received SKI: four single low-dose (0.5mg/kg) intravenous infusions three times weekly. Patients underwent MR imaging before treatment. Depression severity was assessed before and after treatment using the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR). FreeSurfer v6.0 estimated cortical thickness (CT) and subcortical volumes of 103 brain regions. FSL's DTIFit v5.0.11 estimated fractional anisotropy, kurtosis, mean axial, and radial diffusivity for 48 JHU atlas tracts. Random forest regression (RFR) models combined with 500 80-20% split cross-validation folds and nested feature selection predicted individual QIDS-SR percent changes 5 weeks following SKI using pre-treatment imaging features, age, and sex.
Results: Correlation between RFR-predicted and actual QIDS-SR change was $r=0.37$ ($p<0.0001$). The right superior and inferior parietal, bilateral middle temporal, and left insula CT was selected in 99-100% of 500 cross-validation iterations. Overall, these features correlated with QIDS-SR change between $r=0.50$ to 0.55; increased pre-treatment CT associated with poorer sustained outcomes.
Conclusions: Although these results require validation in a larger cohort, we observed a consistent set of pre-treatment temporo-parietal CT features predictive of sustained response to SKI 5-weeks post-treatment.
Supported By: This study was funded in part by a NARSAD Young Investigator Grant to Benjamin Wade (27786) and NIMH grants to Drs. Narr and Espinoza (R01MH092301, K24MH102743, U01MH110008).
Keywords: Ketamine, Treatment Resistant Depression, Machine Learning, Multimodal Imaging

F112. Morphometric Similarity Networks in Childhood Anxiety and Irritability

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Background: Irritability and anxiety frequently co-occur. Few studies examine associations between dimensionally-assessed anxiety or irritability and neural structure. We used a cortical-network based method with multi-parameter structural MRI data to estimate anatomical connectivity within subjects and probe cortical structural features associated with anxiety or irritability.
Methods: T1-weighted scans were acquired in a trans-diagnostic sample of 331 youth (mean age=13.57, 45.78% male) and processed using FreeSurfer (v5.3.0). Morphometric similarity matrices were constructed by computing correlations between regional pairs of MRI feature vectors. Regional nodal degree was calculated by counting edges and thresholding at the 10% most positive correlations. Anxiety and irritability symptoms were assessed using the Screen for Child Anxiety Related Disorders (SCARED) and the Affective Reactivity Index (ARI). Partial least-squares (PLS) found the optimal low-dimensional relationship between nodal degree and symptoms. The cognitive functions co-localizing with cortical regions most associated with PLS components was identified using Neurosynth.
Results: PLS analysis revealed a 3-component solution ($p = 0.045$) with PLS1, PLS2 and PLS3 explaining 34%, 12%, and 10% of the variance in symptoms. These corresponded to both ARI and SCARED, SCARED alone, or ARI alone, respectively. Cortical regions with strongest PLS1 weights

(e.g. medial prefrontal cortex, temporal pole), PLS2 weights (e.g. frontoparietal network, motor cortex) and PLS3 weights (e.g. cingulate cortex, anterior insula) are implicated in social, fear/motor, and default mode network/conflict monitoring functions, respectively.
Conclusions: These findings suggest individual differences in childhood anxiety and irritability can be distinguished by analysis of combined cortical structural features using a network-based approach.
Supported By: NIH Medical Research Scholars Program; NIMH
Keywords: Structural Neuroimaging, Childhood Psychiatry, Partial Least Squares, Surface-Based Morphometry, Mood Disorders

F113. Hippocampal Subfield-Specific Sex Differences in Patients With Major Depressive Disorder

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Background: Recent research has explored hippocampal subregional volumes (HSV) in Major Depressive Disorder (MDD). Here we examined the effects of gender and age on HSV in MDD.
Methods: Data from the multi-site CAN-BIND program was obtained and included 191 subjects with MDD (females = 126) and 165 controls (HC; females = 99). Freesurfer 6.0 subfield-specific pipeline was used for segmentation. Participants were analyzed by gender and age.
Results: HSV significantly differed between MDD and HC in women only. On average, depressed females had a smaller left hippocampal volume (3378+/-300 mm3 versus 3482+/-321 mm3; 3% reduction; $t(223) = 2.492$, $p = 0.013$), left hippocampal tail (533+/-72 mm3 versus 561+/-74 mm3; 5% reduction; $t(223) = 2.882$, $p = 0.004$), right hippocampal tail (545+/-71 mms versus 582+/-70 mm3; 6% reduction; $t(223) = 3.948$, $p = <0.001$), left molecular layer (557+/-54 mm3 versus 573+/-55 mm3; 3% reduction; $U = 5140$, $p = 0.024$) and left subiculum (421+/-42 mm3 versus 440+/-51 mm3; 4% reduction; $t(223) = 3.047$, $p = 0.003$). Age analysis found significant reductions in specific HSVs in MDD during early reproductive years (20-35 years of age) in women only. In women over age 35, differences were only significant in the right hippocampal tail (536+/-69 mm3 versus 575+/-64 mm3; 7% reduction; $t(98) = 2.792$, $p = 0.006$).
Conclusions: Gender and age are important variables to consider in assessing HSV in MDD. More specifically, small hippocampal tail volumes may be more likely in women, particularly young women.
Supported By: Ontario Brain Institute, Canadian Institutes of Health Research, Lundbeck, Bristol-Myers Squibb, Pfizer, Servier
Keywords: Affective Neuroscience, Sex Differences, Mood Disorders, Brain Magnetic Resonance Imaging (MRI)

F114. Dynamic Functional Alterations of the Emotional Face Processing Network in Young People With Depression

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Background: Emotional face processing is altered within major depressive disorder (MDD), likely stemming from a negative attentional bias. Despite this, limited research has investigated the relationship between brain mechanisms and symptomology during adolescence. The present study examined effective connectivity during emotional processing in youth with MDD compared with healthy controls.
Methods: This study recruited 68 unmedicated, help-seeking youth with moderate to severe MDD (Mean age = 19.6, SD = 2.8) and 71 healthy controls (Mean age = 20.1, SD = 2.9). The fMRI paradigm included three conditions: one shape matching and two implicit face processing tasks. To construct the dynamic causal models, six volumes of interest were extracted: V1, inferior occipital gyrus, fusiform gyrus, amygdala, dlPFC and vmPFC. Bayesian model averaging (BMA) was then used to calculate parameter estimates.
Results: In both groups, task performance was associated with common activation within the face processing network. Comparison of BMA parameter estimates demonstrated significantly greater modulation between the vmPFC and amygdala during sad face processing in patients with MDD, $t(102.7) = -2.1$, $p = .04$, but decreased modulation between dlPFC and amygdala for fearful faces, $t(137) = -3.7$, $p < .001$. Within patients, fear modulation between fusiform gyrus and dlPFC was correlated with baseline depressive symptom severity ($r = -.40$ $p = .001$).
Conclusions: Patients with depression show distinct connectivity alterations as they process sad and fearful faces. The alterations in patients with MDD are associated with symptom severity and thus may be a potential target for clinical intervention.
Supported By: NHMRC
Keywords: Major Depressive Disorder (MDD), Dynamical Causal Modeling, Functional Neuroimaging, Emotional Face Processing

F115. Common and Dissociable Disruptions in Reward Circuit Functional Connectivity in Bipolar Disorder and Obesity

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Background: Obesity, an important cardiovascular risk factor (CVRF), is associated with important clinical characteristics of bipolar disorder (BD) among both adults and youth. Although previous task-based and resting state functional magnetic resonance imaging (fMRI) studies support alterations in the reward circuit in obesity and BD independently, patterns of altered resting state functional connectivity (rsFC) that link obesity and BD remain unclear.
Methods: A seed-to-voxel analysis was used to compare rsFC of the ventral striatum, orbitofrontal cortex (OFC), and frontal polar cortex (FPC) in 87 adolescents, including 35 normal weight BD, 18 overweight BD, and 34 normal weight healthy controls (HC).
Results: Compared to HCs, BD patients (both normal weight and overweight) showed reduced negative rsFC between the left ventral striatum and the posterior cingulate cortex (PCC), a region of the default mode network (DMN) as well as increased rsFC between the OFC and the cerebellum. Overweight BD patients showed increased rsFC between the OFC and cerebellum compared to normal weight participants (both HC and BD) as well as altered connectivity within the FPC and between the FPC and multiple regions, including the insula.
Conclusions: The current study isolated common and dissociable patterns of rsFC in the reward circuit in adolescent BD and obesity. Reduced negative functional connectivity between the ventral striatum and DMN (PCC) may reflect ineffective disengagement of the reward circuit during rest in adolescents with BD. Furthermore, altered connectivity within the FPC and between the FPC and insula may be characteristic of adolescent BD-overweight comorbidity.
Supported By: Ontario Mental Health Foundation; Canadian Institutes of Health Research (CIHR)
Keywords: Bipolar Disorder, Adolescence, Resting State Functional Connectivity, Reward Circuitry, Obesity

F116. Gender Differences in Stability of Brain Functional Connectivity

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Background: Understanding gender differences of the brain's intrinsic functional architecture may lead to a better understanding of the pathophysiology of many psychiatric disorders whose prevalence differs between genders. Recently, the dynamic brain functional connectivity (FC) has emerged as a major topic in resting-state functional magnetic resonance imaging (rs-fMRI) studies, and possible associations have been reported between several psychiatric disorders and the temporal stability of brain FCs. However, little is known about whether or not there is a gender difference in brain FC stability.
Methods: The analyzed sample consisted of 337 healthy volunteers from the Human Connectome Project (HCP) data, which were randomly separated into two demographically matched subsamples (N = 168 and N = 169). Rs-fMRI data were preprocessed via HCP convention and dynamic functional networks were constructed across a wide range of density (1% ~ 50%) using the sliding-window approach, with nodes defined by the Cole-Anticevic Brain-wide Network Partition. Temporal correlation coefficient was calculated at each density and compared using repeated-measures analysis of covariance models with density as within-subject factor and gender as between-subject factor, covarying for age, education and head motion.
Results: Female volunteers showed significantly higher temporal correlation coefficients than male volunteers in both the two subsamples ($p = 0.0006$ and $p = 0.00004$, respectively), suggesting their brain FCs are more stable over time.
Conclusions: Our findings provide important evidence of gender differences in brain FC stability and highlight the importance of controlling for gender in dynamic rs-fMRI studies.
Keywords: Gender Differences, Resting State Functional Connectivity, BOLD Functional MRI, Dynamic Functional Network Connectivity (dFNC)

F117. Intrinsic Brain Functional Connectomes in Bipolar Disorder

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Background: Connectomics allows for comprehensive description of brain network architecture and provides a novel framework to understand psychiatric disorders. Using this approach, we systematically characterized alterations across the whole brain connectome and in well-established large-scale functional brain networks in euthymic bipolar disorder (BP) individuals.
Methods: Twenty-four euthymic BP and 34 age/gender matched healthy controls (HC) completed 5 fMRI tasks on a 3T MRI scanner. Intrinsic functional connectivity was analyzed from these tasks and was used to map inter-regional connectome matrices. We parcellated each individual's brain image into 333 cortical and 10 subcortical brain regions to map the whole brain connectome. We also mapped connectivity matrices for the default mode, central executive, cingulo-opercular,

cingulo-parietal, dorsal/ventral attention, salience, negative/positive affect, sensory motor, auditory and visual brain networks. Network-based statistics with permutation testing (corrected $p<0.05$) were then used to compare these connectome matrices between BP and HC.
Results: Whole brain connectome functional connectivity in BP subjects relative to HC was characterized by an overall reduction. This was also reflected in the central executive, cingulo-opercular, dorsal attention, auditory and sensory motor networks. In contrast, BP subjects had significant hyperconnectivity in the default mode network compared to HC.
Conclusions: Our results suggest that bipolar disorder is characterized by alterations in intrinsic brain networks that underlie self-referential mental activity, tonic alertness and top-down control of executive functioning and attention. Notably, our patient group was euthymic during testing, and thus these alterations may represent trait characteristics.
Supported By: National Health & Medical Research Council of Australia
Keywords: Connectomics, Bipolar Disorders, Intrinsic Connectivity Networks, Brain Functional Connectome, Functional MRI

F118. Ketamine and Attentional Bias to Threat: Dynamic Causal Modeling of AMPA and NMDA Connectivity Estimates From Magnetoencephalography

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Background: The glutamatergic modulator ketamine elicits rapid antidepressant response in patients with treatment-resistant depression (TRD). Recent work has suggested that AMPA-mediated glutamatergic neurotransmission following synaptic potentiation leads to increased gamma-band power following ketamine, which might explain how ketamine influences mood. This research sought to extend these findings by probing magnetoencephalographic (MEG) gamma-band responses during an attentional bias to threat task in TRD patients, while also measuring differences in AMPA- and NMDA-mediated connectivity.
Methods: MEG data were collected from 19 drug-free TRD patients during a dot probe task with emotional faces. Data were collected at baseline and 6-8 hours following both ketamine and placebo-saline infusions. Source-localized gamma power was projected using the multiple sparse priors routine in SPM12, and dynamic causal modeling (DCM) was used to measure changes in AMPA- and NMDA-mediated connectivity.
Results: Source-localized gamma estimates identified a network of brain regions showing enhanced stimulus-evoked responses. DCM comparisons between two plausible models of message-passing between early visual (EV) and inferior frontal gyrus (IFG) demonstrated direct, recurrent connections between these regions better fit the data. Parametric empirical Bayes applied to AMPA and NMDA connection estimates demonstrated that ketamine increased the posterior probability for NMDA-mediated modulations on forward connections from both EV to IFG and amygdala to IFG.
Conclusions: These findings add to a growing literature showing that attentional bias to threat recruits a network of brain regions. It also adds to a growing literature on gamma-band responses following ketamine administration. Finally, these findings highlight a role for ketamine in modulating emotional face processing in TRD.
Supported By: Intramural Research Program at the National Institute of Mental Health, National Institutes of Health
Keywords: Magnetoencephalography, Major Depressive Disorder (MDD), Ketamine, Treatment Resistant Depression, Cognition

F119. Age Trajectory of Deep White Matter Intensity in Bipolar Disorder Type-I Using MRI

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Background: Myelin development in the cortex follows an "inverted U" trajectory across the healthy lifespan, peaking in middle adulthood. This can be seen using myelin-sensitive magnetic resonance imaging (MRI) signals such as the T1-weighted/proton density-weighted (T1/PD) ratio. It has recently been shown that in Type-I bipolar disorder (BD) the T1/PD MRI signal in the cortex follows a significantly flattened age trajectory. In this study we investigate myelin development in the deep white matter in patients with BD by looking at the age trajectory of the T1/PD MRI signal.
Methods: We analyzed a sample of Type-1 BD ($n=45$) and healthy controls ($n=51$) aged 17-45 years matched between-groups on age, sex & BMI. We collected T1/PD MRI images at 3 Tesla to produce 1mm isotropic whole brain images. These were segmented using FreeSurfer v.6.0. The average signal in deep white matter was fit to this model in controls and BD groups separately: Signal = Age + Age^2.
Results: The model significantly fit the control data (p-uncorrected=0.0216) as an inverted quadratic with a peak around 36 years old. This is similar to the myelin trajectory that is observed in the healthy cortex. The fit in BD was not significant (p-uncorrected=0.97).
Conclusions: We show that there is an inverted U trajectory in the T1/PD MRI signal of deep white matter in healthy adults and that this trajectory was not present in BD Type I. Taken together with findings in the cortex, this suggests whole-brain myelin abnormalities in BD. Future work could investigate all subcortical structures using the technique.
Supported By: CIHR
Keywords: Bipolar Disorder-I, White Matter, Structural Magnetic Resonance Imaging, Intracortical Myelination, Aging

F120. Parsing Distress in a Transdiagnostic Sample: Relationship Between Impulsive Sensation-Seeking and Intrinsic Functional Connectivity of Large-Scale Networks

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Background: Abnormalities in reward processing may lead to anhedonia or elevated sensation-seeking, contributing to psychological distress. This analysis aimed to define groups of young adults (half of whom were distressed/help-seeking) based on self-report measures of reward sensitivity, and to assess group differences in intrinsic functional connectivity (iFC).
Methods: Distressed (DS; n=125) and healthy (HC; n=132) young adults (18-25 years old) completed questionnaires assessing sensation-seeking, anhedonia, and mood/anxiety. Participants underwent a neuroimaging protocol, including a 6-minute resting-state scan. K-means cluster analysis was performed to define groups based on self-report measures. After preprocessing and extracting networks, we tested whether groups differed according to (1) seed-based iFC, using seeds key to reward/emotion processing (ventral striatum, ventrolateral prefrontal cortex, and bilateral amygdala) and (2) network-based iFC, using the Network Based Statistic (NBS) to assess iFC of large-scale networks (i.e. default mode network; DMN, cingulo-opercular network; CON, frontoparietal network).
Results: We identified a three-group solution that separated HC (n=112), DS with high impulsivity/sensation-seeking (n=40; HIGH), and DS with low sensation-seeking (n=48; LOW). Compared to HC, HIGH showed increased iFC between left amygdala and bilateral insulae (left: t=5.19, corrected p=.001; right: t=4.12, corrected p=.008). Using NBS, HIGH vs. HC showed increased iFC between bilateral amygdalae and a cluster in CON (corrected p=.03). In contrast, LOW vs. HC showed increased iFC within a cluster in the DMN (corrected p=.02).
Conclusions: Using a clustering algorithm in a trans-diagnostic sample, we identified two distressed groups that separated according to reward-sensitivity/impulsivity and showed distinct patterns of iFC in large-scale networks.
Supported By: R01MH100041
Keywords: Intrinsic Connectivity Networks, Reward Responsiveness, Young Adulthood

F121. Examining the Relationship Between a Continuous Measure of Bipolarity and Gray Matter Volume in Unmedicated Individuals With Unipolar and Bipolar Depression

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Background: Given the overlapping symptomatology and genetic diatheses of major depressive disorder (MDD) and bipolar disorder (BD), some investigators have argued that these conditions exist on a continuous spectrum. The bipolarity index (BI) is a scale that considers bipolarity as a continuous construct and was developed to assess confidence in bipolar diagnosis. Here we explored whether BI scores correlated with gray matter volume (GMV) in a sample of unmedicated unipolar and bipolar depressed individuals.
Methods: 158 subjects (139 with MDD, 19 with BD) in a major depressive episode were assigned BI scores using a modified BI scale based on available clinical research data. T1-weighted MRI scans were obtained and processed with SPM12 (CAT12 toolbox). Whole brain cluster-wise regression of BI scores was performed on GMV. Data were thresholded with voxel-level $p<0.001$ and FWE-corrected cluster-level $p<0.05$. Age, sex, and total intracranial volume were included as covariates.
Results: GMV was inversely associated with BI score in four regions (largest cluster: left lateral occipital cortex, cluster size (1.5mm)=2195; peak-T=4.47; $p<0.001$, smaller clusters in bilateral angular gyri and right frontal pole). Clusters were no longer significant after controlling for diagnosis. GMV was not associated with BI score within the MDD cohort alone.
Conclusions: BI scores were associated with decreased GMV in unmedicated subjects with MDD and BD, but these associations appeared driven by categorical diagnosis. Future work will examine other imaging modalities in association with BI scores, and consider elements of the BI scale most likely to be related to brain structure.
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Keywords: Major Depressive Disorder (MDD), Bipolar Disorder, Voxel Based Morphometry, Gray Matter Volume, Bipolarity

F122. Koro Syndrome Displaced Rostrally: Nasal Retraction Syndrome

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Background: Nasal retraction as a variation of Koro-like syndrome associated with Bipolar mania and psychosis has not heretofore been reported, such a case is presented.
Methods: 54-year-old right handed female admitted for mania believed that her nose was disintegrating and retracted into her face. she also complained of inability to smell. Patient was paranoid fearing that staff were going to drink her blood. She stated, “I’m from another planet and came here to save the world, and that gang members are taking out organs and selling them.”
Results: Mental Status Assessment: Disheveled, hyperactive, distrustful, hyper verbal, poor impulsivity, labile affect, inattentive, flight of ideas with delusional thought content. Cranial Nerves (CNs): CN I: Alcohol Sniff Test: 0 cm (Anosmia). Cerebellar: Finger to nose: end point dysmetria bilaterally. Slow rapid movements of left upper extremity. 3++ throughout

and Pendular knee and ankle jerk were 4+ with sustained clonus. Positive reflexes include jaw jerk, Bilateral Hoffman reflexes, and bilateral Palmomental reflexes.
Conclusions: Koro-like syndrome variation with nasal retraction has not heretofore been reported. The specified delusion for this individual remains unclear, possibly, the nidus for this anosmia which she suffered in a primitive way with associations of an absent proboscis. Presence of this syndrome with absence of schizophrenia may suggest it's occurrence in mood disorders. Presence of diffuse atavistic reflexes suggests wide spread damage to the Cortex bilaterally, consistent with encephalopathy. Presence of Jaimas Vu postulates possible Temporal Lobe Epilepsy. Further exploration for presence of this taxon in psychiatric and neurologic disorders is warranted.
Keywords: Delusions, Mood disorders, Depression, Anxiety, Mania, Psychotic

F123. Comparison of fMRI Emotional Processing Tasks Used for Detecting Effects of Ketamine and Predicting Response in Depression

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[1]National Institute of Mental Health

Background: Neuroimaging has been used to examine the effects of ketamine, a rapid-acting antidepressant, on brain activity. Previous research has used various types of emotional processing tasks, yet it is unclear which task(s) may be most effective for detecting the impact of ketamine. We compared two such tasks to examine the differential results for ketamine's effects and for prediction of response to ketamine.
Methods: Participants included 33 unmedicated patients with MDD who received infusions of ketamine (0.5 mg/kg) and placebo, two weeks apart. At baseline and two days after each infusion, participants were scanned at 3T fMRI during an emotion evaluation task and a dot probe attentional bias task. We conducted fMRI analyses of each task to examine effects of ketamine, and to test for baseline activation predictive of antidepressant response (voxel-level $p<0.001$; cluster-level FWE-corrected $p<0.05$).
Results: While both tasks showed differences in brain activity between post-ketamine and post-placebo scans, the emotion evaluation task showed more robust differences, with larger and more significant clusters across the brain. For the analysis of baseline activation predicting response to ketamine, there were fewer significant results, but more findings again in the emotion evaluation task.
Conclusions: Our findings showed that both tasks detected effects of ketamine, yet there were greater effects in the emotion evaluation task. This type of task focused on processing emotional stimuli may be more effective in demonstrating differences in brain activity associated with ketamine, as compared to an attentional bias task. This is valuable for future research related to ketamine's effects on brain function.
Supported By: NIMH Intramural Research Program
Keywords: Functional MRI, Ketamine, Major Depressive Disorder, Emotional Processing

F124. Mapping the Neural Correlates of Mood and Anxiety Disorders Onto Research Domain Criteria: A Meta-Analysis of 226 Task-Related Functional Imaging Studies

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Background: Mood and anxiety disorders are highly comorbid and characterized by persistent negative states. This study sought to identify shared abnormalities in brain activity across mood and anxiety disorders that might underpin their clinical overlap.
Methods: Systematic literature review of functional magnetic resonance imaging literature over the last decade identified 226 studies that compared task-related brain activity between healthy individuals ($n = 4755$) and patients with mood, post-traumatic stress and anxiety disorders ($n = 4507$). The Research Domain Criteria framework was used to code task contrasts according to their corresponding domain and construct. Quantitative meta-analyses were conducted to identify clusters of convergence of the peak coordinates of whole-brain case-control differences. Statistical inference was based cluster-forming voxel-level threshold of $p < 0.001$, with family-wise error correction.
Results: Three right-sided transdiagnostic clusters of hypoactivation, mainly associated with dysfunction in tasks of cognitive control, were identified in the inferior prefrontal cortex/insula, the inferior parietal lobule and the putamen. At a lower level, transdiagnostic clusters of hyperactivation, primarily associated with dysfunction in tasks corresponding to the negative valence system, were detected in the perigenual/dorsal anterior cingulate cortex, the left amygdala/parahippocampal gyrus, and the left thalamus.
Conclusions: These results demonstrate that the overlap between mood, post-traumatic stress and anxiety disorders involves shared dysfunction in brain regions associated with cognitive and negative valence system that could serve as a foundation for developing neuroscience informed interventions for prevention and treatment.
Supported By: R01
Keywords: Meta-Analysis, Research Domain Criteria (RDoC), Mood Disorders, Task fMRI

F125. Magnetoencephalography of the Suicide Implicit Association Task

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[1]National Institute of Mental Health

Background: Suicide is difficult to predict as many individuals are unwilling to report their ideations/intentions. The Suicide

Implicit Association Task (S-IAT) is a behavioral task using reaction time to compare associations between the self/life and self/death relationship. A positive score on the task is associated with risk for suicide attempt. The S-IAT has recently been adapted for neuroimaging. Using pilot data from an ongoing study, we extend these findings using magnetoencephalography (MEG) to measure S-IAT electrophysiological correlates.

Methods: MEG was collected from subjects (n=22) during an adapted S-IAT; 4 acutely suicidal (AS) patients, 5 patients with a history of suicide attempts (HS), 6 patients with depression but no suicide attempts (DP), and 7 healthy volunteers (HC). We examined stimulus-evoked gamma band (30-58 Hz) responses, as previous findings suggest gamma is a surrogate marker of homeostatic balance.

Results: Behaviorally, AS patients did not demonstrate implicit biases (p=0.65). HCs also did not demonstrate implicit biases (p=0.24). However, both HSs and DPs exhibited significant biases toward self/life associations (p<0.05). MEG source analyses demonstrated that a network of regions including early visual, anterior ventral temporal, and inferior frontal cortex were activated during the task. When contrasting self/life vs self/death trials directly, left inferior frontal cortex exhibited higher gamma for self/life, while right ventral fusiform cortex exhibited higher gamma for self/death.

Conclusions: We demonstrate the S-IAT can detect implicit biases in our patient sample. We also demonstrate selective MEG activation for self/life versus self/death trials, highlighting potential target regions for mediating suicide risk.

Supported By: NIH

Keywords: Depression and Suicide, Magnetoencephalography, Neuroimaging, Suicide Attempts, Behavior Markers

F126. Nucleus Accumbens Volume Predicts Allostatic Load and is Moderated by Sex and Treatment Modality in Youth With Depression and Obesity

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Background: Youth with depressive disorders and obesity share reward circuit anatomical and functional abnormalities. These disorders can be conceptualized under an allostatic load (AL) model, or cumulative wear and tear on the body. Modification of AL may help improve overall health outcomes. While studies have examined the role of sex and treatment type on depression outcomes, none have evaluated relations between structure in this reward circuit and AL, or how sex and treatment modify this relation. This study aimed to examine the relation between the reward hub nucleus accumbens (NAcc) volume and AL, and how sex and treatment moderated this relation.

Methods: Sixty-nine youth aged 9-17 with depression and obesity were assessed on psychometrics, systemic AL markers, and NAcc volume analyzed with FreeSurfer. We controlled for age, IQ, and peer-victimization given previous evidence related to NAcc volume.

Results: The model revealed a significant relation between AL and NAcc (p=.0485). There was a significant NAcc volume by sex by treatment interaction (p=.0339) such that, in males not in treatment, smaller NAcc related to higher AL, while larger NAcc related to higher AL in males in treatment. Total AL was lower in the treatment group. A similar pattern was seen in female youth, but AL stratification by NAcc volume was lost with treatment.

Conclusions: These findings reveal a signification relation between NAcc volume and AL and moderation by sex and treatment. These data suggest that both AL and NAcc volume may be important markers of disease remission in youth.

Supported By: National Institute of Mental Health (R01MH106581; Singh)

Keywords: Nucleus Accumbens, Sex Differences, Allostatic Load, Adolescent Depression, Prediction of Treatment Outcome

F127. Neural Correlates of Emotion Processing in Youth at Familial Risk for Mood Disorders

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Background: Youth at familial risk for major depressive (MDD) and bipolar (BD) disorders have aberrant face emotion processing. However, dysregulation in emotion processing that distinguishes between youth at high risk for MDD and BD are not well understood.

Methods: We examined fMRI data during an implicit emotion processing in healthy offspring of parents with BD (BD-risk, n=29), MDD (MDD-risk, n=44), and healthy controls (HCLs, n=28). We conducted voxelwise whole-brain analyses to differentiate between BD-risk, MDD-risk, and HCLs during the processing of positive (happy) and negative (fearful) faces. We also conducted context-dependent connectivity analyses. Parameter estimates in regions that showed significant differences between BD-risk, MDD-risk, and HCLs were also correlated with depression severity, mania severity, and global functioning.

Results: The BD-risk group showed decreased activation in the left putamen (Z=4.38, FWE-corrected p=0.002) and right putamen (Z=4.63, FWE-corrected p=0.0004) compared to MDD-risk and HCLs when processing happy versus calm faces. During positive emotional processing, the BD-risk youth also showed decreased left putamen connectivity with the left anterior cingulate cortex (ACC) compared to MDD-risk and HCLs (Z=4.04, FWE-corrected p=1.04 × 10^-5). Stronger connectivity between the left putamen and left ACC in BD-risk youth correlated with higher global functioning (r(93)=.244, p=.020).

Conclusions: The putamen and ACC are important regions for reward and emotion regulation. BD-risk youth compared to MDD-risk youth recruit these regions less effectively while processing positive face emotions. Differential activation and connectivity of these regions may result in aberrant emotion

processing that distinguishes between youth at risk for BD and MDD.
Supported By: Ford Foundation Predoctoral Fellowship; the National Science Foundation Graduate Research Fellowship Program; Stanford's DARE Fellowship; NIMH (grant K23MH085919); Stanford Child Health Research Institute
Keywords: Functional Magnetic Resonance Imaging, Major Depressive Disorder (MDD), Bipolar Disorder, Emotional Facial Processing, Youth

F128. Structural Magnetic Resonance Imaging for Individual Predictions for Electroconvulsive Therapy Remission Utilizing Machine Learning

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Background: Biomarkers predictive of individual response to electroconvulsive therapy (ECT) are informative for clinicians and patients when considering the balance of risk and benefit for the treatment. We aimed to investigate the accuracy of predicting an individual's ECT response by utilizing machine learning to analyze structural magnetic resonance imaging (MRI) data.
Methods: Twenty-seven depressed patients who received clinically indicated ECT were recruited. Clinical demographics and pretreatment structural MRI data were used to build two models that predict remission and post-ECT Hamilton Depression Rating Scale (HAM-D) scores. We used elastic-net regularization for feature selection and built two models using support vector machine (SVM). A leave-one-out cross-validation (LOOCV) was used to validate model performance. We investigated whether MRI data could improve model accuracy when compared to models that used only clinical variables.
Results: Compared to models that include only clinical variables, the models including both clinical and structural MRI data improved the prediction of ECT remission: the prediction accuracy improved from 74% to 93%. Features selected consistently across all individuals for predicting remission included volumes in the gyrus rectus, the right anterior lateral temporal lobe, the cuneus, and the third ventricle.
Conclusions: Pretreatment structural MRI data improved the individual predictive accuracy of ECT remission, and only a small subset of features was important for prediction.
Keywords: Electroconvulsive therapy (ECT), Melancholic Depression, Magnetic Resonance Imaging, Support Vector Machines, Prediction of Treatment Outcome

F129. Preliminary Findings of a Microvascular-Neurostructural Link in Adolescents With and Without Bipolar Disorder

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Background: Neuroimaging studies have found anomalous regional brain structure among youth with bipolar disorder (BD). Thus far, it is not known whether anomalous cerebral microvasculature is associated with BD-related neurostructural differences. We examined this potential association using retinal vascular photography, a proxy of cerebral microvascular pathology.
Methods: 49 adolescents (n=25 BD, n=24 healthy controls [HC]), aged 14-19 years, underwent 3T MRI and retinal vascular photography. T1-weighted images were processed through FreeSurfer to yield cortical thickness, as well as volume and surface area (SA) values for five ROIs: amygdala, hippocampus, anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), and ventromedial prefrontal cortex (vmPFC). Retinal photographs were taken following pupil dilation with a Topcon TRC 50 DX, Type 1A camera. Retinal arterial and venular caliber were measured, and the arteriovenular ratio (AVR) was computed. Wider arteriolar and narrower venular caliber are associated with better cerebral and vascular health.
Results: AVR was not significantly different between groups ($t=1.69$, $p=0.097$). In the BD group, higher arteriolar caliber was associated with larger prefrontal volume ($r=0.44$, $p=0.03$). In the HC group, narrower venular caliber was associated with greater vlPFC thickness ($r=-0.57$, $p=0.004$) and greater AVR was associated with smaller left amygdala volume ($r=-0.49$, $p=0.01$).
Conclusions: These preliminary findings demonstrate associations between retinal vascular caliber and brain structure among adolescents in regions relevant to BD, and to cognition and emotion in general. Prospective studies with larger samples are warranted to evaluate the directionality of these findings and to evaluate for group-by-retinal vascular interactions.
Supported By: OMHF; BBRF
Keywords: Bipolar Disorder, Neuroimaging, Retinal Photography, Mood Disorders, Microvessels

F130. Subfield-Specific Hippocampal Volumes in Youth at Risk for Mental Illness

Nikita Nogovitsyn[1], Amelia Srajer[1], Meghan Muller[1], Paul Metzak[1], Stefanie Hassel[1], Roberto Souza[1], Signe Bray[1], Catherine Lebel[1], Benjamin Goldstein[2], Sidney Kennedy[3], Zahinoor Ismail[1], Andrea Protzner[1], Jean Addington[1], and Glenda MacQueen[1]

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Background: Hippocampal volume (HV) alterations can be present before the onset of psychosis in those individuals who are at clinical risk for psychosis with subthreshold symptomatology. However, it is unclear whether sub-field specific HV changes parallel the progression of SMI from the premorbid through the distress and attenuated syndromes to the discrete disorder phases. We investigated baseline HV in adolescents at various stages of risk for SMI.
Methods: The sample consisted of 182 participants (12-25 years) from the Canadian Psychiatric Risk and Outcome (PROCAN) study. There were four study groups: individuals

with early mood symptoms (Stage 1a, n=43) and subthreshold psychotic symptoms (Stage 1b, n=70); asymptomatic youth at risk due to family history of SMI (FHR, n=32) and healthy controls (HC, n=37). MRI scans were segmented using FreeSurfer 6.0 hippocampus subfield-specific workflow.
Results: One-way ANOVA followed by Bonferroni tests revealed group differences within left fissure ($F(3,181)=5.8$, $p<.01$), CA4 ($F(3,181)=3.1$, $p<.05$) and GC-ML-DG $F(3,181)=2.5$, $p=.05$) and right CA1 $F(3,181)=3.3$, $p<.05$). FHR participants were more likely to have proportionally smaller CA4 as compared to HC ($R2=.31$, $F(1,69)=4.4$, $p<.05$, controlled for total brain volumes (TBV). Stepwise linear regression revealed associations between trauma scores and left CA4 and fissure volumes ($R2=.05$, $F(1,181)=5.9$, $p<.01$); depressive symptoms were associated with left fissure, parasubiculum and right CA1 volumes ($R2=.14$, $F(1,181)=10.6$, $p<.001$).
Conclusions: Differential patterns of selective hippocampal volume deficits characterize risk stages for SMI. Isolated subfield-specific volume reductions may precede the shift to the symptomatic risk stage.
Supported By: This work was supported by the Brain Canada Foundation and the Mathison Centre for Research & Education at the University of Calgary.
Keywords: Hippocampus, Clinical High-Risk States for Psychosis, Clinical Staging, Structural MRI, FreeSurfer

F131. Multimodal Graph Theoretical Brain Networks and the 9-Year Cumulative Disease Load of Depression and Anxiety

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Background: Major depressive disorder (MDD) and anxiety disorders have been associated with deficits in functional and structural brain networks. It remains unclear how disease load impacts
Methods: Seventy-seven patients with MDD and/or anxiety disorders and 34 healthy controls underwent structural diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rsfMRI). Graph theory was used to extract topological characteristics of both structural and functional brain networks. We examined the association between graph theoretical measures and cumulative disease load measured at five time points over nine years preceding the imaging assessment.
Results: In structural brain networks, higher disease load was associated with lower path length and higher global efficiency (suggesting a shift from small-world architecture toward random networks) and increased betweenness centrality of the motor cortex and superior parietal gyrus. In functional brain networks, cumulative disease load was associated with higher local efficiency in default mode network (DMN) regions and lower efficiency of the left inferior frontal gyrus
Conclusions: Higher disease load was associated with differential structural and functional brain network properties, reflected in loss of small-world characteristics in structural networks and increased functional connectivity of DMN regions.
Keywords: Major Depression, Anxiety Disorders, Brain Networks, Graph Theory, Multimodal Imaging

F132. The Relationship Between Ibuprofen, Peroxisome Proliferator-Activated Gamma Receptor Gene Expression, and Neural Activation During an Emotional Faces Task

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Background: Both animal and human studies suggest that ibuprofen may have antidepressant effects. Ibuprofen may exert such effects as an agonist for peroxisome proliferator-activated gamma receptors (PPARγ). Activation of PPARγ in the context of stress has anti-inflammatory effects and may protect against depression. The present pharmaco-fMRI study was conducted to examine the effect of ibuprofen and PPARγ gene expression on emotion-related neural circuitry.
Methods: Twenty healthy control participants (10 female) completed three fMRI scans involving an emotional faces task. Placebo or ibuprofen (200 and 600 mg) doses were administered one hour before the task began in a pseudo-randomized order and double-blind fashion. After each scan, participants provided whole blood samples for PPARγ gene expression. Dose and PPARγ main and interaction effects on brain activation (faces minus shapes) were assessed with a linear mixed effects model; subject was included as a random effect. Whole-brain results were considered significant at voxel-wise $p<.005$, corrected for multiple comparisons (>96 voxels).
Results: No significant effects were found for ibuprofen dose. Greater PPARγ gene expression was positively correlated with BOLD activation in medial prefrontal cortex, posterior cingulate cortex, and precuneus ($p<.005$). An interaction between PPARγ and ibuprofen dose on BOLD activation was observed in the precuneus ($p<.005$).
Conclusions: At the doses used, ibuprofen did not demonstrate significant effects on neural activation during emotional face processing. However, a PPARγ-linked pathway may relate to the "default-mode" activity involved in self-referential

processing. Future studies are needed to clarify the generalizability and functional impact of these findings for mental health.
Supported By: William K. Warren Foundation
Keywords: Brain imaging, fMRI, PPARgamma, Ibuprofen, Emotional Face Processing

F133. Cerebral Blood Flow is Altered According to Mood States in Adolescents With Bipolar Disorder

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Background: Multiple prior studies have examined cerebral blood flow (CBF) in relation to mood states in adults with bipolar disorder (BD). We set out examine CBF in regards to mood states in adolescents early in the course of BD, regarding which little is known.
Methods: 129 adolescents (mean age 17.34+/-1.42 years) were recruited, including 72 BD (28 hypomanic/mixed, 19 depressed, 25 euthymic) and 57 healthy controls (HC). CBF was ascertained using pseudocontinuous arterial spin labeling (ASL) magnetic resonance imaging (MRI). Region of interest (ROI) analysis (amygdala, anterior cingulate cortex (ACC), middle frontal gyrus, and total gray matter) was complemented by whole brain voxel-wise analyses. Within-BD regression analysis using age and sex as covariates examined the association of mania and depression severity with CBF.
Results: In ROI analyses, CBF differed between groups in the ACC ($F=2.89$, $p=0.04$), with post-hoc analyses showing higher CBF in the euthymic group than in HC. An inverse relationship was found between depression scores and CBF in the ACC ($\beta=-0.32$, $p=0.02$). In corrected voxel-wise analyses, CBF in the euthymic BD group was significantly higher than in the HC group in temporal, precentral, and occipital regions.
Conclusions: Elevated regional CBF in euthymic BD adolescents, divergent from prior findings of reduced regional CBF in BD adults, may relate to abnormal developmental trajectories in BD adolescents. Higher CBF in euthymic BD adolescents may reflect compensatory perfusion mechanisms required to maintain euthymia. Longitudinal studies are needed to understand the progression of perfusion abnormalities in adolescents and young adults with BD.
Supported By: Ontario Mental Health Foundation (OMHF), Canadian Institutes of Health Research (CIHR).
Keywords: Bipolar Disorder, Adolescents, Cerebral Blood Flow, Mood Symptoms

F134. Association of Neuroinflammation With Duration of Untreated Major Depressive Disorder

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Background: People with major depressive disorder (MDD) exhibit increasing persistence of major depressive episodes (MDE), however, evidence for neuroprogression is scarce. Microglial activation is implicated in neuroprogression and may be measured with PET imaging applying [18F]FEPPA to bind translocator protein (TSPO). This study examined the relationship of TSPO total distribution volume (VT) with duration of untreated MDD, as well as predictors of total illness duration and antidepressant exposure.
Methods: 50 MDD subjects and 30 controls underwent [18F]FEPPA PET to measure TSPO VT in prefrontal cortex (PFC), anterior cingulate cortex (ACC) and insula (INS). Duration of untreated MDD, and the combination of total duration of disease and duration of antidepressant treatment were investigated to assess their predictiveness of TSPO VT.
Results: Duration of untreated MDD was a strong predictor of TSPO VT ($p<0.0001$), as were total illness duration ($p=0.0021$) and duration of antidepressant exposure ($p=0.037$). In subjects who had untreated MDD for $\geq$10 years, TSPO VT was 29−33% greater in the PFC, ACC, and INS than in subjects who were untreated for $\leq$9 years. TSPO VT was also 31−39% greater in the primary regions of subjects with long duration of untreated MDD compared with controls ($p=0.00047$).
Conclusions: TSPO VT, is greater in subjects with chronologically advanced MDD with long periods of no antidepressant treatment than in MDD subjects with short periods of no antidepressant treatment, which is strongly suggestive of a different illness phase. Consistent with this, the yearly increase in microglial activation is no longer evident when antidepressant treatment is given.
Supported By: CIHR
Keywords: Positron Emission Tomography, Major Depressive Disorder (MDD), Neuroprogression, Microglial Activation, Translocator Protein (TSPO)

F135. Modeling Mania at the Cellular Level

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Background: In vitro models of disease are essential to preclinical and translational attempts at understanding human diseases. Within psychiatric research, there is an increased ability to examine living neuronal cells directly in the form of induced pluripotent stem cell (iPSC) lines or olfactory neuroepithelial cell progenitor (ONP) lines. However, to be able to examine these cells directly, one needs to be able to model, at the cellular level, complex conditions that have behavioral, not just physiological, manifestations.
Methods: For cells in culture to model mania they must: 1) display a known physiologic abnormality known to occur in manic humans (construct validity); 2) the induced physiologic abnormality must be correctable with a known antimanic agent (predictive validating); and 3) demonstrate changes in activity or excitability under conditions that are mimicking “mania” (face validity).
Results: Addition of glutamate to ONP, an excitatory neurotransmitter which is believed to be an important aspect of mania in humans, can induce elevated intracellular sodium

concentration which is a known and well-demonstrated abnormality in cells of humans with mania. Furthermore, treatment with lithium normalizes intracellular sodium concentrations elevated by glutamate ONLY in ONPs obtained from bipolar individuals and NOT in cells obtained from non-bipolar subjects. Finally, glutamate-treatment of ONPs will induce apoptosis preferentially in ONPs obtained from bipolar patients than ONPs from non-bipolar individuals.
Conclusions: ONP derived from subjects that have bipolar illness can be modeled to exhibit 'mania' by the addition of glutamate.
Keywords: Cell Culture, Cellular Model, Bipolar Disorder-I, Glutamate, Intracellular Sodium

F136. Cerebral Blood Perfusion Predicts Response to Antidepressant Treatment in Major Depressive Disorder

To see this abstract, please see Oral Abstract #O14.

F137. Detecting Emotion From Passively Recorded Speech Segments

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Background: PRIORI is a system for recording and analyzing speech collected passively. There are 81 subjects from the Prechter Bipolar Disorder (BD) Program that have used PRIORI for up to one year. A subset is the basis for a study of emotional patterns in BD.
Methods: A subset of 17,237 segments from 12 BD subjects was annotated for activation and valence of the speech segments using human annotators and a 9-point Likert scale. Machine learning analysis used a deep feed-forward neural network (FFNN) that operates on the eGeMAPS feature set, and a convolutional neural network (CNN) classifier that operates on log Mel-frequency bank (log-MFB) features.
Results: The mean of both emotion ratings during manic states is more positive and activated compared to the corresponding within-subject ratings during depressed states (t-test with $p < 0:01$). The distribution of emotion ratings between subjects is significantly different (one-way ANOVA $p < 0.01$). A Tukey-Kramer post hoc test of the 66 possible pairwise subject comparisons. found activation to be significantly different in 51 cases and valence was found to be significantly different in 48 cases ($p < 0:01$). CNN modeling showed a Pearson Correlation Coefficient of 0.712 and 0.405 for activation and valence.
Conclusions: Emotion is an intermediate measure of speech and acoustic features related to mood states and may be a useful predictor of subsequent mood state changes. Human annotation of emotional states from speech may be useful in training computational algorithms in predictive modeling of mood states.
Supported By: NIMH, NSF, Prechter Bipolar Research Program, Tam Foundation
Keywords: Bipolar Disorder, Emotion, Mood, Speech Markers, Mobile Health Application

F138. A Combined Reinforcement-Learning Drift-Diffusion Model to Understand Choice Behaviour in Remitted Depression and Relapse After Antidepressant Discontinuation

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Background: 30% of patients in remission relapse after antidepressant discontinuation within 6 months, but no established predictors of relapse exist. Understanding the mechanisms underlying reduced engagement in activities in depression might help to predict relapse.
Methods: As part of a longitudinal patient study, we conducted a physical effort task in remitted, previously depressed, patients (n=73) and matched healthy controls (HC, n=33). Patients discontinued their antidepressant medication after the measurement and were followed up for 6 months to assess relapse. To model the decision process, we built combined reinforcement-learning drift-diffusion models (RL-DDM).
Results: Across models, increased effort sensitivity robustly distinguished patients, and an increased boundary those who would go on to relapse after antidepressant discontinuation. The most parsimonious according to formal model comparison included a post-decision wavering option and a progressive reduction in the decision boundary. In this model, patients had a longer non-decision time ($p=0.0091$), were more sensitive to effort ($p=0.014$) and more likely to waver after high-effort choices ($p<0.0001$) compared with controls. Patients who relapsed (n=21) showed an increased boundary compared to patients without relapse (n=37). While the boundary effect was significant in all models without gradual boundary reduction ($p<0.02$), it weakened after allowing for a gradual collapse of boundaries with number of trials ($p=0.07$).
Conclusions: Effort sensitivity is increased after remission on antidepressant medication in patients. Patients who go on to relapse after antidepressant discontinuation appear to need more information prior to committing to a decision
Supported By: Swiss National Science Foundation project grant to Q.J.M.H. (320030L_153449/1)
Molecular Imaging Network Zurich (MINZ)
Keywords: Major Depression, Relapse after Antidepressant Discontinuation, Reinforcement-Learning Drift-Diffusion Model, Computational Psychiatry, Anhedonia

F139. Decoding of Cognitive Flexibility State Using Behavior and Pre-Frontal Cortical Local Field Potentials

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Background: Accurately measuring cognitive processes is a key challenge for psychiatry. Such cognitive processes can be estimated through brain activity and/or behavioral responses. In this work, we estimated a cognitive flexibility state using behavior and neural data. Furthermore, we used striatal electrical stimulation
Methods: Five humans performed a multi-source interference task (MSIT) with simultaneous recordings of reaction time (RT) and local field potential (LFP) from cortical and subcortical brain structures. We stimulated in the dorsal and ventral striatum during some of these trials. We used a state space modeling framework to estimate a cognitive flexibility state from RT. We then related the cognitive state to spectral power of the LFP in theta (4-8 Hz), alpha (8-15 Hz) and high gamma (65-200 Hz) bands. A statistically principled process then selected neural features to formulate a neural decoder for
Results: Striatal stimulation significantly reduced RT across 5 subjects ($p<0.02$). We could use 8-15 neural features to reliably decode the cognitive flexibility state. Cognitive states estimated from neural features and behavior had an average correlation of 0.6. The root mean squared error between these decoded
Conclusions: Using both behavior and neural features recorded during the performance of a cognitive task, we can decode an underlying cognitive flexibility state and control this state using striatal stimulation. This framework can be used to design closed loop electrical stimulation to improve cognitive flexibility in patients
Supported By: DARPA
Keywords: MSIT, Local Field Potentials, Reaction Time Variability

F140. The Effects of Cortisol Administration on Emotion, Stress Reactivity, and Brain Activity in Depression

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Background: Circulating cortisol levels rise when people experience physical and psychological stressors. Cortisol is also elevated and dysregulated in individuals experiencing symptoms of depression. It is widely assumed that cortisol plays a role in generating the subjective feeling of emotions that accompany both stress and depression. It is also possible that cortisol is elevated in stress and depression to coordinate physiological processes that are unrelated to subjective feelings. The assumptions that cortisol promotes feelings of stress and symptoms of depression have rarely been formally tested. This series of studies aims to test how cortisol administration influences the subjective experience of emotion and the neural correlates of emotion in healthy individuals and medication-free individuals experiencing symptoms of depression.
Methods: This series of studies was structured as a double-blind placebo-controlled crossover study. Participants were randomly assigned to receive a 0.65mg/kg oral cortisol or a placebo pill then crossed over. Participants rated their emotional reactions to emotion-inducing pictures/videos, rated their emotional reactions to undergoing the socially evaluated cold-pressor test (SECPT), and completed an fMRI scan to quantify the brain response to sadness. Participants included 33 healthy individuals and 17 individuals experiencing symptoms of depression (BDI-II, range 16-47).
Results: Cortisol did not produce robust effects on the emotional response to pictures/videos or responses to the SECPT. However, cortisol did reduce sadness-induced subgenual cingulate activity.
Conclusions: These data suggest that cortisol may not be responsible for generating the subjective feelings of stress or depression. Instead, cortisol may be modulating brain activity patterns that indirectly impact emotional brain networks.
Supported By: NIMH K01
Keywords: Cortisol, Depression, Emotion, Stress

F141. Effects of Subcallosal Cingulate Deep Brain Stimulation on Emotion Regulation in Patients With Treatment Resistant Depression

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Background: The subcallosal cingulate (SCC) is involved in emotional regulation (ER) through connections with limbic and frontal regions. Maladaptive ER strategies (decrease in reappraisal and increase in suppression) contribute to negative emotion and negative bias in depression. Here we examined the respective effects of SCC-deep brain stimulation (DBS), adjunctive cognitive behavioral therapy (CBT) and depression recovery on ER strategies in patients with treatment resistant depression (TRD).
Methods: Twenty-one patients with TRD received SCC-DBS. All patients were offered 12 weeks of individual CBT after 6 or 12 months of DBS. Changes in depression severity and ER were evaluated using the Hamilton Depression Rating Scale (HDRS-17) and Emotion Regulation Questionnaire (ERQ) respectively over a period of 15 months post-DBS.
Results: The overall group did not demonstrate change over time in ERQ reappraisal ($p = 0.18$) or suppression ($p = 0.22$). Responders ($\geq$48% reduction in HDRS) at 6 months showed significant increase in reappraisal scores ($p = 0.005$), whereas responders at 12 months showed significant decrease in suppression scores ($p = 0.048$) compared to non-responders. Adding CBT did not improve ERQ or HDRS scores in

responder or non-responder groups. Decreases in HDRS correlated with decreases in suppression at 0-6 months ($p = 0.001$) and 0-12 months ($p = 0.007$).
Conclusions: Successful SCC-DBS is associated with improvement in adaptive emotional regulation (increase in reappraisal and decrease in suppression). Since add-on CBT had minimal effect on ER strategies and depression, the observed improvement in depression and ER may be related to DBS induced changes in SCC activity and connectivity.
Supported By: AIHS
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Emotion Regulation

F142. One or More Antidepressants for Better Outcome

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Background: The APA guidelines for the treatment of depression support the use of a single antidepressant at an adequate dose prior to changing to another one or to augmenting with another medication. In practice, many patients end up taking more than one antidepressant. Following is a retrospective review of the two options in a general practice.
Methods: A retrospective chart review was performed on all unipolar major depression patients seen in a private outpatient psychiatric clinic. Patients were given the PHQ-9 depression screening at every visit. Data collected included PHQ-9 scores, medication history, diagnostic history, and demographics. Patients were included if they had a diagnosis of unipolar depression, were on 1 antidepressant at baseline, and then maintained on one or more antidepressants.
Results: 259 patients were included in the study with an average number of 13 visits. 76% of patients were on 1 antidepressant at their most recent visit, compared to 24% who were on 2 or more. Patients who were on 2 or more antidepressants scored lower on the PHQ-9 compared to their intake score by an average of 6.0 points, compared to 4.7 for patients still on only one. Patients on multiple antidepressants also had significantly lower CGI-improvement scores (2.2 vs 2.5, $p<.05$).
Conclusions: The more severe the depression, the more likely it is that more than one antidepressant will be needed to achieve remission, not unlike the treatment of diabetes mellitus or hypertension where the severity of symptoms leads to more medications being used to gain control over the illness.
Keywords: Antidepressant response, Unipolar Major Depression, Combining antidepressants

F143. Do Age and Sex Moderate the Association of Inflammatory Cytokines and Anhedonia in Major Depressive Disorder? Findings From CO-MED Trial

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Background: Aging is associated with low-grade increases in systemic inflammation. While sex-differences in the association of inflammation and anhedonia were reported recently, the role of aging-associated inflammation in pathophysiology of anhedonia remains unknown.
Methods: Bioplex Pro^{TM} human cytokine multiplex kit was used to measure levels of interleukin (IL)-1 beta, 4, 5, 6, 17, interferon gamma (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) in plasma of Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants with major depressive disorder (MDD, $n = 166$). Anhedonia was measured with three items of the clinician-rated Inventory of Depressive Symptomatology. Due to previously-reported sex-differences, we conducted separate generalized linear models for males and females with anhedonia as dependent variable and age-(categorized as <45 and ≥ 45 years)-by-biomarker interaction as the primary independent variable after controlling for body mass index.
Results: In females ($n=117$), there was a significant interaction of age with IL-1beta ($p=0.019$), IL-4 ($p=0.012$), IL-5 ($p=0.042$), IL-17 ($p=0.046$) and IFN-gamma ($p=0.037$) but not for IL-6 ($p=0.121$), IL-13 ($p=0.732$) and TNF-alpha ($p=0.121$) in predicting anhedonia. There were no significant age-by-biomarker interactions in males ($n=49$). Among women aged ≥ 45 years ($n=57$), higher levels of IL-1beta ($t=3.15$, $p=0.003$), IL-4 ($t=3.43$, $p=0.001$), IL-5 ($t=3.05$ $p=0.004$), IL-17 ($t=2.20$, $p=0.032$) and IFN-gamma ($t=2.90$, $p=0.006$) were associated with greater severity of anhedonia. None of these immune biomarkers were significantly associated with anhedonia in females aged <45 years ($n=60$).
Conclusions: Aging in females is associated with greater severity of inflammatory-cytokine mediated anhedonia. Future studies are needed to evaluate age- and sex-specific differences in immune dysregulation underlying MDD.
Supported By: NIMH N01 MH-90003; Center for Depression Research and Clinical Care at UT Southwestern; Hersh Foundation
Keywords: Sex Differences, Inflammation, Anhedonia, Major Depressive Disorder (MDD), Interleukin-17

F144. Predicting the Individual Development of Traumatic Stress Symptoms Using a Preclinical Rat Model of Predator Exposure Stress

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Background: An estimated 12-20% of Soldiers exposed to psychological trauma during the course of a deployment in present-day conflicts go on to develop adverse symptoms of post-traumatic stress disorder (PTSD). It is projected that a larger percentage of Soldiers develop adverse symptoms of combat operational stress reactions (COSR) or acute stress disorder (ASD) in the immediate aftermath of trauma exposure, but incidence rates are unknown at this time. Observations after other traumatic incidents such as motor vehicle accidents indicate that 13-20% of individuals develop ASD. An animal model encompassing both early and later response to

traumatic stress will be useful for understanding both the development of traumatic stress symptoms as well as providing a translational model for drug testing and development.

Methods: Our laboratory measures both exploratory and anxiety-like behaviors in male rats under basal conditions and following a single-day sequential exposure to three predator species (snake, ferret and cat) to model a threat to life traumatic stress. Previously gathered data using predator exposed (n = 32) and control (n = 33) rats were analyzed to understand the time-course of traumatic stress-related behaviors.

Results: Preliminary analyses indicate that predator exposure results in increased anxiety-like behavior compared to control animals. Additionally, rats showing increased anxiety-like behaviors at baseline also demonstrate elevated anxiety-like behaviors across time compared to animals showing low anxiety-like behaviors at baseline.

Conclusions: There are individual differences in anxiety-like response to predator exposure that can be used to model the trajectory of human response to traumatic stress. Additional predictive factors are being evaluated.

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Keywords: Post Traumatic Stress Disorder, Acute Stress Disorder, Animal Model, Predator Exposure Stress

F145. Extremely Weak Relationship Between Gyrification and Intelligence

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Background: Increased gyrification (folding of the cerebral cortex) is associated with superior cognitive abilities in humans, but the strength of this relationship is unclear.

Methods: We used structural brain images to calculate an index of local gyrification (LGI) at thousands of points on the cortical surface, and performance on batteries of cognitive tests to calculate an index of general intelligence (g), in two large samples of related individuals (total N = 2,974).

Results: There were positive and statistically significant LGI−g correlations, both phenotypic and genetic, in many cortical regions. These correlations were not explained by mediating roles of height, intracranial volume (ICV), cortical area, or cortical thickness. Crucially, however, these correlations were all extremely weak. Phenotypically, LGI explained negligible variance of g at a typical vertex. Even when all LGIs were considered together, at least 89% of the phenotypic variance of g remained unaccounted for. LGI−g correlations were considerably smaller, on average, than ICV−g and area−g correlations in the same participants. We found no evidence to support the hypothesis that LGI was more strongly correlated with g in regions implicated by the parieto-frontal integration theory of intelligence.

Conclusions: The findings speak to an emerging potential issue in large-scale observational neuroimaging studies—as samples grow larger, smaller and less interesting relationships have the potential to be labelled as statistically significant. Future large-scale studies must report the strengths of their observed effects clearly so that brain-behavior relationships can be properly evaluated in terms of their contribution to our understanding of human cognition.

Supported By: Work supported by the following NIMH grants: MH078143, MH078111, MH083824, MH059490.

Keywords: Intelligence, Local Gyrification, Genetic Correlation, Family Study

F146. Compensation in the Anterior Insula Following Bilateral Amygdala Damage

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Background: Recent animal work has implicated the amygdala and mid-insula in a neuroanatomical circuit that selectively involves the perceptual gating of physiological signals from the body. Building on our previous study demonstrating that humans with amygdala damage show diminished cardiorespiratory interoception, here we used fMRI to examine the compensatory role of the insula in the processing of cardiorespiratory signals.

Methods: One patient with focal bilateral amygdala damage (BG) and 25 healthy comparators (HC) received randomized double-blinded bolus infusions of isoproterenol (0.5, 2 micrograms) and saline during BOLD fMRI scanning at 3 Tesla. Throughout each 4-minute infusion scan participants rated the overall intensity of perceived cardiorespiratory sensations by rotating a dial.

Results: BG exhibited intact albeit delayed cardiorespiratory sensation ratings relative to HC despite similar heart rate responses. While HCs showed significant activation focused in the mid insula during peak stimulation at the 0.5 and 2 mcg doses, BG displayed significant activations ($p<0.001$, corrected) in the bilateral anterior insula. When activation in the HC group shifted towards the anterior and posterior insula

during the recovery period, BG's activation remained focused in the anterior insula.
Conclusions: Despite her amygdala damage BG demonstrates a continued ability to perceive cardiorespiratory sensations during isoproterenol stimulation. However, she appears to use a different sector of her brain, the anterior insula, to sense changes in interoceptive state. These findings raise the possibility that the anterior insula serves a compensatory function facilitating the perception of interoception signals when amygdala and mid-insula communication is disrupted.
Supported By: NIH K23, NIH/NIGMS CoBRE, The William K. Warren Foundation
Keywords: Anterior Insula, Amygdala, Interoception, Physiological Perturbation, Amygdala Lesion

F147. Going Digital? Understanding the Impact of Technical Variability on Neurocognitive Assessment

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Background: Shifting neurocognitive assessment from paper-and-pencil to digital format allows greater standardization of administration, higher precision of measurement, and the collection of a broader range of performance metrics. Here, we examine the impact of device characteristic scores from a digital implementation of a Trail-Making Test (Forms A/B), to illustrate the challenges of shifting from a paper-and-pencil assessment to a hardware and software platform-based assessment.
Methods: 24,007 participants completed a digital Trail-Making Test (Forms A/B) across a range of personal computer and mobile devices through our digital research platform TestMyBrain.org. We examined effects of input type and screen size on performance, controlling for differences in demographic characteristics that vary by device.
Results: Restricting our sample to 7,020 participants age 18-25 (to minimize the contribution of age-related effects), participants completed Trails significantly faster on iPad (touchscreen-input) as compared with Macintosh personal computer (mouse-input) [Cohen's d=0.79, $p < 5e\text{-}16$]. Looking at touchscreen devices alone, participants completed Trails significantly faster on iPad (large screen) as compared with iPhone (smaller screen) [Cohen's d=1.46, $p < 5e\text{-}16$]. These effects of input type and screen size were comparable to the largest between group effects typically seen in clinical research studies in neuropsychiatry.
Conclusions: Translation of neurocognitive tests from paper-and-pencil to digital is nontrivial, and it has consequences beyond a change in format. Controlling for effects of device hardware and software choices when analyzing digital neuropsychological assessment results is vital to protect the validity of scientific outcomes and clinical interpretation.
Supported By: NIA U2CAG060408 Ambulatory Methods for Measuring Cognitive Change
Keywords: Neurocognitive tests, Digital devices, Clinical assessment, Technical variability

F148. 301 Cognitive Loci Identified in Large-Scale GWAS Meta-Analysis

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Background: Two recent large-scale GWAS have amassed sample sizes in excess of 300,000 individuals for genomic discovery of general cognitive ability (Davies et al. 2018; Savage et al. 2018). Here, we extend these efforts using meta-analytic approaches, accounting for sample overlap, to identify novel variants and genes associated with cognitive function.
Methods: Sample overlap meta-analysis available in the most recent version of METAL (Willer et al., 2010; ver. 2018-08-28) and Multi-Trait Analysis of GWAS (MTAG; Turley et al., 2018) were carried out to merge GWAS summary statistics from the two studies mentioned above. Results from METAL and MTAG were further annotated using Functional Annotation and Mapping of GWAS (Kyoko et al., 2018).
Results: We identified 301 loci associated with general cognitive ability, of which 55 loci were novel from input GWAS and 37 loci were novel to lookups of other MTAG studies (Hill et al., 2018; Lam et al., 2017). 11 of the novel loci harbored variants which are likely functional (CADD, Regulome Scores, 3'5' UTR, Exonic), with novel associations to genes (e.g., ACER3, CADM4) implicating a role for myelination in general cognitive ability. The PNPO gene was also identified as a potential candidate for nootropic applications.
Conclusions: Large-scale genomic association studies continue to be necessary for the identification of functional loci associated with cognition. Ongoing identification of cognitively actionable loci and variants is crucial, particularly in the development and application of pharmacological compounds for the treatment of cognitive deficits in psychiatric disorders.
Supported By: R01 MH117646
Keywords: Neurocognition, GWAS, Meta-analysis, Neurodevelopment, Neurogenetics

F149. The Effects of Cognitive Reappraisal Training to Enhance Emotion Regulation in Borderline and Avoidant Personality Disorder Patients: Evidence From Self-Reported Affect Ratings and Neuroimaging

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Background: Emotional instability is a difficult-to-treat feature of a number of mood and personality disorders. We have shown previously that when patients with borderline

personality disorder (BPD), the prototypical disorder of affect dysregulation, attempt the highly adaptive emotion regulatory strategy of cognitive reappraisal, they are impaired in their ability to reappraise as assessed by affect self-reports and neural activity. In this study we examined whether BPD patients and a psychopathological control group of avoidant personality disorder (AvPD) patients could be trained to enhance emotion regulation and normalize neural activity over time.

Methods: At each of six sessions, BPD (n=19), AvPD (n=22) and healthy control (HC) (n=18) participants were shown negative social emotional images and instructed to employ cognitive reappraisal by distancing, which involves appraising stimuli as objective, impartial observer. On sessions 2 through 5, subjects were trained in distancing. fMRI data were acquired at sessions 1, 5, and 6. Sessions 1-5 occurred every 1-2 days: session 6 occurred two weeks after session 5.

Results: After reappraising, BPD subjects rated negative pictures more negatively ($p<.01$, two-tailed) than HCs on sessions 1,2,3, but reduced their negative ratings to levels comparable to the HC's by sessions 4,5 and 6. AvPDs showed a response by session 2. On session 5 compared to session 1, BPD's showed a decrease ($p<.05$,one-tailed) in right amygdala activity when reappraising vs. looking at negative images. AvPDs and HCs did not.

Conclusions: These data represent the first evidence that longitudinal training can increase reappraisal success and normalize reappraisal neural activity in any patient population.

Supported By: NIMH R01

Keywords: Emotion Regulation, Borderline Personality Disorder, Brain Imaging, fMRI, Avoidant Personality Disorder, Cognitive Reappraisal

F150. Machine Learning Method Predicting Differences in EMA Suicidal Ideation Scores After Randomized Treatment

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Background: Ecological Momentary Assessment (EMA) records individuals' ratings of emotions, thoughts, behaviors, and stressors, in real time during participants' daily lives. To take advantage of complex temporal interrelationships between variables, in a study of suicidal patients, we compared Mixed-Effects regression models (MEMs) with Recurrent Neural Networks (RNNs) in assessing predictive accuracy and measuring treatment response.

Methods: Eighty participants with Borderline Personality Disorder were randomized to either medication (SSRIs) or psychotherapy (Dialectical Behavior Therapy; DBT), and engaged in a week of EMA pre- and post-treatment. RNNs were fit with severity of suicidal ideation (SI) as outcome and stressful events and baseline traits as predictors; optimized for predictive accuracy using cross-validation on baseline EMA. For comparison, a MEM was fit separately on pre-and post-treatment data. Both models were then used to predict SI for subjects' post-treatment.

Results: MEMs did not find significant differences between severity of SI in the two randomization group pre-or post-treatment (pre: b (SE)=-.12 (.95), p=.90; post: b (SE)=-.03 (1.16), p=.98). A single-layer RNN with 6 input nodes outperformed other RNNs or MEMs for predicting SI during baseline EMA (RNN RMSE=3.46; MEM RMSE=4.63), and performed comparably in predicting SI during the post-treatment period, compared to MEM (RNN RMSE=5.32; MEM RMSE=5.13). The baseline RNN, but not the MEM, model performed significantly better in predicting post-treatment EMA SI in the medication group than in the DBT group (Mean RMSE difference=0.48, SE=0.24, p=.02).

Conclusions: RNNs model different aspects of EMA data than MEMs and may be used to discern differences in treatment response.

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5R01MH061017-10

Keywords: BPD, Machine Learning, Ecological Momentary Assessment, Suicidal Ideation, Cognitive Behavior Therapy

F151. Intelligence Moderates the Link between Psychopathy and Aggression, but Only for Men

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Background: Psychopathy is considered one of the most important constructs for understanding the risk of aggressive behavior. Prior theorists suggested that psychopathy is particularly harmful because individuals with the disorder have intact or higher levels of intelligence, which supports the versatility in their aggression. Although in theory this is logical, there remains a scarcity of research to conclude this. Thus, the aim of the present study is two-fold: To test what facets of psychopathy are associated with intelligence, and to test if intelligence moderates the link between psychopathy and aggression.

Methods: In a large community sample of men (n=314) and women (n=174), we conducted a hierarchical regression to test which of four Psychopathy Checklist: Screening Version (PCL:SV; Hart et al., 1995) facets predicted intelligence using the Raven's Progressive Matrices (Raven et al., 2000). Using hierarchical regressions, we tested if intelligence moderated the association between the PCL:SV four facets and aggression using the Aggression Questionnaire (Buss & Warren, 2000).

Results: We found a negative relation between intelligence and the lifestyle psychopathy facet, and there were no sex differences. Intelligence moderated the link between psychopathy and aggression for men, but not women. Specifically, aggression was predicted by higher antisocial facet scores in men with low intelligence.

Conclusions: These findings indicate that intelligence does not play a role in psychopathy-related aggression for women, but it increases risk for men who are high on the antisocial facet of psychopathy.
Supported By: This research was funded by the National Institute on Drug Abuse and the Fogarty International Center under award number R01DA021421 (PI Jasmin Vassileva).
Keywords: Psychopathy, Intelligence, Aggression, Women, Violence

F152. Lifetime Physical Abuse Moderates the Psychopathy-Violence Link Differently for Men and Women

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Background: Psychopathy has been long associated with violence. Yet, research testing for sex differences in this association is sparse. Research that does exist shows notable differences for men and women, and suggests environmental factors play a significant role in influencing these associations. A key environmental factor is lifetime physical abuse (LPA). The current study tested if LPA moderated the psychopathy-violence link differently for men and women.
Methods: In a community sample of men (n=369) and women (n=204), we assessed the 4-facet model of psychopathy with the Psychopathy Checklist: Screening Version, LPA with the Addiction Severity Index, and violence with the Aggression Questionnaire. Data were analyzed using hierarchical linear regressions.
Results: In women, violence was predicted by LPA, and the affective and antisocial facets. In men, LPA and the antisocial facet predicted violence. The results also showed LPA moderated the association between affective psychopathic traits and violence for both men and women, albeit differentially. For women, high levels of affective psychopathic traits predicted violence, but only for those with a history of LPA. In contrast, violence in men was predicted by low affective psychopathic traits but only for those with a history of LPA.
Conclusions: Results show that LPA and psychopathy generally increase the risk of violence for men and women. However, the moderating role of LPA in the link between psychopathy and violence differs for men and women. These sex differences highlight the need for female-responsive interventions to target sex-specific risk factors for violence.
Supported By: R01DA021421 (JV) by NIDA and Fogarty International Center
Keywords: Psychopathy, Sex differences, Violence, Abuse, Interpersonal Violence, Childhood Trauma, Hair Cortisol, Stress, Abuse

F153. Aging and Treatment Resistant Auditory and Visual Hallucinations in Individuals With Schizophrenia Spectrum Disorders

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Background: A portion of individuals with schizophrenia spectrum disorders experience improvement in severity of auditory (AH) and visual (VH) hallucinations over time. Yet, little is known regarding the course of treatment-resistant AH/VHs, e.g., whether any aspect shows a pattern toward improvement with age. Understanding any such nuance may shed light on treatment development efforts.
Methods: 132 participants ages 19-60 were administered the Chicago Hallucination Assessment Tool (CHAT), a semi-structured interview assessing severity of hallucinations across physical, emotional, and cognitive domains. Correlational analyses were used to examine the relationship between current age and CHAT scores, as well as paired t-tests to assess differences between participants' worst and current hallucinations.
Results: 68% reported antipsychotic medication completely stopped or significantly reduced their AHs; 49% reported this for VHs. Individuals' with current treatment-resistant AH severity had significantly lower severity across all domains compared to their worst. Age did not significantly correlate with any AH domains. Current compared with worst VH physical, cognitive, and total scores were significantly lower. Significant positive relationships were found between age and frequency of current negative emotion associated with VHs ($r=0.49$, $p=0.01$) and degree of current emotional distress caused by VHs ($r=0.43$, $p=0.02$).
Conclusions: The findings suggest that individuals with treatment-resistant hallucinations do experience some alleviation of hallucination severity as compared to their "worst" times. However, overall, characteristics of AH/VHs do not seem to dramatically improve or worsen with age. The exception was that older adults seem more bothered by VHs compared to younger adults.
Supported By: NIMH
Keywords: Schizophrenia Spectrum, Auditory Hallucinations, Visual Hallucinations, Treatment Resistant Hallucinations, Aging and Schizophrenia

F154. Hallucination Severity and Stress in Individuals With Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder

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Background: Several studies have shown stress contributes to the initial onset of psychosis, but its role in chronic psychosis symptom exacerbation is less understood. The current study of individuals with chronic psychotic disorders investigates the relationship between stress and severity of psychosis symptoms broadly as well as at a detailed level within auditory (AH) and visual hallucinations (VH). The aim is to identify whether any dimension of hallucination severity is more linked to stress, vs stress having a broad impact on symptoms.
Methods: 47 participants were administered the Psychological Stress Index (PSI), the Positive and Negative Syndrome Scale (PANSS), and the Chicago Hallucination Assessment

Tool (CHAT), which generates a total score and scores on three severity dimensions: physical (PSD), cognitive (CSD), and emotional (ESD). Correlational analyses were used.
Results: Significant correlations: PSI and AH-PSD (r=0.429, p=0.006), AH-CSD (r=0.382, p=0.016), AH-ESD (r=0.599, p=0.00005). AH subscales intercorrelated r=~0.4-0.6. Only VH-CSD significantly correlated with PSI (N=20, r=0.607, p=0.005). VH subscales intercorrelated (r=0.08-0.6).

PANSS total and subscale scores significantly correlated with PSI (r=0.47-0.79). Number of current hallucination modalities was correlated with PSI (n=47, r=0.37, P=0.01).
Conclusions: As expected, but previously not documented, higher stress levels were associated with greater general psychosis symptom severity, greater number of sensory modalities of hallucinations, and all dimensions of AH severity, but only the cognitive disruption aspect of VH severity. Hallucinations in different sensory modalities may differ in sensitivity to stress. Longitudinal studies are needed to assess whether stress precipitates or simply accompanies more severe psychosis.
Supported By: NIMH
Keywords: Psychosis, Phenomenoloy, Hallucinations, Stress

F155. Negative Content and Distress Across Hallucination Sensory Modalities

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Background: Evidence suggests that auditory hallucinations (AH) in clinical samples are predominantly negative in content. Whether this extends to visual (VH), tactile (TH), olfactory (OH), and gustatory (GH) hallucinations is unknown. Consistently negative content across modalities may indicate a common mechanism. To address this, we compared the degree of negative content and distress between hallucinations across sensory modalities.
Methods: Participants were 144 individuals recruited from the clinic and community diagnosed with a psychotic disorder and who endorsed lifetime hallucinations in at least two modalities. They were administered the Chicago Hallucination Assessment Tool, a semi-structured interview. The degree of negative content and distress related to past/worst hallucinations was rated on a 0-4 scale and compared between modalities using paired samples t-tests. Pearson correlations characterized the relation of negative content and distress within each modality.
Results: AH were significantly more negative than VH (n=126, p=0.000), TH (n=77, p=0.034), and OH (n=47, p=0.019), and GH at a trend level (n=22, p=0.089). Distress levels were highest for AH compared to each modality (all p<0.03). Content and distress were correlated within AH, TH, OH (all r's>0.5, p=0.000), VH (r=.332, p=0.000), and GH (r=.345, p=.116).
Conclusions: AH were experienced as more negative and distressing than hallucinations in other modalities. Correlations of negative content and distress ratings within each modality supported a conclusion that differences across sensory modalities negative content are not due to differential sensitivity of the ratings. Overall, these results suggest the auditory modality is more vulnerable to negative, distressing hallucination content than other sensory modalities.
Supported By: NIMH
Keywords: Hallucinations, Psychosis, Schizophrenia, Schizoaffective Disorder, Sensory Modalities

F156. Genuine and Nongenuine Smiles in Adolescents at Clinical High-Risk for Psychosis

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Background: Blunting in positive facial expressions are features of a number of psychopathologies, including psychotic disorders. However, it is unknown what the nature of blunting in positive facial expressions are in adolescents at clinical high-risk (CHR) for psychosis and whether motor and/or limbic neural circuitry underlie these emotional behaviors.
Methods: Presently, a total of 42 CHR and 42 control participants underwent video-recorded clinical interviews. One-minute segments of these interviews were human coded for genuine and nongenuine smiles. Additionally, imaging analyses were conducted to examine functional (using independent components analysis) and structural (regional volumes in the caudate, putamen, amygdala, and accumbens area) relationships between genuine and nongenuine smiles and limbic and motor areas.
Results: Results revealed that the CHR group displayed significantly lower genuine, $t(82) = -3.06$, $p < .001$, $d = .67$, and nongenuine smiles, $t(82) = -4.01$, $p < .001$, $d = .88$, compared to the control group. Additionally, the ICA analysis indicated increased genuine smiles related to increased variability in temporal cohesion within the limbic components in CHR youth compared to controls, beta = 0.005, $t(66) = -.206$, $p = .04$. Structurally, increased nongenuine smiles related to lower left putamen volumes (an area at the interface between emotion and motion) within the CHR group, $r = -.39$, $p = .02$.
Conclusions: These findings indicate (1) blunting in expressivity is observed prior to the onset of psychosis and (2) there may be meaningful functional and structural neural differences underlying abnormalities in these emotional behaviors that involve motor and limbic areas.
Supported By: RO1
Keywords: Clinical High-Risk States for Psychosis, Emotion, Brain Imaging, Motor, Psychosis

F157. Transcriptional Changes in the Stress Pathway are Related to Symptoms in Schizophrenia and to Mood in Schizoaffective Disorder

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Background: Altered levels of stress-signalling transcripts have been identified in post-mortem brains of people with schizophrenia, and since stress effects may be expressed throughout the body, there should be similar changes in peripheral cells. However, the extent to which these markers are altered in peripheral white blood cells of people with schizophrenia is not known. Furthermore, how peripheral cortisol and stress-related mRNA are associated with negative symptom severity and emotional states in people with schizophrenia versus schizoaffective disorder has not been determined.
Methods: Whole blood samples were collected from 86 people with schizophrenia and 77 healthy controls. Total RNA was isolated, cDNA was synthesized, and stress-signalling mRNAs (NR3C1, FKBP5, FKBP4, PTGES3 and BAG1) were determined. Stress and symptom severity scores were measured by the Depression, Anxiety and Stress Scale, and the Positive and Negative Syndrome Scale, respectively.
Results: We found increased FKBP5 mRNA, $Z(156) = 2.5$, $p = 0.01$, decreased FKBP4 mRNA, $t(155) = 3.5$, $p \leq 0.001$, and decreased PTGES3 mRNA, $t(153) = 3.0$, $p \leq 0.01$, in schizophrenia and schizoaffective disorder cohorts combined compared to healthy controls. Stress-related peripheral mRNA levels were differentially correlated with negative emotional states and symptom severity in schizoaffective disorder (β's = 0.34 - 0.56, p's = .05 - .001) and schizophrenia (β's = -0.25 − 0.38, p's = .04 - .03), respectively.
Conclusions: Therefore, molecules of the stress-signalling pathway differentially contribute to clinical features of schizophrenia versus schizoaffective disorder.
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Keywords: Stress, Schizophrenia, Schizoaffective Disorder, Symptoms

F158. Changes in Emotion Processing Network Following Social Cognitive Training in Individuals With Schizophrenia

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Background: Deficits in social cognition are prominent features of schizophrenia that play a large role in functional impairments and disability and are associated with altered activity in functional networks that support abilities such as emotion recognition. Targeted cognitive training has been proposed as a potential intervention to address cognitive and behavioral deficits and has been shown to improve cognitive functioning in individuals with schizophrenia. This study tests whether targeted cognitive training designed to specifically focused on social cognition would alter the activation in functional networks engaged in facial emotion processing, especially those involving the amygdala and superior temporal sulcus.
Methods: 36 individuals with schizophrenia spectrum disorders were included in the study. Subjects underwent clinical evaluations and functional MRI session prior to and subsequent to completing 40 hours (over ~8 weeks) of either targeted social cognitive training using SocialVille (brainhq.com) or a computer game control condition. Resting state fMRI was acquired as well as fMRI during performance of an emotion recognition task. Changes in emotion processing network activation was evaluated using seed-based connectivity analyses and psychophysiological interaction.
Results: Training was associated with altered activity within the emotion processing network, including the amygdala and superior temporal sulcus. In addition, altered connectivity including increased connectivity between the amygdala and regions including the medial prefrontal cortex was found using psychophysiological interaction analyses.
Conclusions: These results suggest that targeted social cognitive training may be effective in altering functional network connectivity in networks associated with psychosis and may be a useful tool for intervention in individuals with psychotic disorders.
Supported By: Rush University Psychiatry Department Funding
Keywords: Schizophrenia, Emotion, BOLD fMRI, Resting State fMRI, Social Cognitive Training

F159. Short-Term Exposure of Cuprisone Induces Behavioral Alterations Related to Some of the Symptoms of Schizophrenia

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Background: Cuprizone is a copper chelating agent known to induce demyelination upon 6-8 weeks of exposure, resulting in conditions reminiscent to multiple sclerosis. Recent reports suggest inflammatory responses in the CNS as evidenced by increased expression of GFAP, Iba1, and IL6 at the beginning of cuprizone exposure but prior to the induction of demyelination. Interestingly, this observation coincided with behavioral changes, such as cognitive impairment and augmented response to amphetamine. Here, we examined the effect of short-term exposure of cuprisone on rodent behavioral phenotypes.
Methods: C57BL/6J mice were fed with diet containing 0.2% cuprizone for 10 days. On day 11, the diet was switched back to normal food. A broad array of behavioral testing was commenced after 7 days of the cuprizone exposure and ended on day 13.
Results: Mice fed with cuprizone displayed distinct behavioral alterations in comparison to those with control diet. We observed less anxiety-like phenotype, a deficit in sociability,

and altered prepulse inhibition. However, we did not see changes in locomotor and cognitive function.
Conclusions: In the present study, we found a distinct set of behavioral alterations upon short-term cuprizone exposure, which are similar to some, but not all, of core symptoms of schizophrenia. Considering clinical heterogeneity of schizophrenia, we speculate this paradigm would represent a subpopulation of schizophrenia patients, providing a unique opportunity for drug discovery research.
Keywords: Cuprizone Short-Term Exposure (CSE), Animal Behavior, Schizophrenia, Neuroinflammation

F160. Samidorphan, an Opioid Receptor Antagonist, Mitigates Olanzapine-Induced Metabolic Dysfunction in Female Rats

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Background: A combination of olanzapine (OLZ) and samidorphan (SAM), designed to mitigate OLZ-induced weight gain while maintaining antipsychotic efficacy, is currently under development for the treatment of schizophrenia. In previous nonclinical studies, SAM normalized OLZ-induced increases in adiposity and mitigated OLZ-induced weight gain. The current studies assessed the effects of OLZ and SAM on glucose clearance and insulin sensitivity prior to measurable changes in weight and/or body composition.
Methods: Female rats were treated with a long-acting injectable formulation of OLZ pamoate in combination with SAM administered via osmotic mini-pump for 48hr. An insulin tolerance test and a hyperinsulinemic-euglycemic clamp (HIEC) were used to assess insulin sensitivity, glucose turnover, glycolysis, and glycogen synthesis. Adipose, muscle, and liver tissues were harvested to measure glucose uptake.
Results: OLZ significantly decreased glucose clearance. SAM alone had no effect, but restored whole body glucose clearance in OLZ-treated rats. In HIEC experiments, OLZ alone, SAM alone, and the combination did not affect glucose turnover, glycolysis, or glycogen synthesis. OLZ decreased hepatic insulin sensitivity and glucose uptake in muscle, while increasing uptake in adipose tissue. Co-administration of SAM did not restore hepatic insulin sensitivity but did restore/partially normalize glucose uptake in fat and muscle, respectively.
Conclusions: SAM did not affect OLZ-induced changes in glucose infusion rates but did normalize changes in glucose clearance in female rats. OLZ-induced adiposity may be driven by lowering glucose availability in muscle but raising availability in adipose tissue. Based on these nonclinical data, SAM mitigates several metabolic abnormalities associated with OLZ independent of weight gain.
Supported By: Alkermes, Inc.
Keywords: Olanzapine, Samidorphan, Glucose, Insulin, Preclinical Study

F161. Effects of Metabotropic Glutamate 2/3 Receptor Activation on Deficits of Neural Network Function Induced by Optogenetic Inhibition of Parvalbumin-Positive Interneurons in the Mouse Prefrontal Cortex

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Background: Patients with schizophrenia show EEG abnormalities (Danjou et al. 2018). Parvalbumin-positive (PV) interneurons are crucial for maintaining the cortical excitatory/inhibitory (E/I) balance necessary for the generation of these electrical activity patterns. Their function is reduced in patients (Chung et al. 2016). To model this in mice, we used optogenetics, auditory stimulation (ASSR) and tetrode recordings in the medial prefrontal cortex (mPFC). Furthermore, we investigated the effect of the mGlu2/3R agonist LY379268 on neural network function during optogenetic inhibition of these interneurons.
Methods: We expressed an inhibitory opsin (Arch) or eYFP in PV interneurons in the mPFC of PV-Cre mice (n=9 and n=6, respectively) and implanted tetrodes and optic fibers. After recovery, mice were administered either vehicle or the mGlu2/3 agonist LY379268 (3 mg/kg) and electrophysiological recordings were performed during 40 Hz ASSR stimulation. Optogenetic light was delivered randomly during half of ASSR stimuli.
Results: Light inhibition increased basal gamma power ($p<0.001$). During ASSR stimulation, light decreased inter-trial-coherence (ITC; $p<0.001$) and signal-to-noise ratio (SNR; strength of 40Hz over other frequencies, $p<0.01$). LY379268 modulated the light-induced ITC decrease ($p<0.05$) and SNR ($p<0.001$). In the absence of light, LY379268 decreased basal gamma, and increased power, ITC and SNR ($p<0.001$ for all) during ASSR.
Conclusions: Optogenetic inhibition of PV interneurons induced an E/I imbalance reflected in basal gamma oscillation and ASSR ITC. Activation of mGlu2/3R by LY379268 influenced the light-induced changes in network activity, indicating that mGlu2/3R might counteract aberrant neuronal activity in cortex, and represents a promising approach for improving cognitive function in patients.
Supported By: Boehringer Ingelheim Pharma GmbH & Co. KG
Keywords: Cognitive Impairment, Gamma Oscillation, Optogenetics, mGlu2, ASSR

F162. Construction of a Mouse Model of Mismatch Negativity (MMN)

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Background: MMN is a potential biomarker associated with dysfunctions in auditory processing and cognitive function in schizophrenia patients. To accelerate the usage of MMN in preclinical research, we established a mouse model of MMN.
Methods: C57BL/6 mice were implanted with tripolar electrodes in the CA3 subregion of hippocampus. A week after the surgery, the mice were presented with auditory stimuli composed of 6,000 tones at 85 dB SPL with 500 msec intervals. Standard and deviant tones were either 4 or 12 kHz with 100 msec duration. Frequency of deviant tones were 2 % as sequential probability. All Event related potentials were recorded after 5 hr of acclimation. Data was analyzed using EEGLAB.
Results: Mice displayed augmented negative peaks between 50 and 70 msec in response to 4 kHz deviant stimuli while standard was 12kHz. Similarly, the augmented negative peak was observed when the deviant and standard stimuli were flipped to 12 and 4 kHz, respectively. To mimic pathogenic features of schizophrenia, the mice were treated with an NMDAR antagonist, MK-801, and subjected to MMN recording. At a dosage producing cognitive impairment, hyper locomotor, and prepulse inhibition deficits, we detected a decrease in the negative peak amplitude but not a positive peak induced by the deviant stimuli.
Conclusions: In the present study, we established a mouse model of MMN and validated the recording paradigm with the NMDAR antagonist. This paradigm will be useful to not only evaluate the efficacy of therapeutic compounds but also characterize transgenic mouse lines modeling psychiatric disorders.
Keywords: Electroencephalography (EEG), Mismatch Negativity, Psychiatric Disease, Drug Discovery, NMDA Antagonists

F163. A Psychiatric Disease-Related Circular RNA Controls Neuronal Function and Cognition

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Background: Circular RNAs (circRNAs) are a novel category of long non-coding RNAs is that are derived from the circularization and covalent joining of backspliced exons and/or introns. Although circRNAs are particularly enriched in the mammalian brain their mechanism of action and significance for psychiatric disorders still remain elusive.
Methods: We used cutting edge circRNA profiling and validation in postmortem brains and stem cell-derived neuronal cultures from patients with schizophrenia (SCZ) and bipolar disorder (BD) and manipulated the expression of circRNAs in neuronal cultures and in vivo, while performing electrophysiological, and behavioral analysis, respectively.
Results: Here, we show that circHomer1, a neuronal-enriched circRNA derived from Homer protein homolog 1 (HOMER1), is reduced in the orbitofrontal cortex (OFC) and in stem cell-derived neuronal cultures from patients with SCZ and BD and in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia. Interestingly, changes in circHomer1 in both the OFC and DLPFC of subjects with SCZ were found to be significantly associated the age of onset of the disease. Using in vivo knockdown of circHomer1 in mouse OFC, we show that it inhibits the synaptic localization of Homer1b and is necessary for OFC-mediated reversal learning. Moreover, we demonstrate that circHomer1 inhibits neuronal excitability and binds to an RNA-binding protein that can increase its synaptic localization. Furthermore, we demonstrate that in vivo knockdown of Homer1b in mouse OFC can rescue the specific effects of circHomer1 on behavioral flexibility.
Conclusions: Collectively, our data introduce a novel psychiatric disease-associated circRNA that regulates synaptic gene expression, neuronal function, and cognition.
Supported By: NARSAD/ Brain & Behavior Research Foundation Young Investigator Grant (FP00000839)
Keywords: circRNA, Schizophrenia, Bipolar Disorder, Cognition, Stem cells

F164. Ultrastructural Localization of Classical Complement Cascade Signaling Protein C1q in Rhesus Macaque Dorsolateral Prefrontal Cortex

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Background: The dorsolateral prefrontal cortex (dlPFC) mediates high-order cognition, and is markedly afflicted in schizophrenia. Recurrent excitation in layer III dlPFC pyramidal cell microcircuits subserves working memory (WM). Impairments in WM in schizophrenia are thought to arise from dendritic spine deficits in dlPFC layer III and might be a consequence of aberrant neuroinflammatory cascades and microglia-mediated excessive pruning during adolescence. Recently, various studies propose critical roles for complement cascade signaling in driving spine loss in schizophrenia. However, the precise anatomical distribution of complement proteins in dlPFC layer III microcircuits is unknown.
Methods: Using high-spatial resolution immunoelectron microscopy, we interrogated the subcellular localization of C1q, the initiating protein of the classical complement cascade, in aged monkey dlPFC with naturally-occurring spine loss. The anatomical distribution of C1q was examined in critical cellular subcompartments (e.g., synapses) and organelles (e.g., mitochondria and smooth endoplasmic reticulum), which are susceptible in schizophrenia.
Results: The ultrastructural localization of C1q was robustly associated with astrocytes ensheathing glutamatergic synapses and glial leaflets in the neuropil. We also found significant labeling in presumed asymmetric glutamatergic axospinous and axodendritic synapses, both within the plasma membrane and intracellular subcompartments, often near dysmorphic

mitochondria, putatively "tagging" the most vulnerable neuronal elements for phagocytosis via microglia.
Conclusions: In aggregate, these findings reveal novel intraneuronal distribution patterns for classical complement-dependent pathways and suggest microglia might be aberrantly overactive during adolescence to mediate spine loss in schizophrenia. The upregulation of C1q might be a product of amplified feedforward cAMP-PKA stress signaling in dlPFC layer III microcircuits.
Supported By: NIH DP1AG047744-01
Keywords: Dorsolateral Prefrontal Cortex, Inflammation, Pyramidal Cell, Working memory, Complement System

F165. Using CRISPR/Cas9-Based Epigenetic Editing to Study the Role of Schizophrenia-Related Alterations in DNA Methylation on Dendritic Spine Density

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Background: Dendritic spine density (DSD) is reduced in postmortem superior temporal gyrus (STG) from schizophrenia (SZ) subjects. We previously found that DNA methylation (DNAm) at two synapse-related genes, BAIAP2 and DLG1, is altered in SZ subjects. Based on these findings and the role of DNAm in gene transcription, we hypothesize that reduced DSD in SZ results, in part, from changes in BAIAP2 and DLG1 transcription caused by alterations in DNAm.
Methods: We first measured the abundance of BAIAP2 and DLG1 transcripts in postmortem STG from subjects with SZ (N=20) and control subjects (N=20), and related them to existing DNAm levels and DSD. Then, we used a CRISPR/Cas9-based tool to alter BAIAP2 and DLG1 DNAm in a region-specific manner in cell culture (HEK cell and primary neuronal culture) to assess for a causal relationship between SZ-related DNAm alterations and transcript abundance/DSD.
Results: We found expression of BAIAP2 transcripts were increased, and DLG1 transcripts were decreased, in postmortem STG from SZ subjects relative to controls. Further, we found that inducing SZ-related DNAm alterations in HEK cell culture led to transcript alterations similar to those observed in postmortem STG from SZ subjects (e.g., hypermethylation of 5' DLG1 led to lower DLG1 transcript abundance). The results of similar experiments in primary neuronal cultures are pending.
Conclusions: These findings provide evidence that a CRISPR/Cas9-based tool can be used to alter DNAm in a region-specific manner in cell culture systems in order to assess for causal relationships between SZ-related DNAm alterations and local gene transcription/DSD.
Supported By: NIH Grant K23 MH112798 (BCM)
Keywords: Schizophrenia, DNA methylation, Epigenetics, Human Postmortem Brain, Dendritic Spine

F166. Characterizing Na+/H+ Exchangers in Schizophrenia Brain

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Background: Schizophrenia is characterized by widespread deficits in protein trafficking, but the cause for this remains unclear. Enzymes mediating post-translational modifications that direct intracellular trafficking work optimally at specific pH ranges, so alterations in organellar pH could disrupt trafficking. Na+/H+ Exchangers 6-9 (NHE6-9) regulate organellar pH by de-acidifying compartments to which they are targeted. For example, hypoxia-induced acidification of cancer cell lines leads to overacidification of endosomes through a RACK1-mediated redistribution of NHE6 from endosomes to the plasma membrane. Similarly, there is decreased brain pH and increased RACK1 expression in dorsolateral prefrontal cortex (DLPFC) in schizophrenia indicating a similar redistribution of NHEs may occur. To date, NHEs have yet to be characterized in schizophrenia.
Methods: We measured NHE6/9 in postmortem DLPFC of individuals with schizophrenia (n=24) and comparison subjects (n=24) by Western blot. We also measured compartment-specific expression of NHE6/9 in fractionated tissue.
Results: NHE6/9 antibodies were validated in human brain. Controlling for age, sex, PMI, and pH, total tissue levels of NHE6 in DLPFC were unchanged in schizophrenia ($p=0.57433$) while NHE9 was increased 33% ($p=0.01214$). NHE6/9 were found to be enriched in subcellular fractions also enriched for Rab5/7.
Conclusions: The lack of change in NHE6 is not necessarily unexpected as others have demonstrated a redistribution of NHE6 without change in total protein levels. Next steps will be to validate antibodies to NHE7/8, to characterize total tissue levels of each, and to quantify NHE6-9 distribution within subcellular compartments and plasma membrane to determine if distribution is altered in schizophrenia.
Keywords: Endosomes, Tissue pH, Subcellular Fractionation, Dorsolateral Prefrontal Cortex

F167. Multiplexed Single-Nucleus RNA Sequencing of Postmortem Human Prefrontal Cortex in Schizophrenia and Bipolar Disorder

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Background: Emerging technologies for single-cell transcriptomics now allow for high-throughput assessment of how molecular pathologies are partitioned across distinct neuronal circuitry and cellular subpopulations, advancing our understanding of circuitry-based information processing and its dysfunction in psychotic illness.

Methods: Postmortem human prefrontal cortex BA10 tissue samples were microdissected from a cohort matched for age, gender, and postmortem interval from schizophrenia, bipolar disorder, and control subjects. Cellular nuclei were isolated by gradient centrifugation and nuclei from multiple individuals were pooled and then used for single-nucleus RNA sequencing experiments on the 10X Genomics Chromium platform.
Results: Preliminary data analysis identifies multiple distinct cellular populations within BA10, including neuronal and glial subpopulations. Deconvolution of this data is not trivial and we find the cell-hashing approach the be more successful than genotype based deconvolution. Comparison between diagnostic groups is ongoing and demonstrates diagnosis-associated transcriptomic shifts in specific cellular subpopulations, suggesting distinct subpopulations of GABAergic interneurons are impacted differently by the pathophysiology of these disorders.
Conclusions: Single-cell genomics technologies promise to revolutionize our knowledge of the "parts list" of the cellular machinery of the human brain, as well as how molecular pathologies are distributed among those functional units in psychiatric illness. This ongoing project demonstrates the power of assessing single-cell transcription within the human brain to elucidate the molecular pathology of psychotic disorders at a resolution not previously possible, offering insights into how this pathology operates within the complex cytoarchitecture of the human brain.
Supported By: NIMH K08
Keywords: Human Postmortem Brain, Single Cell Type Sequencing, Schizophrenia, Bipolar Disorder, Prefrontal Cortex

F168. Increased Protein Insolubility in Brains From a Subset of Patients With Schizophrenia

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Background: The mechanisms leading to schizophrenia are likely to be diverse. However, there may be common pathophysiological pathways for subtypes of the disease. In the present study, we tested the hypothesis that increased protein insolubility and ubiquitination represent one such pathway underlying a subtype of schizophrenia.
Methods: Autopsied brains of individuals with and without schizophrenia provided by the University of Pittsburgh, University of Texas Southwestern, and Harvard were subjected to sarkosyl fractionation, separating proteins into soluble and insoluble fractions. Insoluble protein and ubiquitin levels were quantified for each insoluble fraction, with normalization to total homogenate protein. Mass spectrometry analysis was performed to identify the proteins in the insoluble fractions. The potential biological relevance of the detected proteins was assessed using Gene Ontology Enrichment and Pathway Analyses.
Results: A subset of patients with schizophrenia showed an increase in protein insolubility and ubiquitination in the insoluble fraction. Mass spectrometry of the insoluble fraction revealed that cases with increased insolubility and ubiquitination exhibited a similar peptide expression by principal component analysis. The proteins that were significantly altered in the insoluble fraction were enriched for pathways relating to axon target recognition and nervous system development and function.
Conclusions: This study suggests a pathological process related to protein insolubility for a subset of patients with schizophrenia. Determining the molecular mechanism of this subtype of schizophrenia could lead to a better understanding of the pathways underlying the clinical phenotype in some patients with major mental illness, as well as to improved nosology and the identification of novel therapeutic targets.
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Keywords: Protein Insolubility, Ubiquitination, Schizophrenia, Autopsy Brains

F169. Increased mRNA Levels of Microglial Markers of Phagocytosis in Schizophrenia

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Background: Schizophrenia (SZ) is a severe psychiatric disorder associated with cognitive disturbances linked to dysfunction within the prefrontal cortex (PFC). Genetic studies have implicated microglia-related genes as risk factors for the disorder; however, the specific contribution of microglia to the underlying molecular pathophysiology is unknown. Emerging evidence demonstrates that microglia are involved in the phagocytosis of dendritic spines. Given well-known evidence of spine deficits in the PFC of SZ subjects, these findings suggest that elevated microglia-mediated phagocytosis of spines may contribute to spine deficits in the disorder. Therefore, we tested the hypothesis that microglia-related markers of phagocytosis are elevated in the PFC in SZ.
Methods: Quantitative PCR was used to assess transcript levels of microglia-specific markers that mediate phagocytosis in the PFC of 62 matched pairs of SZ and unaffected comparison subjects.

Results: ANCOVA analyses revealed significantly increased transcript levels of multiple microglial markers involved in phagocytosis, including the TAM receptor tyrosine kinases Axl and MerTK, in SZ subjects relative to comparison subjects. In contrast, inhibitors of phagocytosis, such as the sialic acid receptor Siglec-11, were unchanged in the disorder.
Conclusions: These results suggest that SZ subjects have higher levels of critical molecular machinery that supports microglial phagocytosis in the PFC and consequently may play a role in spine deficits in the disorder. Future studies that investigate the relationship between microglia-mediated phagocytosis and spine alterations may help further elucidate mechanisms underlying cognitive dysfunction in SZ and guide the identification of novel pharmacologic targets.
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Keywords: Microglia, Dendritic Spines, Schizophrenia, DLFPC, mRNA

F170. Distinct Laminar and Regional Patterns of Markers of GABA Neuron Subtypes in Monkey Prefrontal and Visual Cortices

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Background: Evidence of GABA neuron dysfunction is a common finding in postmortem studies of certain psychiatric illnesses. Although they utilize similar gene products for neurotransmission, subtypes of GABA neurons are distinguished based on the expression of different molecular markers. Transcript levels of many of these gene products are known to differ between prefrontal (PFC) and primary visual (V1) cortices, but whether the laminar patterns of expression are conserved or different between these regions is not known.
Methods: Layers 2 and 4 were laser microdissected in the PFC and V1 from 15 monkeys. PCR was used to quantify levels of transcripts involved in GABA neurotransmission (GABA synthesizing enzymes (GAD67 and GAD65), vesicular GABA transporter (vGAT), and GABA reuptake transporter (GAT1), markers of GABA subtypes: calretinin, vasoactive intestinal peptide (VIP), calbindin, somatostatin, cholecystokinin, cannabinoid 1 receptor (CB1R), and parvalbumin, and GABAA receptor units: GABRA1 and GABRA2.
Results: Three patterns emerged: First, some transcripts (GAD67, GAD65, vGAT, GAT1) showed no consistent regional or laminar differences. Second, many transcripts were more highly expressed in layer 2 and in PFC (calretinin, VIP, calbindin, somatostatin, cholecystokinin, CB1R, GABRA2). Third, parvalbumin and GABRA1 were more highly expressed in layer 4 and V1. These patterns were consistent across each animal studied.
Conclusions: Although markers of GABA neurotransmission are conserved across layers and regions, markers of unique GABA neuron subtypes show similar differences between layers in each region. The specific distribution patterns of these GABA neuron markers might underlie the differential vulnerabilities of GABA neuron subtypes in psychiatric illnesses.
Supported By: DA023109
Keywords: GABA, Cortex, Parvalbumin Interneurons, Somatostatin Neuron, VIP Interneurons

F171. Biochemical Pathways Modulated by Typical and Atypical Antipsychotics in Human Oligodendrocytes

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Background: Schizophrenia is an incurable mental disorder, in which symptoms usually are managed by antipsychotics. It has been increasing interest in the effects of antipsychotics beyond their neuronal targets and oligodendrocytes are one of the major candidates. Thus, our aim was to evaluate the molecular effects of antipsychotics upon the proteome of oligodendrocytes.
Methods: Cells were treated (8h) with four antipsychotics as it follows: Group 1 – 10 μM chlorpromazine; Group 2 – 50 μM haloperidol; Group 3 – 50 μM quetiapine; Group 4 – 50 μM risperidone; Group 5 – chlorpromazine and haloperidol vehicle solution (0.01 M HCl); Group 6 - quetiapine and risperidone vehicle solution (DMSO). Each treatment was performed in biological triplicates. Cells had their proteins extracted and analyzed by quantitative proteomics to investigate changes in protein expression triggered by antipsychotics.
Results: In average, 1580 oligodendrocyte proteins were identified across the different treatments. Chlorpromazine, haloperidol, quetiapine and risperidone treatments modulated the expression of 195, 316, 19 and 197 proteins, respectively. All antipsychotics affected the expression levels of some proteins and these differences were common among treatments (i.e. proteins belonging to spliceosome machinery) and others were specific to each antipsychotic analyzed, which are: ion transport, by chlorpromazine; mitochondrial organization and biogenesis, by haloperidol; regulation of nucleobase, by quetiapine; and ribosome biogenesis and assembly, by risperidone.
Conclusions: Proteins and associated pathways shown here may shed light on the biochemical pathways involved in the mechanisms of action of antipsychotic drugs.
Supported By: FAPESP; Instituto Serrapilheira; Cnpq - CAPES
Keywords: Schizophrenia, Proteomics, Atypical Antipsychotics, Typical Antipsychotics, Oligodendrocytes

F172. Subcellular Proteome Analysis of iPSC-Derived Neural Cells From Schizophrenia Patients Reveals Alterations Related to Neurodevelopment

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Background: Schizophrenia is a severe psychiatric disorder of neurodevelopmental origin that may affects up to 1% of the world's population. To date, little is known about the neurodevelopmental aspects of schizophrenia in molecular terms, despite the evidence of altered cellular processes, including mitochondrial dysfunction. To overcome this, we studied the mitochondrial and nuclear proteomes of neural stem cells (NSCs) and neurons derived from induced pluripotent stem cells (iPSCs) from schizophrenia patients versus healthy controls.
Methods: Schizophrenia and control NSCs and neurons were obtained from iPSCs from three subjects diagnosed with schizophrenia and three unaffected controls. Mitochondrial and nuclear fractions were obtained from NSCs and neurons and proteins were extracted, digested and prepared for shotgun proteomic analyses to compare changes in protein expression levels between schizophrenia and control samples.
Results: Mitochondrial proteome of schizophrenia cells revealed 84 differentially regulated proteins in NSCs and 169 in neurons. These were involved in oxidative phosphorylation, tricarboxylic acid cycle and cell redox homeostasis. Nuclear proteome analyses revealed 215 differentially regulated proteins in NSCs and 144 in neurons in schizophrenia. They were associated to DNA repair, mRNA stability and cell cycle. Moreover, analysis of the proteome of neurons revealed altered expression levels of 311 proteins in schizophrenia, and they were mostly involved in axonal guidance signaling and glycolysis.
Conclusions: This study evidences alterations in pivotal cellular processes during neurodevelopment and could be involved with the establishment of schizophrenia as well as the phenotypic traits observed in adult patients.
Supported By: Fapesp; Instituto Serrapilheira, CNPq, Capes
Keywords: Schizophrenia, Neurodevelopment, Proteomics, Induced Pluripotent Stem Cells (iPSCs), Mitochondria

F173. Electroconvulsive Seizures Induce Autophagy by Activating the AMPK Signaling Pathway in the Rat Frontal Cortex

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Background: It is uncertain how electroconvulsive therapy (ECT)-induced generalized seizures result in the potent therapeutic effects on various neuropsychiatric disorders. Accumulating evidence supports the involvement of autophagy system in the treatment of neurodegenerative disorders as well as in the action mechanisms of antidepressants and antipsychotics.
Methods: The effect of electroconvulsive seizure (ECS) on the autophagy and its association with the AMP-activated protein kinase (AMPK) signaling pathway were investigated in the rat frontal cortex using immunoblot, immunohistochemistry, and transmission electron microscopy analyses. AMPK inhibitor compound C or autophagy inhibitor 3-methyadenine was intracerebroventricular (i.c.v) injected.
Results: Repeated ECS treatment for 10 days (E10X) increased p-Thr172-AMPKα immunoreactivity in rat frontal cortex neurons. Activating AMPK with E10X also increased phosphorylation of upstream effectors, such as LKB1, CaMKK, and TAK1, and of its substrates, ACC, HMGR, and GABABR2. ULK1 is another AMPK substrate that activates the autophagic process. The E10X treatment increased p-Ser317-ULK1 immunoreactivity in the rat frontal cortex. At the same time, LC3-II and ATG5−ATG12 conjugate immunoreactivity increased, indicating activation of autophagy. An i.c.v injection of the compound C attenuated the ECS-induced increase in ULK1 phosphorylation, as well as the protein levels of LC3-II and the Atg5−Atg12 conjugate. Transmission electron microscopy clearly showed an increased number of autophagosomes in the rat frontal cortex after E10X treatment, which was reduced by i.c.v treatment with the 3-methyadenine and compound C.
Conclusions: Our results show that repeated ECS treatments in the rat frontal cortex activated autophagy through the AMPK signaling pathway in vivo.
Supported By: Basic Science Research Program through NRF funded by the Ministry of Science, Information and Communication Technologies, Republic of Korea (2017R1D1A1B03035649)
Keywords: Electroconvulsive Therapy (ECT), Autophagy, AMPK, Ulk1

F174. Testosterone Modulation of Sex Steroid and Dopamine−Related mRNAs During Adolescence in the Mesolimbic Pathway

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Background: The disproportionate effect and earlier onset age of schizophrenia in males suggests a relationship between adolescent increases in testosterone and disease pathophysiology. Sex steroid hormones can modulate dopaminergic transmission and subcortical hyperdopaminergia underlies psychosis in schizophrenia. We investigated whether testosterone modulates sex steroid and dopamine-related mRNAs via androgenic or estrogenic effects during adolescence in the mesolimbic dopaminergic pathway.
Methods: Male Sprague-Dawley rats underwent sham surgery or gonadectomy at PND45. Gonadectomised rats received testosterone (androgenic and estrogenic), dihydrotestosterone (androgenic), 17β-estradiol (estrogenic) or empty (endogenous sex steroids removed) silastic implants (n=13-16/group) and brains were dissected at PND60. Sex steroid [androgen receptor, 5α-reductase, estrogen receptors (ER), and aromatase] and dopamine (tyrosine hydroxylase, dopamine transporter, dopamine receptors, and breakdown enzymes) −related mRNAs were measured (qPCR) in the ventral tegmental area (VTA) and ventral striatum (VS).
Results: Androgen-related mRNAs were unchanged by treatment. In the VTA, ERα [H(4)=11.41, p=0.02], aromatase

[F(4,71)=2.64, p=0.04] and D1 receptor [trend; F(4,68)=2.25, p=0.07] were decreased by dihydrotestosterone, while ERβ [F(4,68)=3.83, p=0.01) was increased by testosterone and catechol-o-methyl transferase [F(4,71)=4.65, p=0.002] was increased by androgens and decreased by estrogen. In the VS, aromatase [H(4)=12.57, p=0.01] was decreased by gonadectomy, while D2 receptor [F(4,67)=2.0, p=0.1] was trend increased by gonadectomy which was attenuated by dihydrotestosterone.
Conclusions: During adolescence, androgens may alter the VTA's ability to respond to estrogens, potentially reducing the neuroprotective effects of estrogens. Androgens may contribute to maintenance of dopamine receptors in the mesolimbic pathway, suggesting dopaminergic signalling is sensitive to changes in sex steroids during adolescence with potential implications for schizophrenia onset.
Supported By: NH&MRC Project grant #1020981
Keywords: Sex-Steroid Hormones, Adolescence, Gene Expression, Ventral Tegmental Area, Ventral Striatum

F175. Prefrontal Co-Expression of miR-137 Target Genes is Related With Prefrontal Activity During Emotion Recognition

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Background: Schizophrenia risk is associated with multiple genes. Co-expression is a possible mechanism mediating the orchestrated contribution of these genes to risk. As key regulators of co-expression, miRNAs with a proven involvement in Schizophrenia such as miRNA-137 can be nodes of convergence of risk on the disorder system-level phenotypes. We hypothesized that miRNA-137 target genes converge in a co-expression pathway associated with Schizophrenia risk and that co-expression of these genes is linked with system-level phenotypes previously related with miRNA-137.
Methods: In two independent samples of human postmortem PFC, we detected via Weighted-Gene-Co-expression-Network-Analysis a co-expression module enriched for genes targeted by miRNA-137 and GWAS-associated with Schizophrenia. We validated WGCNA findings by miRNA-137 CRISPR knock-out and overexpression in Neuro2A cells. Finally, we computed an index of co-expression of this gene-set (Polygenic-Co-expression-Index, PCI) and in two independent samples of healthy volunteers (N1=289; N2=71) we probed PCI as predictor of fMRI-assessed brain activity during emotional stimuli.
Results: We detected a module enriched for miRNA-137 target and Schizophrenia risk genes. CRISPR demonstrated the causal effect of miRNA-137 KO/OE on expression of genes in this module. FMRI showed PCI to predict PFC activity during face recognition (PCI positively correlated with right PFC activity during implicit processing; Sample1 and Sample2 p(FWE)-Bonferroni-corrected= .004 and .04, respectively).
Conclusions: Our results suggest that miRNA-137 may co-regulate genes that are part of a co-expression pathway including a significant proportion of schizophrenia genes. The functional role of these genes is confirmed by molecular experiments and is supported by the neuroimaging findings of genetically predicted co-expression.
Supported By: Fodazione con il Sud "Capitale ad alta qualificazione" Grant
Keywords: Schizophrenia, Imaging Genetics, Gene Co-Expression Network, miRNAs, Emotional Facial Processing

F176. Dysregulation of the IRE1α Pathway of the Unfolded Protein Response in Schizophrenia

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Background: Abnormalities in protein localization, function, and post-translational modifications (PTMs) have become targets of schizophrenia (SCZ) research. As a major contributor to the synthesis, folding, trafficking, and modification of proteins, the endoplasmic reticulum (ER) is well-positioned to sense cellular stress. The unfolded protein response (UPR) is an evolutionarily conserved adaptive reaction to environmental and pathological perturbation in ER function. Protein-misfolding events have been observed in a variety of disorders and may contribute to both the initiation and the progression of disease through ER stress. To cope with ER stress, a signaling network called the UPR is activated. The UPR is a highly orchestrated and complex cellular response which is mediated through three known ER transmembrane stress sensors, protein kinase RNA-like ER kinase (PERK), activating transcription factor-6 (ATF6), and inositol requiring enzyme 1α (IRE1α). Regulating all of these pathways is the ER chaperone BiP.
Methods: We measured the total expression of proteins by western blot analysis involved in UPR-regulated pathways in the dorsolateral prefrontal cortex (DLPFC) from 22 matched pairs of SCZ and comparison subjects.
Results: We found abnormal protein expression of multiple elements of the IRE1α pathway in SCZ, including decreased phosphorylation of IRE1α and increased protein expression of sXBP1. In addition, we found increased mRNA expression of ratio of sXbp1/uXbp1 which drives upregulation of sXBP1 protein.
Conclusions: These findings suggest an abnormal pattern of UPR activity in SCZ. Dysregulation of this system may lead to abnormal responses to cellular stressors and contribute to protein processing abnormalities previously observed in SCZ.
Supported By: National Institutes of Health Grant MH53327 (JHMW)
Keywords: Schizophrenia, Endoplasmic Reticulum, Unfolded Protein Response, Inositol Requiring Enzyme 1α, XBP1

F177. Altered O-GlcNAcase (OGA) Activity and Evidence for Substrate-Specific O-GlcNAc Abnormalities in Schizophrenia Brain

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Background: O-GlcNAcylation is a unique post-translational modification that involves the dynamic cycling of O-linked β-N-acetylglucosamine (O-GlcNAc) on a wide variety of proteins. We previously found reduced protein levels of O-GlcNAcase (OGA), which removes O-GlcNAc, in the superior temporal gyrus (STG) in schizophrenia (SZ), while expression of O-GlcNActransferase (OGT), which attaches O-GlcNAc, is unchanged. Unexpectedly, when we measured O-GlcNAc levels we did not find increased total O-GlcNAcylation and instead found reduced O-GlcNAcylation of protein populations of 5 distinct molecular masses. To reconcile these findings, we assessed OGA enzyme activity levels in the same subjects.
Methods: To determine OGA activity, we incubated post-mortem STG homogenates from age- and sex-matched pairs of SZ and non-psychiatrically ill comparison subjects (N=14 pairs) with 4-methylumbelliferone labeled GlcNAc, which fluoresces when GlcNAc is liberated by hexosaminidase activity. We measured fluorescence values in triplicate at 10 minute intervals over 2 hours and normalized these values to the OGA protein level for the same subject. Non-linear regression with the Michaelis-Menten equation was used to determine the Vmax for each subject and between group differences were assessed by paired Student's t-test.
Results: The Vmax of normalized OGA activity was 40% higher [$t(13)=2.91$, $p=0.012$] in SZ relative to paired comparison subjects.
Conclusions: Although the protein level of OGA is reduced in SZ STG, OGA enzyme activity is concurrently increased. Since O-GlcNAc reductions in SZ appear to be substrate specific, our current finding suggests that dysregulated O-GlcNAc cycling may only occur on a subset of proteins or may represent a cell-type specific defect in the disorder.
Supported By: NIMH R01 MH53327; UAB Department of Psychiatry and Behavioral Neurobiology
Keywords: Post-Mortem Brain, Glycosylation, O-GlcNAc, Post-Translational Modifications, Enzyme Activity

F178. Transcriptome Profiling in hiPSC-Derived Cell Lines From Schizophrenia Subjects Identifies Neuron-Specific Alterations in Expression of Extracellular Matrix Genes

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Background: Human induced pluripotent stem cells (hiPSC) have revolutionized the study of the biological mechanisms of schizophrenia (SCZ) and other psychiatric disorders as they allow for the establishment of brain cellular models that account for a patient's genetic background. Here we conducted an RNA-sequencing profiling study of cell lines derived from hiPSCs generated from lymphoblastoid cell lines (LCL) of subjects, including a multiplex family, from the population isolate of the Central Valley of Costa Rica (CVCR).
Methods: LCLs, hiPSCs, neural precursor cells (NPCs), cortical neurons, and astrocytes derived from 6 healthy controls and 7 SCZ subjects were generated using standard methodology. RNA from these cells was sequenced using Illumina HiSeqTM2500. Cell composition analysis was performed by CIBERSORT. Normalization and differential expression (DE) analysis were performed using DESeq2 (FC $>$ 1.5 or $<$0.067 and FDR $<$ 0.3) in patients compared to controls in each brain cell type. Gene set enrichment analysis was performed using DAVID 6.8.
Results: hiPSC-derived neurons were responsible for 94.4% of the variance seen on DE analyses, where 454 differentially expressed genes (DEGs) were identified in neurons. Neuronal DEGs were enriched in pathways related to extracellular matrix organization and system development, further supporting a role for alterations in extracellular matrix proteins and impairments in synapse formation during brain development as an underlying mechanism in SCZ.
Conclusions: Our results highlight the importance of cell type when studying molecular alterations underlying SCZ and demonstrate the utility of hiPSC cells derived from multiplex families to identify specific and significant gene network alterations in SCZ.
Supported By: This study was supported by a University of Texas System (UT BRAIN) award (CWB) and a Brain and Behavior Research Foundation (NARSAD) Young Investigator Award (LS).
Keywords: Schizophrenia, hiPSCs-Derived Neurons, RNA-seq, Extracellular Matrix, Gene Networks

F179. Abnormalities in the AKT-mTOR Signaling Pathway in Schizophrenia

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Background: Cognitive dysfunction is observed in majority of Schizophrenia (SZ) patients. The AKT-mTOR signaling cascade is critical for cognitive function. AKT is a serine-threonine kinase which requires phosphorylation at S473 and T308 for complete activation. mTOR is a kinase that forms 2 distinct complexes- mTORC1 and mTORC2 and is phosphorylated at S2448 and S2481 sites for activation in both

complexes. mTORC1 facilitates ribosome biogenesis and protein translation and acts downstream of AKT. mTORC2 regulates actin dynamics and acts upstream of AKT. Dysregulated phosphorylation of key proteins in this pathway can contribute to altered protein synthesis and actin dynamics, which have been implicated in SZ pathophysiology. Therefore, in this study, we are investigating abnormalities in the AKT-mTOR signaling pathway in SZ.

Methods: We used post mortem DLPFC from 22 matched pairs of SZ and comparison subjects. Using western blot analysis, we measured protein expression and phosphorylation of AKT and mTOR as well as their interacting proteins such as GβL, Raptor, Rictor, p70S6K, S6RP and 4EBP1.

Results: We found decreased levels of AKT and GβL protein expression in SZ DLPFC. Phosphorylated forms of AKT (S473), mTOR (S2448) and S6RP (S235/236 and 240/244) were also found to be reduced.

Conclusions: Our findings suggest that the AKT-mTOR signaling pathway is downregulated in SZ DLPFC. Given the importance of this pathway in synaptic plasticity via its regulation of protein synthesis and cytoskeletal organization, these abnormalities may represent a mechanism underlying cognitive dysfunction in SZ. Future studies will investigate the integrity of mTORC1 and mTORC2 complex formation in SZ.

Keywords: Schizophrenia, AKT-mTOR Signaling, DLPFC, Protein Expression, Phosphorylation

F180. Temporal Dynamics of miRNAs in Human DLPFC and its Association With miRNA Dysregulation in Schizophrenia

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Background: Brain development is dependent on programmed gene expression, which is both genetically and epigenetically regulated. Post-transcriptional regulation of gene expression by microRNAs (miRNAs) is essential for brain development. As abnormal brain development is hypothesized to be associated with schizophrenia, miRNAs are an intriguing target for this disorder. The aims of this study were to determine the temporal dynamics of miRNA expression in the human dorsolateral prefrontal cortex (DLPFC), and the relationship between miRNA's temporal expression pattern and dysregulation in schizophrenia.

Methods: This study used next-generation sequencing to characterize the temporal dynamics of miRNA expression in the DLPFC of 109 normal subjects (second trimester−74 years of age) and miRNA expression changes in 34 schizophrenia patients.

Results: Unlike mRNAs, the majority of which exhibits a wave of change in fetuses, most miRNAs are preferentially expressed during a certain period before adolescence. It is noted that in schizophrenia patients, miRNAs normally enriched in infants tend to be up-regulated, while those normally enriched in pre-adolescents tend to be down-regulated, and the targets of these miRNAs are enriched for genes encoding synaptic proteins. The targets of miRNAs preferentially expressed in infants over-represent genes associated with schizophrenia. Additionally, miR-936 and miR-3162 were found to be increased in the DLPFC of patients with schizophrenia unrelated to antemortem treatment or substance abuse.

Conclusions: The findings from this study reveal the temporal dynamics of miRNAs in the human DLPFC, implicate the importance of miRNAs in DLPFC development before adolescence, and suggest a possible link between dysregulation of infant-enriched miRNAs and schizophrenia.

Supported By: NIMH IRP, NHLBI IRP

Keywords: miRNAs, Postmortem, Schizophrenia, Brain Development

F181. A Randomized, Single-Blind, Parallel-Group Study to Evaluate the Effects of TS-134 on Ketamine- Induced Bold Signals in Resting fMRI in Healthy Adult Subjects

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Background: Therapies targeting glutamatergic system for schizophrenia have yielded mixed results across studies to date, and there is a critical absence of validated target-engagement biomarkers. We evaluated the dose-dependent target engagement of TS-134, a metabotropic glutamate receptor 2/3 (mGlu2/3) agonist using ketamine-evoked pharmacoBOLD in healthy volunteers.

Methods: This was a single-blind (investigators/analysis/subjects), randomized, placebo-controlled study, with ketamine-phamacoBOLD administered at screening and after six days of titrated TS-134/placebo. Eligible subjects had a Screening pharmacoBOLD fMRI response in the dorsal anterior cingulate cortex (dACC) $>0.5\%$.

Results: 59 subjects (25 high-dose [60 mg]; 24 low-dose [20 mg]; 10 placebo) had two evaluable pharmacoBOLDs assessments each, with no significant baseline differences in pharmacoBOLD or demographics (all $p>0.11$). A non-significant, difference between the low-dose and placebo groups with moderate effect size for dACC peak ($d=0.31$), and moderate effect size on %change from baseline ($d=0.52$) was observed. Effects at high-dose were comparable to those of placebo. Consistent with Phase I studies, Treatment Emergent AE (TEAE) of nausea/vomiting were time-on-drug dependent, while dizziness and somnolence were dose dependent.

Conclusions: Results of this TS-134 target engagement study showed a greater target engagement (suppression against ketamine-evoked pharmacoBOLD) at 20 mg than that of 60 mg. Unexpectedly, large placebo effects were seen in the TS-134 study, reducing power to detect between group differences.

Results comparing to a parallel study of another mGlu2/3 agonist, pomaglumetad, will be presented.

Supported By: Taisho Pharmaceuticals
Keywords: BOLD Functional MRI, mGlu2, Schizophrenia, Fast-Fail

F182. Improving Insight into Psychosis With Transcranial Direct Current Stimulation in Schizophrenia

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Background: Impaired insight into psychosis is a common feature of schizophrenia that contributes to antipsychotic medication nonadherence and poor clinical outcomes. Currently, there are no established treatment strategies to improve insight in patients with schizophrenia. In this pilot randomized sham-controlled study, we aimed to investigate the effects of transcranial direct-current stimulation (tDCS) on insight in patients with schizophrenia. We targeted the posterior parietal area (PPA), a brain region associated with impaired insight.
Methods: Participants with an DSM-IV diagnosis of schizophrenia or schizoaffective disorder with impaired insight (>3 PANSS G12) were included. All participants received either active or sham twice-daily dual-hemisphere biparietal stimulation for 10 days across 2-weeks. The anode was placed over the right-PPA and the cathode was placed over the left-PPA. Insight was assessed using the VAGUS, a 10-point scale that has both self-report (VAGUS-SR) and clinician-rated versions (VAGUS-CR). Change in insight from baseline was assessed after 2-weeks, and weekly thereafter for 4-weeks.
Results: Sixteen participants (8 active and 8 sham) were included. Active compared to sham tDCS significantly improved insight into psychosis as assessed by the VAGUS-SR ($t=-2.69$, $p=0.018$, Cohen's $d=1.34$) and the VAGUS-CR ($t=-2.60$, $p=0.021$, Cohen's $d=1.30$) at 2 weeks. There were no significant changes in insight at the follow-up visits.
Conclusions: Our results suggest dual-hemisphere biparietal tDCS may improve insight in patients with schizophrenia, which are consistent with prior studies that similarly found improved insight with cathodal stimulation of the left-PPA. Larger randomized sham-controlled studies are needed to confirm the clinical feasibility of tDCS in patients with schizophrenia.
Supported By: Ontario Mental Health Foundation (OMHF), Canadian Institute of Health Research (CIHR)
Keywords: Schizophrenia, Schizoaffective Disorder, Transcranial Direct Current Stimulation (tDCS), Insight into Illness

F183. Study of Anxiety Disorders in Community Based Schizophrenia Patients

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Background: The existence of a co-morbid anxiety disorders (ADs) correlates with positive and negative symptoms of schizophrenia; higher levels of anxiety were associated with greater hallucinations, withdrawal, depression, hopelessness, better insight and poorer function. Anxiety symptoms have a significant negative impact on the quality of life of patients with schizophrenia. Even studies report that the impact of anxiety symptoms on quality of life was greater than that of depressive symptoms. There is lack of studies from community samples.
Methods: Two hundred and twenty-seven patients were recruited from two ongoing community interventional projects in this cross-sectional and descriptive study.
Results: 7.9 % of schizophrenia patients were suffering from ADs where the anxiety disorder symptoms have started after the psychotic symptoms. Out of this, we found 11.1 % of patients to have two & three ADs; Panic Disorder and Social Phobia (Panic Disorder > Social Phobia) was found to be most common in the group. Almost 50% of these patients were never treated.
Conclusions: Keeping in mind a high prevalence and a high treatment gap for the anxiety disorders in this population, clinicians need to be vigilant about assessing and treating Anxiety Disorders in community-based schizophrenia patients.
Keywords: Schizophrenia, Anxiety Disorders, Community Samples, India

F184. White Matter Structural Integrity and Working Memory Resilience to Stress in Schizophrenia

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Background: Schizophrenia (SZ) is characterized by profound cognitive deficits, including impaired working memory (WM). The impact of stress on WM function and its neurobiological mechanisms in SZ has yet to be clarified. Structural integrity of white matter tracts may represent a neurobiological mechanism implicated in both WM function and resilience to stress.
Methods: Participants included 42 patients with SZ and 33 healthy comparison subjects (HC) who completed diffusion tensor imaging (DTI) and an N-back WM task, which was administered before and after induction of social evaluative stress using the Trier Social Stress Test. White matter integrity (FA) in six a priori tracts was investigated in relation to WM function and WM resilience to social evaluative stress in SZ and HC.
Results: Across SZ and HC, integrity of right superior longitudinal fasciculus (SLF) predicted WM performance in the non-stressful condition, whereas integrity of right cingulate gyrus of the hippocampus was related to WM resilience after induction of social evaluative stress, over and above the effects of group (SZ vs. HC).

Conclusions: These findings suggest that in both SZ and HC, WM performance relies on the integrity of different white matter tracts under stressful conditions than it does under typical conditions. Integrity of right cingulate gyrus of the hippocampus may facilitate compensatory hippocampal engagement that promotes WM resilience to stress. Therefore, preserving or enhancing hippocampal white matter integrity may be an important objective for interventions that aim to improve cognitive function and resilience in SZ.
Supported By: NIMH Grant P50 MH066286; UCLA Graduate Summer Research Mentorship Award; UCLA Graduate Research Mentorship Award
Keywords: Schizophrenia, Working Memory, Stress Resilience, Diffusion Tensor Imaging (DTI)

F185. The B-SNIP Biomarker Profiles in Clinically-Unaffected Relatives: Contributions of a Subjective Family History Report

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Background: The presence of a family history (FH) is used as an indicator of genetic vulnerability to psychosis, while patients who don't report a FH are considered "sporadic" cases in which environmental factors are thought to play roles. This distinction has important clinical implementations, particularly in predicting outcomes. Here, we investigated whether this distinction corresponds to differences in biomarker profiles in clinically-unaffected relatives of psychosis probands in the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) sample.
Methods: Using biotype factors derived from a large biomarker panel (including cognitive, eye-tracking, and electrophysiological paradigms (Clementz et al., AJP, 2016)), we investigated biomarker profiles of unaffected relatives of "familial" cases (URF, n= 123), unaffected relatives of "sporadic" cases (URS, n= 126) and healthy participants with no FH (HP, n= 232).
Results: Among nine biotype factors, only the antisaccade factor (AF) showed a significant between-group difference among URF, URS and HP ($F(2,478)=14.60$, $p<0.001$). Both URF and URS showed higher antisaccade error rate (AER) ($p<0.001$) and AF ($p<0.001$), indicating lower performance compared to HP; but no between-group differences in URF vs. URS. Furthermore, increased AER was associated with younger age at first hospitalization in psychosis probands whose relatives had high AER (n=165, p=0.03), but not in probands whose relatives had low AER (n=155, p=0.983), based on median-split.
Conclusions: These results demonstrate that the AF represents a biomarker of psychosis vulnerability, while FH appears to provide limited contribution to familial biomarker distinctions. Biomarker profiles directly assessed in relatives may offer more reliable information, which could contribute to more precise outcome predictions.
Supported By: NIMH grants MH-077851, MH-078113, MH-077945, MH-077852, and MH-077862
Keywords: Biomarkers, Family History, Endophenotypes, Antisaccades, Eye Tracking

F186. Characterization of Pre-Deviant Standard Effects on MMN and P3a in Schizophrenia: Findings From Consortium on the Genetics of Schizophrenia (COGS)

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Background: MMN and P3a responses are thought to depend on the number of pre-deviant standards, such that longer trains of standard stimuli evoke larger MMN/P3a responses. This effect is thought to reflect the violation of an increasingly stronger memory trace established by standard stimuli and represents a novel framework for understanding information processing deficits in schizophrenia (SZ). Herein, we report the effect of pre-deviant standard stimuli train length on MMN and P3a in the COGS-2 study.
Methods: Healthy subjects (HS, n=769) and SZ patients (n=901) underwent EEG testing during their participation in the multi-site COGS-2 study. MMN and P3a response were binned in groups based on pre-deviant standard train lengths of 1-3, 4-6 and >7 stimuli in order to balance trial counts.
Results: For both MMN and P3a, longer pre-deviant standard trains were associated with larger responses in both HS and SZ. Significant group, pre-deviant bin, and group x pre-deviant bin effects were detected for both MMN and P3a responses (all p's<0.05). Compared to HS, SZ patient showed attenuated MMN/P3a responses as a function of increasing standard stimuli trains.
Conclusions: These data confirm that deviants following longer trains of standard stimuli are associated with a greater violation of the memory trace in HS, and that this effect is blunted in SZ. Further work will investigate whether indices derived from this analytic framework may be related to genetic, clinical, cognitive, and functional characteristics in SZ patients seen in the COGS-2 study.
Supported By: NIH/NIMH, Sidney R. Baer Jr. Foundation, BBRF, ASCP, APA, VA MIRECC
Keywords: Mismatch Negativity, P3a, Schizophrenia, Predictive Coding

F187. Pre-Stimulus Alpha Power and Contralateral Delay Activity During Visual Working Memory in First Episode Schizophrenia

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Background: Working memory is a core deficit in schizophrenia, which may be related to attention problems. We measured neurophysiological indices of vigilance and working memory in first-episode psychosis participants (FEP) and healthy controls (HC) using concurrent electroencephalography (EEG) and magnetoencephalography (MEG).
Methods: Twenty-seven FEP and 27 matched HC performed a visual working memory task. Participants were cued to covertly attend one visual hemifield, then viewed a sample array of 1 (low-load) or 3 (high-load) colored circles per hemifield for 200ms. One second later, a probe array was presented, and participants indicated whether any attended circles changed color. For vigilance, alpha power at EEG electrode Pz was measured immediately before the sample stimulus. For working memory, Contralateral Delay Activity (CDA) was measured from parieto-occipital EEG sensors and from MEG angular gyrus sources from 300-1000ms post-sample-stimulus-onset. Scalp and source CDA was compared between groups and memory load conditions, and bivariate correlations between alpha power and load-related CDA differences (ΔCDA) were compared between groups.
Results: Load-related differences in CDA were larger for HC than FEP at EEG sensors and MEG angular gyrus sources (p's$<$0.05); however, pre-stimulus alpha power was not significantly different between groups (p$>$0.1). Further, pre-stimulus alpha power was correlated with ΔCDA in HC (r=0.38), but not FEP (r= 0.02; group difference p$<$0.05).
Conclusions: FEP were unable to modulate parietal cortex activity by working memory load to the same degree as HC, despite similar vigilance between groups. This cortical pathophysiology early in the disease course may relate to emerging visual working memory deficits.
Supported By: NIH P50 MH103204
Keywords: Electroencephalography (EEG), Magnetoencephalography, Working Memory, Attention, Parietal Cortex

F188. Altered Self-Related Processing in Schizophrenia and its Relation to Psychopathology: An fMRI Study

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Background: When describing 'voices' patients with schizophrenia typically make statements about their personal involvements: "The voice I hear does not belong to me, it is not my voice, but the voice tells about something relevant to me and my experiences". Misattribution of the voice can be associated with altered neural activations in the midline brain structures (Northoff et al, 2015).
Methods: Using fMRI, we investigated the neural correlates of perception of self-relevant stimuli while listening to recorded audio exerts. Enrolled 20 patients with schizophrenia and 20 healthy controls have listened to the self-recorded statements 'me about me' and 'me about the other', same statements said by another person 'other about me' and 'other about other' (not relevant to the subject). Data was analysed with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). Statistical parametric maps were thresholded at p$<$.001 (FWE corrected at cluster-level). The severity of the psychotic symptoms as measured by PANSS was then correlated with the activations.
Results: In healthy individuals, we identified precuneus and bilateral STG activations when listening to the self-recorded stimuli with the self-relevant statements. Patients elicited less activation of the precuneus. In 'other about me' condition, the difference was found in activations of ACC and MPFC which was more pronounced in healthy controls. Significant inverse correlations were obtained between the positive symptoms subscore and precuneus activation in patients (p$<$0.05).
Conclusions: The study confirms self-related processing in patients with schizophrenia to be associated with altered activation in the cortical midline structures and is presumably related to psychotic symptoms.
Supported By: MH CR AZV 17-32957A and MEYS NPU4NUDZ: LO1611.
Keywords: self-related Processing, Schizophrenia, BOLD fMRI

F189. Deficits and Compensation in Attentional Networks in Schizophrenia

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Background: Deficits in attention contribute significantly to disability in schizophrenia patients (SzP). However, the literature remains mixed about the origin of these deficits. We used a task designed to localize the networks involved in selective visual attention as posited in the Corbetta/Shulman model, and studied their structural and functional integrity in relation the behavior using resting state and task fMRI.
Methods: In 35 SzP and 34 healthy controls (HCs) we collected ~20 minutes of resting state and two task fMRI runs while subjects performed a rapid serial visual presentation (RSVP) task designed to localize the Corbetta/Shulman model networks. Task data were used to define ROIs and networks, which were then used to calculate task activation and resting state connectivity.
Results: SzP and HCs performed similarly on the task, but demonstrated greater activation of early visual cortex and decreased connectivity of both late visual and prefrontal networks (p$<$.05 mc-corrected). In SzP, detection rate strongly correlated with ventral attention deactivation (r=.52) and connectivity of early to late visual (r=.52), right prefrontal to dorsal attention (r=.39), and left task-control to ventral attention (r=.42) networks. Together, these connectivity motifs explained 50% of the detection rate variance in SzP.
Conclusions: We found that the source of attention deficits originates in a combination of late visual and prefrontal areas, and that strengthened connectivity between the networks in the Corbetta/Shulman model may allow the attention networks

to be used to overcome these deficits. These results provide targets for future studies of neuromodulation- and rehabilitation-based treatments.
Supported By: NIMH K23, NARSAD, Leon Levy Foundation, American Psychiatric Foundation, Sidney R. Baer Jr. Foundation
Keywords: TPJ, Visual Processing, Dorsal Attention Network, Ventral Attention Network

F190. Investigation of the Visual Steady-State Response and Cognition in Schizophrenia

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Background: Individuals with schizophrenia (SZ) display cognitive deficits in working memory and inhibition tasks. Some healthy people display similar deficits in cognitive performance without exhibiting symptoms of schizophrenia. Electroencephalographic (EEG) studies of the visual steady-state response (ssVEP) probe the oscillatory capacity of the primary visual cortex and indicate differences based on task demands. This study used ssVEP in healthy comparison groups with High (HCC) and Low (LCC) levels of cognitive control and SZ to determine if altered ssVEP responses in preparation for an ocular-motor response task that varied in cognitive demand were associated with cognition or psychopathology.
Methods: 87 participants (HCC=22, LCC=34, SZ=31) viewed 3 flickering checkerboards that were displayed for 3000ms (central =15 Hz, peripherals =12 Hz) before a cue onset. The evoked response was filtered to isolate the 15 Hz ssVEP. Peak sensors were selected and averaged into 1000ms bin. A mixed design ANOVA and follow up t-tests were conducted to determine group differences over time.
Results: ANOVA results showed significant group, task, and time effects (p's<0.01; SZ<HCC and LCC in first 2000ms bins), and a group by task interaction ($p=0.0117$). Both HC groups showed a task-related reduction in ssVEP in preparation for more cognitively demanding tasks that was not observed in SZ ($p<.01$).
Conclusions: SZ did not demonstrate changes in ssVEP response during more cognitively challenging tasks seen in both HC groups, suggesting a lack of sensitivity to task demands. These findings suggest that oscillatory deficits seen in SZ could be associated with psychopathology rather than general cognitive deficits.
Supported By: NIH Grant MHO94172
Keywords: Schizophrenia, Cognitive Deficits, Steady-State, Electroencephalography (EEG)

F191. Mismatch Negativity Event Related Potential Predicts Real-Life Functioning and Cognitive Performance One Year Later in First Episode Psychosis

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Background: Mismatch negativity (MMN), an event related potential, has been identified as a biomarker of schizophrenia, with deficits related to impaired functioning and cognition in schizophrenia spectrum (SZ) and bipolar (BD) disorders. The present study examined the relationships of MMN with domains of functioning and cognition, and whether MMN predicts functioning and cognition over time.
Methods: Thirty-nine first episode psychosis (FEP) patients (SZ: n=19; BD: n=20) and 32 healthy control subjects (HCs) completed a duration MMN paradigm at baseline, and 21 FEP patients completed a 12-month follow-up assessment. Domains of real-life functioning and cognition were assessed using the Global Assessment of Functioning Scale (GAF), Multnomah Community Ability Scale (MCAS), The Awareness of Social Inference Test Revised (TASIT), Functioning Assessment Short Test (FAST), UCSD Performance Based Skills Assessment (UPSA-B), and the MATRICS (NCCB) Consensus Cognitive Battery.
Results: MMN responses at the Fz site in patients were intact at baseline. However, SZ patients had significantly impaired MMN at follow-up ($p=0.001$). Baseline MMN was correlated with MCAS ($p=0.016$) and UPSA ($p=0.052$) and predictive of follow-up FAST ($p=0.02$). Baseline MMN was correlated with MATRICS processing ($p=0.01$), verbal ($p=0.028$), and social ($p=0.055$) sub-scores and predictive of follow-up processing ($p=0.03$), verbal ($p=0.04$), social ($p=0.04$), and problem solving ($p=0.046$) domains of cognition. Baseline MMN at the T7/TP7 site in patients was correlated with the MCAS social sub-score ($p=0.046$) and predictive of TASIT ($p=0.009$) and FAST ($p=0.033$) at follow-up.
Conclusions: Results provide evidence supporting the MMN response as a predictive biomarker of functional and cognitive domains in psychosis.
Supported By: National Institute of Mental Health [1R01MH109687]:Mei-Hua Hall
Keywords: Mismatch Negativity, First Episode Psychosis (FEP), Functioning, Cognition

F192. Abnormal Insula Functional Connectivity Explains Specific Domains of Psychosis in Schizophrenia

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Background: The insula is a comprised of multiple cortical regions including: dorsal anterior (dAI), ventral anterior (vAI), and posterior (PI), all with distinct connectivity profiles and behavioral functions. Previous studies have shown the insula to be abnormal in schizophrenia. Here we tested the hypothesis that dAI connectivity is related to cognitive impairment, whereas PI and vAI connectivity is related to positive and negative symptoms, respectively, in schizophrenia.
Methods: Resting-state fMRI, cognitive, and clinical data were collected on 82 individuals with schizophrenia and 70 healthy control participants. Whole-brain functional connectivity of three insula regions was calculated and compared

between groups. Associations with hypothesized behavioral measures were tested both for regions demonstrating group differences in connectivity and across the whole-brain.
Results: DAI connectivity with the medial dorsal thalamus was reduced in schizophrenia and correlated with cognitive impairment (r=.24, p=.03). PI demonstrated reduced connectivity with middle temporal gyrus, ventromedial prefrontal cortex, and sensorimotor regions and increased connectivity with bilateral dorsolateral prefrontal cortex (dlPFC) and right somatosensory cortex (cluster-correctedFWE p<.05). PI-dlPFC hyper-connectivity in schizophrenia was associated with more severe positive symptoms (r=.57, p<.001). VAI connectivity with anterior cingulate was increased in schizophrenia but was not associated with negative symptoms.
Conclusions: The functional connectivity of the insula is differentially affected in schizophrenia and may explain specific domains of psychosis. Specifically, the severity of positive symptoms was strongly correlated with increased connectivity between PI (interoceptive awareness) and dlPFC (executive control). This provides evidence for unusual meaning-making of interoceptive signals, in support of the aberrant salience hypothesis.
Supported By: R01 MH102266
Keywords: Insula, Salience, Resting State Functional Connectivity, Positive Symptoms, Cognitive Deficits

F193. White Matter Microstructure and Social Cognition in Early Course Schizophrenia

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Background: Social cognitive impairments have been well documented in schizophrenia; however, there is a limited understanding of the neural underpinnings. This study aims to utilize diffusion tensor imaging (DTI) to investigate the relationship between white matter (WM) structural alterations and social cognition factors in early course schizophrenia. We report baseline results from a longitudinal project examining neurological changes during cognitive remediation therapy (CRT) for identifying potential biological markers for future analysis.
Methods: We analyzed DTI data from 46 patients with schizophrenia using the ENIGMA Tract-Based Spatial Statistics protocol in FSL to extract fractional anisotropy (FA) maps. Partial correlations between all FA measures and three factors of social cognition, including domains of emotion management (EM), theory of mind (ToM), and emotion perception (EP), were investigated and covaried for age and gender. P-values were not corrected for multiple comparisons.
Results: Significant correlations between FA measures and the ToM factor were observed in both the cingulate gyrus (r=0.34, p=0.033) and fornix & stria terminalis (r=0.36, p=.024). Additionally, associations between FA measures and the EP factor were observed in both the splenium of the corpus callosum (r=0.32, p=0.046) and superior longitudinal fasciculus (r=0.32, p=0.048). No significant correlations were found for EM.
Conclusions: We observed significant associations between FA measures and ToM and EP social cognition factors. Future investigations on the longitudinal effects of CRT are warranted for identifying WM regions susceptible to changes and may potentially lead to a greater understanding of the underlying neural correlates of social cognitive impairment in schizophrenia.
Supported By: R01 NIMH MH 92440
Keywords: Schizophrenia, Diffusion Tensor Imaging (DTI), Social Cognition, Cognitive Remediation, White Matter Microstructure

F194. Impairment of Sleep-Dependent Memory Consolidation and Sleep Spindles in Early-Course Schizophrenia and First-Degree Relatives

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Background: A large body of evidence has shown that sleep is critical for memory consolidation, and sleep spindles, a hallmark oscillatory feature of non-rapid eye movement sleep (NREM), facilitates this process. In chronic schizophrenia, both memory consolidation and sleep spindle function are impaired. Here we assessed whether consolidation deficits also exist in early course-patients and their first-degree relatives, and if they correlate with spindle activity.
Methods: Eleven early-course psychosis patients (n = 5 schizophrenia (ECsz), n = 6 non-schizophrenia psychosis (ECnsz), 14 first-degree relatives of psychosis patients (FDR), and 16 healthy controls (HC) participated. Sleep-dependent memory processing on the finger tapping motor sequence task (MST) and a word pairs task (WPT) was investigated. We expected poorer consolidation on both tasks and a correlated reduction in spindle density in the ECsz and FDR groups.
Results: On the MST, HC, FDR, and ECnsz showed 9-16% improvement, while ECsz showed -1% (p = .034, ECsz vs all other groups). For the WPT, HC and ECnsz showed similarly minimal overnight forgetting (2 and 3%), while FDR and ECsz showed significantly more forgetting (11 and 17%; p = .041). Spindle density showed a trend for being lower in EC groups compared to HC and FDR (p = .090), and correlated with MST improvement (r = 0.40, p .048).
Conclusions: Results showed that deficits in MST and WPT memory consolidation and in sleep spindle density, which are seen in chronic schizophrenia, also exist in early course

patients. Furthermore, declarative memory consolidation is also impaired in first-degree relatives of psychosis patients.
Supported By: NIH grants MH107579 and MH044832
Keywords: Sleep, Memory Consolidation, Schizophrenia, Sleep Spindles

F195. NMDAR Antagonism via Ketamine Differentially Modulates Thalamic Versus Hippocampal Brain-Wide Functional Connectivity

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Background: Disruptions in brain-wide resting-state functional connectivity (rs-fcMRI) of thalamic and hippocampal circuits are implicated across neuropsychiatric conditions, including schizophrenia. Such neural system-level disturbances have not been fully mapped onto synaptic-level mechanisms, where pharmacological therapeutic intervention occurs. Antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor is a prevailing pharmacological model for schizophrenia symptoms. Yet, its effects on brain-wide coupling of thalamic and hippocampal systems remain understudied.
Methods: We examined the effect of sub-anesthetic doses of ketamine on thalamic and hippocampal rs-fcMRI in healthy adults (HCS, n=39) relative to a placebo infusion. Neuroimaging was acquired and processed in line with the Human Connectome Project (HCP) methods. rs-fcMRI was computed between individual-specific anatomically-defined thalamic and hippocampal ROIs and all other gray-matter vertices in CIFTI gray-ordinate space. Effects were examined using a 2x2 repeated measures ANOVA model with a factor of Infusion (ketamine vs. placebo) and Seed (thalamus vs. hippocampus). Brain-wide type I error protection was established through nonparametric permutation-based methods.
Results: We observed dissociable effects of NMDAR antagonism on brain-wide thalamic versus hippocampal connectivity. NMDAR antagonism induced thalamo-sensory hyperconnectivity, but reduced thalamo-cortical coupling with bilateral parietal and frontal cortex. Hippocampal effects exhibited the opposite pattern, resembling observations in schizophrenia and findings in 22Q11 deletion syndrome.
Conclusions: These effects indicate that NMDA receptor blockade results in marked brain-wide thalamic-hippocampal alterations, which map onto idiopathic and rare syndrome effects. This underscores the potential for the NMDAR antagonism model for mechanistically informing clinically observable neuromarkers and guiding future pharmacotherapies for pathological brain-wide circuit alterations in patients.
Supported By: NIH Early Independence Award (DP5)
Keywords: Ketamine, NMDA Antagonists, BOLD Functional MRI, Schizophrenia

F196. Early Trauma in Psychotic Patients: Pathway to Peril?

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Background: Research suggests childhood trauma, particularly sexual and physical abuse, may lead to later development of psychosis. 1 Early trauma has been linked to an increased risk for lifetime suicide attempts. 2 The current study examined the prevalence of early trauma in psychiatric inpatients including those with primary Psychotic Disorders as well as the potential association between early trauma and suicide attempts.
Methods: 205 patients admitted to a psychiatric facility with a primary diagnosis of Bipolar, Mood, Not-Otherwise-Specified (NOS) or Schizophrenia Spectrum Disorder completed the Early Trauma Inventory Self-Report (ETI-SR-SF). Statistical analysis using t-tests, chi square, ANOVA and regression analyses were used to compare total ETI-SR-SF and Subscale (General, Physical, Emotional and Sexual Trauma) Scores between diagnostic groups, and to examine the potential relationship between early trauma and suicide attempts. Additionally, demographic covariates: race, age, and gender were investigated.
Results: The presence of childhood trauma significantly associated with lifetime suicide attempts in the psychiatric inpatients ($p<0.05$). The most significant correlation between early trauma and lifetime suicide attempts was in Schizophrenic Disorders (n=47) where early sexual trauma conveyed the strongest (p=0.001) risk for suicide attempts followed by physical (p=0.012), emotional (p=.018) and general (p=0.046) trauma.
Conclusions: Early trauma was associated with increased lifetime suicide attempts in patients admitted for primary Mood, Bipolar, NOS, or Schizophrenic Disorders. However, this preliminary data suggests that early trauma may have a devastating impact on patients with Schizophrenic Disorders as measured by suicidal behavior. Regression analysis showed that trauma subtypes could be significant predictors of suicide attempts (p=0.016).
Keywords: Psychotic Disorders, Early Trauma, Suicide Attempts

F197. Plasma Levels of Anandamide Are Strongly increased in Schizophrenia Patients in the Acute Phase of Illness

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Background: The endogenous cannabinoid system, which mediates the psychoactive effects of cannabis in the brain, may play a key role in the pathophysiology of schizophrenia. While some studies have shown that the levels of anandamide, an endogenous cannabinoid ligand, are increased in the cerebrospinal fluid of schizophrenia patients, studies measuring peripheral anandamide levels have produced inconsistent results.

Here, we sought to determine if the recruitment of patients in the acute phase of illness would produce better results.
Methods: Ninety-two patients with a schizophrenia-spectrum disorder from the psychiatric emergency settings of the Institut Universitaire en Santé Mentale de Montréal and 36 healthy volunteers were recruited. Psychotic symptoms, anxiety, depression and substance use were assessed using self-report questionnaires. Plasma levels of anandamide were measured using liquid chromatography and mass spectrometry. Plasma levels of oleoylethanolamide (OEA), an anorexigenic fatty-acid ethanolamide, were also measured, given that the prevalence of the metabolic syndrome is increased in schizophrenia.
Results: Plasma anandamide levels were significantly increased in schizophrenia patients, relative to controls (Patients: 626.4 pg/mL ±167.7; Controls: 469.8 pg/mL ±110.1; $t=6.2$; $p<0.001$; Cohen's $d=1.0$). Between-group differences remained significant after controlling for metabolic measures. Conversely, peripheral OEA levels did not differ between groups (Patients: 2600.1 pg/mL ±627.2; Controls: 2392.5 pg/mL ±655.1; $t=1.6$; $p=0.11$). In patients, a positive association was found between anandamide levels and depressive symptoms ($t=3.3$; $p=0.001$).
Conclusions: The strong elevation of plasma anandamide levels in schizophrenia patients assessed in the psychiatric emergency setting suggests that anandamide is a potential biomarker of the acute phase of illness. Longitudinal assessments are warranted.
Supported By: Eli Lilly Canada Chair on schizophrenia research; Institut Universitaire en Santé Mentale de Montréal
Keywords: Schizophrenia, Anandamide, Oleoylethanolamide

F198. Antipsychotic-Galantamine-Memantine Combination: Does it Have Enough Missiles to Fire Against the MIGHTY Schizophrenia?

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Background: The objective of this meta-analysis was to examine the efficacy of galantamine for positive, cognitive, and negative symptoms of schizophrenia.
Methods: Seven randomized controlled trials (RCTs) with galantamine in schizophrenia have been conducted to date. The meta-analysis included six RCTs ($N=226$; one study that used galantamine 32 mg [antagonistic action] was excluded). The neuropsychological outcomes in each study were combined into a single overall effect size for cognition.
Results: Cognition significantly improved with galantamine compared to placebo, with a small to medium Hedges' g effect size of 0.233. In the meta-analysis of five RCTs that used galantamine 24 mg (the two studies that used galantamine 16 mg and 32 mg, respectively, were excluded), the Hedges' g effect size for cognitive enhancement was 0.269. Although not statistically significant, positive and negative symptoms also improved with galantamine compared to placebo.
Conclusions: In schizophrenia, targeting only one pathophysiologic mechanism may be insufficient to detect a clinically meaningful signal. Nicotinic-cholinergic and glutamatergic/N-methyl-D-aspartate (NMDA) systems have not been concurrently targeted in schizophrenia in an RCT. In a meta-analysis of RCTs with memantine in schizophrenia, cognitive and negative symptoms significantly improved compared to placebo; positive symptoms were significant at a trend level. Hence, an RCT with this combination with kynurenic acid, mismatch negativity, and brain-derived neurotrophic factor (all are based on nicotinic and NMDA receptors) as target engagement biomarkers is warranted. To treat schizophrenia, we must treat the whole (syndrome), not just the parts (domains). The antipsychotic-galantamine-memantine combination may become the first antischizophrenia treatment.
Supported By: Pillai from NIH/NIMH (MH 097060)
Keywords: Galantamine, Memantine, Mismatch Negativity, BDNF, Schizophrenia

F199. The Positive Dopamine D1 potentiator, DETQ, Ameliorates Subchronic PCP-Induced Cognitive Deficits and Increases Ach Efflux in Human D1R Knock-In Mice

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Background: Diminished dopamine (DA) D1 stimulation may contribute to cognitive impairment in Alzheimer's and Parkinson's diseases, and schizophrenia. However, orthosteric D1 receptor (D1R) agonists produce receptor desensitization and an inverted U-shaped-response, while a positive allosteric potentiator (PAP) did not (Svensson et al JPET 360: 2017).
Methods: We examined the cognitive effects of DETQ, a D1R PAM, in mice genetically modified to express the human D1 receptor ("hD1 mice"), using novel object recognition (NOR) task.
Results: The deficit in NOR produced by subchronic(sc) phencyclidine (PCP), an NMDAR antagonist which models schizophrenia, was reversed by acute treatment with DETQ, with no evidence of an inverted U-shaped response. This was blocked by the orthosteric D1R antagonist, SCH391660. Single doses of D1R agonists, SKF38393 and SKF82958, and the acetylcholinesterase inhibitor, rivastigmine, alone, or the combination of sub-effective doses of both drugs, also restored NOR in scPCP-treated hD1mice. DETQ increased cortical and hippocampal acetylcholine efflux after both acute and (sc) dosing in hD1 mice. Subchronic but not acute, DETQ, inhibited cortical glutamate and GABA efflux. DETQ-induced acetylcholine efflux was absent in scPCP mice, indicating that restoration of NOR in these mice does not require cortical acetylcholine efflux. This is additional evidence that DETQ, previously shown not to cause tolerance, stimulates D1Rs without producing an inverted U-shaped response curve and increases neurotransmitter release in the mPFC and HIP.
Conclusions: A D1 PAM may provide the long sought clinically useful agent to improve various types of cognitive deficits in a variety of neuropsychiatric disorders, including schizophrenia.
Supported By: Eli Lilly & Co and Weisman Foundation
Keywords: Dopamine D1 Receptor, PCP, Acetylcholine, Microdialysis, Neurotransmission

F200. Too Tired to Care: A Combination of Sleepiness and Poor Sleep Continuity Attenuate Reward-Related Brain Activation

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Background: Insomnia, characterized by sleep continuity complaints and daytime symptoms (e.g., sleepiness, fatigue), is a well-replicated risk factor for affective disorders. We examined the independent and combined effects of sleep continuity and sleepiness on reward-related brain function as a putative neural pathway linking insomnia and depression.
Methods: Healthy young adults (n=51; 24.4±2.9years-old; 28-Female) with a range of sleep disturbance completed a week of daily sleep monitoring before a Monetary Incentive Delay fMRI task. Sleepiness upon waking was assessed with sleep diary (None[0]-Very Sleepy[100]) and minutes awake after sleep onset(WASO) with actigraphy. For monetary gain anticipation and receipt contrasts, mean BOLD activation was extracted from 3 bilateral regions of interest: ventral striatum [VS], anterior insula[aIns] and medial prefrontal cortex[mPFC]. BOLD response was assessed as a function of sleepiness and WASO (covariates: age, sex, sleep duration) followed by Johnson-Neyman testing of sleepiness-by-WASO interactions.
Results: Sleepiness moderated associations between WASO and gain anticipation-related VS activation (b=-0.001, p=0.045); greater WASO was related to blunted VS activation at levels of sleepiness>84/100. mPFC activation during gain receipt was attenuated by sleepiness only (b=-0.053, p=0.029). Sleepiness moderated associations between WASO and gain receipt-related aIns activation (b=0.002, p=0.015); a negative WASO-aIns relationship was observed at low sleepiness (sleepiness<29/100) but a positive relationship at high sleepiness (sleepiness>75/100). Depression severity[QIDS-SR] correlated with sleepiness (r=0.44, p=0.001), WASO (r=-0.35, p=0.011), and gain receipt-related mPFC activation (r=-0.38, p=0.006).
Conclusions: The combination of morning sleepiness and poor sleep continuity was associated with blunted activation in reward-related brain regions implicated in depression. Both subjective and objective sleep indices may be important for estimating sleep-related depression risk.
Supported By: K01MH111953; R21MH102412
Keywords: Insomnia, Reward, BOLD fMRI, Actigraphy

F201. Sleepwalking (SW) and Sleep-Related Eating (SRE) Associated With Atypical Antipsychotic Medications: Case Series and Review of the Literature

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Background: Sleep walking (SW) is a parasomnia behavior characterized by repetitious occurrence of ambulation during a partial arousal from non-rapid eye movement (NREM) sleep, typical. Sleep related eating (SRE) is one of the complex sleep behaviors that may accompany sleep walking. SRE is characterized by recurrent episodes of involuntary eating and drinking that occur during partial arousal from NREM sleep. Emerging evidence suggests that atypical antipsychotics can be associated with NREM parasomnia behaviors including SW and SRE.
Methods: A case series (n=5) and a review of the literature of cases of SW, with or without SRE, associated with atypical antipsychotic use. We conducted an online database search (Ovid, MEDLINE, EMBASE, EBSCO, CINAHL) from years April 1996-March 2017 for English language case reports and series on SW, with and without SRE, associated with atypical antipsychotic use.
Results: We identified a total of nineteen cases (n=19) of SW, with and without SRE, associated with use of atypical antipsychotics. The mean age of the sample was 49.37 years (SD = 14.303) with a male predominance (68.4%; n=13). Remission from SW/SRE was noted in all cases with measures including dosage reduction, discontinuation of medication, switching to an alternate antipsychotic medication, and optimal treatment of comorbid obstructive sleep apnea.
Conclusions: Patients taking atypical antipsychotics should be enquired about symptoms of sleep walking and sleep related eating in the setting of unusual sleep behaviors and weight gain. More research is warranted to understand the prevalence, pathophysiology, clinical correlates and effective treatments for parasomnia behaviors associated with atypical antipsychotic use.
Keywords: Sleep Disorders, Atypical Antipsychotics, Non-Rapid Eye Movement Sleep

F202. The Timing of Sleep in Relationship to T. Gondii Serointensity and Seropositivity in the Old Order Amish

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Background: Timing of sleep is regulated by internal (circadian, homeostatic) and environmental factors. Disruption of

timing of sleep is associated with onset and exacerbation of mood disorders and schizophrenia. Toxoplasma gondii (T. gondii), a neurotropic parasite that has been linked with mental illness, can synthetize dopamine and elicit immune-activation, factors that may alter sleep duration and timing. We thus investigated a link between the parasite and mental illnesses via sleep disruption. We hypothesized that T. gondii serointensity and seropositivity will be associated with a phase-delayed sleep pattern.

Methods: 787 participants from the Amish Wellness Study took part. We obtained self-reported sleep onset ($\bar{x}$ = 21.38±0.54), midsleep timing ($\bar{x}$ = 2.58±0.04) and sleep offset ($\bar{x}$ = 1.63±0.14). Whole T. gondii IgG antibodies were assessed with ELISA. We used a linear mixed model by MMAP with adjustment for age, gender and family structure.

Results: T. gondii IgG titers were negatively associated with sleep onset ($p < 0.001$), midsleep ($p < 0.05$) but not sleep offset. T. gondii seropositivity was not significantly associated with sleep timing.

Conclusions: Contrary to our hypothesis, T. gondii IgG serointensity was negatively rather than positively associated with sleep onset and midsleep timing. Thus it is unlikely that sleep timing mediates, even in part, the association between T. gondii and psychiatric illness. The link between T. gondii serointensity and earlier timing of sleep requires replication with objective methods, accounting for confounders, and further mechanistic studies.

Supported By: This work was supported by the Mid-Atlantic Nutrition Obesity Research Center Pilot NORC grant (Postolache, PI), a subaward of the parent grant P30 DK072488 (Mitchell, PI) and from the Joint Institute for Food Safety and Applied Nutrition/UMD, through the cooperative agreement FDU.001418 (Postolache, PI). This study was also supported by the VA Merit Review CSR&D grant 1I01CX001310-01A1 (Postolache, PI).

Keywords: Toxoplasma Gondii, Old Order Amish, Sleep Disturbances, Psychiatric Disorders

F203. Correlation Between Obstructive Sleep Apnea and Olfactory Function: An Attempt to Bring Awareness of an Quality of Life Indicator in the Psychiatric Population

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Background: Obstructive sleep apnea (OSA) can cause significant neuropsychiatric symptoms, which impair the quality of life (QOL). One such indicator of QOL is olfactory functions. We pursued an in-depth literature review of the correlation between OSA and olfactory function. We hypothesize that olfactory function loss can occur in OSA, and managing OSA can improve QOL.

Methods: A literature search was performed covering studies demonstrating the relationship between OSA and olfactory function using PubMed, Cochrane Databases and Ovid Medline. Our inclusion criteria focused on prospective/longitudinal studies, case control studies, only human studies, studies using olfactory parameters and including a diagnosis of OSA by Polysomnography(PSG) as well as Sniffin' Sticks tests for olfactory measurements.

We found 13 studies that were relevant from March 2014 to Aug 2018. We investigated the effects of OSA on the parameters of olfactory function (odor threshold, discriminations, and identification) using Threshold-identification-discrimination scores (TDI).

Results: These studies revealed a strong correlation between the olfactory dysfunction (TDI) and the severity of OSA using the AHI. They reported the negative effect of OSA on olfactory function and testing. Also, they reported that with increasing severity of OSA, TDI scores were significantly decreased and patients had a strong negative correlation with olfactory parameters and right and left olfactory bulb volumes.

Conclusions: This review reveals that OSA can cause robust olfactory dysfunction and possible negative correlation between severity of OSA and olfactory parameters. Also, it reveals that with the management of OSA via CPAP, olfactory functions and QOL improved.

Keywords: Obstructive Sleep Apnea, Quality of Life, Sleep Disorders, Olfaction, Neuropsychiatric Symptoms

F204. Effects of Environmental Tobacco Smoke Exposure on Brain Functioning in Never-Smoking Adolescents

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Background: Differences in event-related potentials (ERPs) related to cue-reactivity, inhibitory control and reward processing between non-smokers and smokers are already identified. However, it is unknown whether environmental tobacco smoke (ETS) exposure in never-smokers results in similar brain changes thereby increasing vulnerability to develop nicotine dependence. Therefore, we tested the association between ETS exposure and ERPs reflecting cue-reactivity (P3, LPP), inhibitory control (N2, P3) and reward processing (anticipation P3 [A-P3], feedback-related negativity [FRN]) among never-smoking adolescents.

Methods: 84 never-smoking adolescents (Non-exposed = 32, Exposed = 52) viewed smoking, neutral and romantic pictures, performed the Go-IfGo-NoGo task and a Monetary Incentive Delay (MID) task, while ERPs were measured. RM-ANCOVAs in the total sample were used, as well as correlational and regression analyses in the exposed subsample. Gender, smoking during pregnancy, familial risk for nicotine dependence and pubertal development were included as covariates.

Results: RM-ANCOVAs showed no relation between ETS exposure and ERPs reflecting cue-reactivity, inhibitory control and reward processing, with exception of the FRN. A reduced FRN for exposed vs. non-exposed adolescents was observed ($F(1, 67) = 4.03$, $p = .049$). Additionally, a negative correlation between ETS exposure and the A-P3 difference score (i.e.,

reward minus non-reward) was observed (r(49)= -.29, p =.042). However, no association in the regression including covariates (beta_ETSexposure = -.22, t (5, 43) = -1.46, p = .152) was observed.
Conclusions: Overall, there are no indications that ETS exposure affects cue-reactivity and inhibitory control. However, there are some indications that ETS exposure impacts reward processing in never-smoking adolescents.
Supported By: KWF (Dutch Cancer Society)
Keywords: Environmental Tobacco Smoke Exposure, ERPs, EEG, Adolescence, Addiction

F205. Loss of Noradrenergic-Derived Galanin Enhances Opioid Reward and Reinforcement

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Background: Galanin is a neuropeptide co-expressed in multiple neurotransmitter systems that modulates opioid-related behaviors in rodents. Here, we sought to investigate whether selective loss of noradrenergic galanin would be sufficient to enhance opioid reward and reinforcement.
Methods: All studies used 3-7 month-old mice lacking galanin in noradrenergic neurons (NE Gal KO), generated by crossing DBHCre and floxed galanin lines, and their wild-type littermates (WT). To study opioid reward, an unbiased 8-day conditioned place preference (CPP) paradigm was conducted with saline and morphine (5 mg/kg) treated groups. Opioid reinforcement was examined via intravenous self-administration studies. Mice were food trained by operant conditioning prior to surgical catheterization of the right jugular vein. After one week of recovery, mice acquired remifentanil self-administration (6.4 μg/kg/infusion) during 1 hour operant sessions on an FR-1 schedule.
Results: NE Gal KO mice formed a statistically significant place preference to 5 mg/kg morphine while WT mice did not (n=8-10 per group, two-way ANOVA with Sidak's post-hoc test, p=.001). For self-administration studies, NE Gal KO mice made significantly more active responses per session than WT over the first 4 days of acquisition (n = 3-5 per group, two-way ANOVA with Tukey's post-hoc test, p<0.05 all time points).
Conclusions: This is the first study to show that loss of galanin in noradrenergic neurons is sufficient to enhance opioid reward and reinforcement. Future studies will evaluate the circuit by which noradrenergic galanin mediates its effects.
Supported By: F31DA044726, R01DA038453
Keywords: Galanin, Opioid, Reward, Reinforcement, Opioid Use Disorder

F206. Neural Mechanisms Guiding Choices for Cannabis and Alternative Rewards in Cannabis Smokers

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Background: Substance misuse is characterised by persistent choices for drugs over other rewards. Neural mechanisms underpinning drug-biased choice in humans are poorly understood. Using an experimental medicine approach, we investigated subjective value (SV) encoding during choices for cannabis and a natural reward (individuals' preferred snacks) in regular cannabis smokers. Effects of cues (cannabis, snack, or neutral) were also assessed.
Methods: Near-daily cannabis smokers (N = 20; 1 female) completed a 6-day, within-subject, inpatient protocol. After sampling the reinforcers (6 cannabis puffs; 6 small snacks), they completed 4 conditions: 1. Neutral cues/cannabis choices; 2. Cannabis cues/cannabis choices; 3. Neutral cues/snack choices; and 4. Snack cues/snack choices. In each, participants were exposed to cues before an fMRI scan during which they chose repeatedly between 0-6 cannabis puffs/snacks and an individualized monetary amount. SV was operationalized as the strength of preference for each choice. Following each scan, two choices were randomly selected for implementation.
Results: There was no effect of cues or interaction between cues and reinforcer type on SV encoding. SVs for cannabis correlated with activation in regions previously shown to encode value for other rewards, including ventromedial Prefrontal Cortex (vmPFC); a similar pattern was not observed during snack choices. Value encoding in vmPFC was greater for cannabis than snack food (Small Volume Correction; p<0.05).
Conclusions: Cannabis smokers had intact value encoding for cannabis but disrupted encoding of non-drug value, consistent with models identifying dysregulated valuation of drug relative to alternative reinforcers as a driver of problematic substance use.
Supported By: NIDA: DA034877; DA044339
Keywords: Neuroeconomics, Cannabis, Subjective Value, Experimental Medicine, Human Behavioral Pharmacology

F207. Multi-Modal Neuroimaging Characterization of Co-Occurring Mild Traumatic Brain Injury and Alcohol Use Disorder

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Background: Alcohol use disorder (AUD) and mild traumatic brain injury (mTBI) commonly co-occur among Veterans leading to exacerbated alcohol craving. We hypothesize that the co-occurrence of these conditions leads to a exacerbated dysfunction, which could be ameliorated with neuromodulatory treatment.

Methods: 20 Veterans were classified into 3 groups based on the Symptom Attribution and Classification Algorithm (Pape, Herrold, et al. 2016) and the Alcohol Use Disorder Identification Test, consumption questions: (1) AUD+mTBI (n=9), (2) AUD only (n=5) and (3) healthy controls (HC, n=6). Structural (MPRAGE), alcohol cue task fMRI, and resting state fMRI data were acquired. Data were analyzed with SPM8 and the VBM8 toolbox. A one-way ANOVA, $p<.01$ with small volume correction using a reward network mask was applied.
Results: Increased alcohol cue-induced activation was observed for AUD+mTBI vs. HC ($p<.01$) and for AUD only vs. HC ($p<0.01$), overlapping within the caudate. Decreased gray matter density was observed for AUD+mTBI vs. both HC ($p<.01$) and AUD only ($p<.01$), overlapping within the insula. There was consistently greater resting state functional connectivity (rsFC) between the hubs of multiple networks and the rest of the brain for AUD+mTBI vs. HC.
Conclusions: There are areas of both overlapping and distinct hyper-responsivity to alcohol cues and gray matter atrophy among Veterans with AUD+mTBI and AUD only. rsFC findings suggest overall hyper-connectivity among Veterans with AUD+mTBI. These results suggest integration of alcohol cue-induced activation and rsFC data to inform neuromodulatory treatments to reduce hyper-connectivity and hyper-responsivity to alcohol cues.
Supported By: VA ORD RR&D CDA-II RX000949-01A2; Edward Hines Jr., VA CINCCH LIP 42-129, and LIP 42-130
Keywords: Alcohol Use Disorder, Mild Traumatic Brain Injury, Multimodal Neuroimaging

F208. Association Between Anterior Cingulate GABA Levels and Attention in Marijuana Using Adolescents

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Background: Chronic marijuana (MJ) use has been associated with alterations in executive functions including attention and inhibitory control as well as neurobiological and neurochemical abnormalities. Impairments in attention and inhibitory function likely play a key role in the initiation and sustained use of various substances-of-abuse including marijuana. Proton (1H) magnetic resonance spectroscopy (MRS) investigations have revealed alterations in prefrontal γ-amino butyric acid (GABA), with lower anterior cingulate cortex (ACC) GABA levels reported for adolescent MJ users. We hypothesized that ACC GABA levels would be associated with attention and inhibitory function in MJ-using adolescents.
Methods: Seven MJ-using and seven healthy adolescents (HC) completed a structured clinical interview to assess MJ use, the parametric Go-NoGo (pGNG) task to assess attention and inhibitory behavior, and a 1H MRS exam to measure ACC GABA concentration expressed as the tissue-corrected, water-normalized GABA level for each subject.
Results: GABA levels were positively correlated with accuracy of "Go" responses ($p=0.029$) and negatively correlated with errors of commission ($p=0.033$) and errors of omission ($p=0.031$) on Level 1 of the pGNG task, which evaluates attention in the MJ group but not in the HC group. No significant between-group differences were observed for GABA levels as well performance on the pGNG task.
Conclusions: These results indicate that GABA levels in the ACC could be involved in the regulation of attentional behavior in MJ using adolescents. Furthermore, it highlights the importance of evaluating the relationship between neurometabolite concentrations and behavior in MJ-using adolescents to understand potential risk factors and/or neurotoxic effects of MJ use.
Supported By: Utah Science Technology And Research (USTAR, Yurgelun-Todd)
Keywords: Marijuana, Adolescence, Proton Magnetic Resonance Spectroscopy, GABA, Anterior Cingulate Cortex

F209. The Effect of Acamprosate Treatment on Cue Reactivity and Central Glutamate Activity in Recently Abstinent Alcohol Dependent Patients: A fMRI and MRS Study

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Background: The study was aimed to explore the effect of two weeks acamprosate treatment on cue reactivity and central glutamate activity in recently abstinent alcohol dependent patients.
Methods: Twenty right handed, male patients of alcohol dependence syndrome were recruited from among the in-patients of Centre for Addiction Medicine, NIMHANS. A functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) scan was performed during visual alcohol cue exposure using Visual Image induced Craving for Ethanol (VICE) paradigm in a 3T machine before and after two weeks of acamprosate treatment. All subjects were followed up to 6 weeks.
Results: In fMRI at the baseline a significant reactivity to alcohol was observed at bilateral anterior cingulate cortices (ACC), bilateral posterior cingulate cortices, bilateral medial frontal gyrus, bilateral occipital lingual gyrus, left cuneus and left middle occipital gyrus. After two weeks of acamprosate treatment there was a significant deactivation of left dorsal and ventral anterior cingulate. In MRS Significant reduction of glutamate (Glu) ($P= 0.011$) and Glutamate-Glutamine (Glx) ($p= 0.047$) peaks were observed at the right ACC after two weeks of acamprosate treatment. Reduction of Glx peak at left ACC was significantly positively correlated with subjective craving measurements ($p= 0.032$). There were no correlations detected between fMRI BOLD signal reductions and Glu/ Glx reductions.
Conclusions: ACC is a potential target for therapies aimed at reducing the cue induced brain activation which may promote abstinence in the chronic alcohol users. Reduced glutamate activity at ACC with acamprosate treatment validates its anti-glutamatergic mechanism of action.

Keywords: alcohol dependence, anterior cingulate cortex, acamprosate, cue reactivity

F210. Preliminary MRI Evidence of Abnormal Neuromelanin Accumulation in the Substantia Nigra in Cocaine-Use Disorder

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Background: Neuromelanin-sensitive MRI (NM-MRI) is a novel method that may afford a means to interrogate the dopamine system in vivo using non-invasive MRI. Neuromelanin is a product of dopamine metabolism that accumulates in neurons of the substantia nigra (SN) over the lifespan. Recent work by our group has validated its utility as a marker of dopamine function. Abnormalities in the dopamine system in cocaine-use disorder (CUD) have been observed using PET imaging but NM-MRI has never been applied to this group.
Methods: Individuals with CUD (n=20), controls matched on tobacco use (n=20), and non-smoking healthy controls (n=20) were scanned using a 2D gradient-echo NM-MRI sequence with magnetization transfer. NM-MRI signal was measured voxelwise within the SN relative to a midbrain white-matter reference region. A voxelwise linear regression analysis of NM-MRI signal within the SN compared cocaine users to matched controls. A permutation-based method was used for multiple-comparisons correction.
Results: Voxelwise analysis within the SN found cocaine users had increased NM-MRI signal compared to tobacco users (324 of 1807 SN voxels at $p<0.05$, pcorrected=0.025, permutation test; mean within-mask Cohen's d=1.4). Extracted signal from cocaine-related voxels was also higher in cocaine users than non-smoking controls (Cohen's d=1.3). Most cocaine users could be classified relative to all 40 healthy controls based on extracted NM-MRI signal from cocaine-related voxels (area under the receiver operating characteristic curve=0.85).
Conclusions: Based on these early results, NM-MRI may hold promise as a candidate non-invasive biomarker for cocaine exposure and addiction severity, one that could perhaps aid with treatment selection and response monitoring.
Supported By: Dana Foundation, NIMH
Keywords: Addiction, Brain Magnetic Resonance Imaging (MRI), Cocaine Addiction, Neuromelanin-Sensitive MRI

F211. Functional Neuronal Alterations During Fear Conditioning and Extinction Recall in Alcohol-Dependent and Healthy Individuals With and Without Early Life Stress

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Background: Previous studies have reported a link between early life stress (ELS) and an increased risk for alcohol dependence (AD) later in life. Neurobiological alterations in stress and fear regulating brain regions in AD could fundamentally mediate this association. However, no study has assessed neuronal functioning during fear conditioning and extinction in AD to date.
Methods: A classical fear conditioning paradigm was conducted in 43 healthy controls (HC; 17 with ELS, 26 without ELS) and 43 alcohol-dependent individuals (AD; 26 with ELS, 17 without ELS) utilizing 3T-MRI. BOLD responses for CS+ (conditioned stimuli predicting electrical shocks) and CS- (conditioned stimuli predicting no shocks) trials during acquisition of fear conditioning and extinction recall were analyzed using SPM-ANCOVAs controlling for age and comorbid smoking.
Results: We found significant differences between the four groups (AD±/ELS±) during the acquisition of CS+ versus CS- in the bilateral amygdala ($pFWE\leq.02$), ventromedial prefrontal cortex (vmPFC; $pFWE<.001$), insular cortex ($pFWE<.001$), and rostral anterior cingulate cortex (rACC; $pFWE<.02$). Regarding fear extinction recall, groups differed significantly in response to CS+ in the left amygdala (pFWE=.019), bilateral hippocampus ($pFWE<.03$), vmPFC ($pFWE<.001$), insular cortex ($pFWE<.001$), and rACC ($pFWE<.03$); while CS- elicited altered BOLD responses in the left amygdala ($pFWE<.05$), bilateral vmPFC and insular cortex (all $pFWE<.001$).
Conclusions: For the first time comparing individuals with and without AD and ELS, we observed significant functional alterations during fear conditioning and extinction recall in brain regions crucially involved in stress/emotion processing. As hypothesized, these alterations were most pronounced in alcohol-dependent individuals who had experienced moderate-to-severe ELS.
Supported By: NIH: ZIA-AA000242, ZIA-AA000125; DFG: CH1936/1-1
Keywords: Alcohol Dependence, Fear Conditioning and Extinction, Early Life Stress, Childhood Trauma, Amygdala

F212. Desynchronized Lower Alpha Rhythms Were Associated With Functional Ischemia in the Prefrontal Cortex in Heroin Patients After Protracted Abstinence: A Concurrent EEG-fNIRS Study

Hada Fong-ha Ieong[1] and Zhen Yuan[2]

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Background: Chronic and recurrent opiate insult injuries brain tissue and can cause serious pathophysiological changes in hemodynamic and its subsequent inflammatory responses. Prefrontal cortex (PFC) has been a target for drug addiction, in large part, because of its well-known executive functioning and

its strong connection with limbic reward regions. However, the mechanism underlying the systems-level neuroadaptations during abstinence has not been fully characterized across drug classes. The objectives of our study were to determine which neural oscillatory activity contributed to the chronic effect of opiate exposure on abstinence and whether the activity could be coupled with neurovascular information in the PFC.
Methods: We employed resting-state functional connectivity to explore alterations in 8 heroin-dependent patients who stayed abstinence (>3 months) (HD) compared with 11 control subjects. A bimodal non-invasive neuroimaging strategy was applied to combine electrophysiological signals indicative of neural synchrony and the oscillatory activity through electroencephalography (EEG) with hemodynamic signals indicative of cerebral blood oxygenation in small vessels in the PFC through function near-infrared spectroscopy (fNIRS). Machine learning was used to obtain associations between EEG and fNIRS modalities to improve precision and localization.
Results: HD patients show desynchronized lower alpha rhythms through EEG measurement and decreased rsFC and connectivity strength through fNIRS measurement in PFC network. Moreover, asymmetric interhemispheric excitability evidenced by hemodynamic patterns in PFC was observed, suggesting that the cerebrovascular abnormality in this region may be a marker for heroin protracted abstinence.
Conclusions: Asymmetric excitability in PFC and cerebrovascular injury were found in heroin addiction after protracted withdrawal through electrovascular neuroimaging.
Supported By: Other: Fundo para o Desenvolvimento das Ciências e da Tecnologia of the Macao government
Keywords: Opioid Addiction, Synchronization Likelihood, Cerebral Blood Oxygenation, Neurovascular Coupling, Translational Neuroscience

F213. Cortical Plasticity in Heroin and Methamphetamine Addiction

Molly Lucas[1], Qingming Liu[2], Wei Wu[3], Ting Liu[2], Faizan Badami[3], Corey Keller[3], Amit Etkin[3], and Tifei Yuan[2]

[1]Stanford School of Medicine, [2]Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, [3]Stanford University

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is a form of non-invasive brain stimulation used to treat psychiatric disorders. Concurrent single-pulse TMS and electroencephalogram (TMS-EEG) have been used as a probe to understand cortical circuit-based differences across people. Here, we used a single session of 10Hz rTMS as a diagnostic probe in search of a biomarker for heroin and methamphetamine addiction.
Methods: Participants included heroin (N=71) and methamphetamine (N=64) patients (post-withdrawal, no mixed-drug use), as well as healthy controls (N=30) in Nanjing and Hangzhou, China. Subjects received single-pulse TMS to three brain sites (F3, F4, and P3), following which, each person underwent one session of 10Hz rTMS to F3. Baseline spTMS was repeated to measure changes before and after rTMS. Whole-brain source estimates were made from channel-space data using weighted Minimum Norm Estimate (wMNE). Event-related spectral perturbation (ERSP) was calculated by baseline correcting the time-frequency power.
Results: Following single-session rTMS, there was a decrease in alpha power (P3 stim) in the healthy controls following rTMS around 200ms post stimulation in the bilateral Control Network ($p < 0.05$); the opposite was true in both drug groups, where there was an increase in alpha power ($p < 0.05$).
Conclusions: While healthy controls showed desynchronization of alpha following parietal stimulation, both addiction groups instead showed alpha synchronization in the same regions. This may indicate a metaplastic shift due to long-term drug use. Although heroin and methamphetamine have quite different acute effects on users, this suggests that the underlying changes induced by addiction are overlapping.
Supported By: NIH, Other
Keywords: Transcranial Magnetic Stimulation (TMS), Addiction, Methamphetamine Addiction, Heroin, Electroencephalography (EEG)

F214. Alcoholics in the Family Increases Risk of Depression

Francisco Ramirez[1], Neil Nedley[1], and Vinicius Seidel[2]

[1]Nedley Clinic, [2]Weimar Institute

Background: To examine the relationship between those who grew up with alcoholics in their immediate family and depression. Growing up with an alcoholic family member may have an influence on people's mental health. The presence of alcohol while growing up may also influence one's ability to recover from depression and anxiety.
Methods: Participants met once a week for 2 hours for 8 weeks. Meetings consisted of a 45-minute DVD presentation and group discussion. The program was run by trained facilitators and did not include a doctor-patient relationship. The program emphasized healthy behaviors such as plant- based diets, exercise, proper sleep, among others. Each participant completed a mental health test at baseline and the end of the program. It measured depression, demographics, and patient history, including growing up with alcoholics.
Results: From n=5861 that finished the program, n=2991 grew up with an alcoholic. The mean age was 52.4, SD 14.5. Baseline mean depression was 13.3, SD 7.54. End mean depression was 7.14, SD, 6.18, the change was significant t-test $t(2990)=51.41$ and $p<0.001$. Those who did not grow up with an alcoholic had a mean age of 52.4, SD 15.6. Baseline mean depression score was 10.9, SD 7.38. Their final mean depression score was 5.97, SD, 5.73. The change in mean depression scores was significant t-test $t(2869)=44.04$ and $p<0.001$.
Conclusions: Growing up with an alcoholic family member seems to increase depression scores. The program was successful in lowering the depression scores of participants with and without an alcoholic family member.
Keywords: Alcohol, Depression, Educational Intervention

Saturday, May 18, 2019

POSTER SESSION 3
5:00 P.M. - 7:00 P.M.

S1. Evaluating how CRP Effects Risk for PTSD-Like Behaviors in Trauma-Exposed Mice

Samantha Friend[1], Sorana Caldwell[1], Rahul Nachnani[2], April Crossan[3], Mei Hua Gao[4], H. Kirk Hammond[4], and Victoria Risbrough[4]

[1]UCSD School of Medicine, [2]Penn State College of Medicine, [3]Cuyamaca College, [4]San Diego Veterans Affairs Health Services

Background: Increasing evidence suggests inflammation plays a role in psychiatric disorders caused by trauma exposure. Studies suggest post-traumatic stress disorder (PTSD) is associated with altered serum C-reactive protein (CRP) and CRP gene mutations. We examined the potential causal role of CRP in mouse models for PTSD, hypothesizing that CRP expression may confer a higher risk for PTSD-like behavior.
Methods: Avoidance and conditioned fear processes were tested in CRP null male and female C57BL6J mice. Male wild-type C57BL6J mice received an intra-jugular injection of 1011 genome copies of AAV8.CRP or AAV8.Null and four weeks later were tested in the predator stress model for PTSD which assesses enduring avoidance behavior and trauma-specific fear responses 1-2 weeks after exposure to a feline predator.
Results: CRP null female mice have at baseline enhanced recall fear extinction (FCRP=1.794, n=15, p=0.0053). Despite near three-fold protein level increases (17.63 pg/mL for AAV8.CRP vs. 6.34 pg/mL for AAV8.null), male mice with AAV8.CRP overexpression did not confer a higher risk for PTSD avoidance-like behaviors or alter cued fear extinction in males after predator stress.
Conclusions: Loss of CRP signaling supports increased fear extinction in females but not males. Males also do not show CRP overexpression effects, suggesting females may be more susceptible to CRP effects on PTSD-relevant behaviors. Future studies will examine how constitutive CRP expression contributes to fear behaviors after trauma, as well as how CRP overexpression contributes to trauma effects in female mice. Studies are ongoing regarding how CRP alters peripheral and central immune response after trauma.
Supported By: NIMH R25 MH101072; VA Merit Award BX002558-01
Keywords: PTSD - Posttraumatic Stress Disorder, C-reactive Protein, Animal Model, Inflammation, Inflammatory Markers

S2. Alterations in Fear Associated Learning Activation and in Brain Structure During PTSD Development

Hong Xie[1], Roberta Redfern[2], Kristopher Brickman[1], Brian Kaminski[2], Israel Liberzon[3], and **Xin Wang**[1]

[1]University of Toledo, [2]Promedica Health System, [3]University of Michigan

Background: Changes in fear associated learning (FAL) activation and in structures of active regions have been associated with chronic PTSD symptoms. Increasing studies suggest early and progressive post-trauma changes in emotion-neurocircuitry may underlie PTSD development. To study PTSD development, we longitudinally explored changes in FAL activation and in related brain structures over initial months post-trauma.
Methods: Functional and structural MRI brain measures were performed at 2 weeks and 12 months, while PTSD diagnosis was assessed at 3- and 12-months post-trauma. FAL task during fMRI tested acquisition, extinction, and extinction recall to conditioned stimulus (CS+) paired with white noise.
Results: 2 weeks after trauma, survivors with PTSD (subsequently diagnosed at 3 months) had greater activation in left lateral frontal cortex during CS+ acquisition, less activation in anterior cingulate and parietal cortices during CS+ extinction, and greater activation in medial prefrontal cortex during extinction recall to CS+ than survivors without PTSD (corrected $p < 0.05$). Preliminary analyses of structural MRI further suggest cortical thinning in left frontal pole and inferior frontal cortices during the 12 post-trauma months in survivors with PTSD vs without at the time (time by diagnosis interaction $P < 0.05$).
Conclusions: Present findings suggest differences in early post-trauma fear learning function and in structural brain changes over the first year between survivors who do or do not develop PTSD. We are presently examining these early findings further to better understand early post-trauma functional and structural brain changes leading to fear learning deficits in survivors with PTSD.
Supported By: 5R01MH110483
Keywords: PTSD - Posttraumatic Stress Disorder, Fear Conditioning And Extinction, MR Structural Imaging, fMRI

S3. Visualizing the Cholinergic System in Health and Disease

Mala Ananth[1], Mark Slifstein[1], Nikhil Palekar[2], Ramin Parsey[2], David Talmage[1], Lorna Role[1], and Christine DeLorenzo[1]

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Background: In the central nervous system, cholinergic neurons of the basal forebrain (BFCNs) exert tight, context specific control over cortical processes. The enormous reach of their projections makes cholinergic axonal arbors difficult to maintain and vulnerable to loss. Post-mortem studies have demonstrated that decreases in cholinergic markers accompany decline in cognitive function. As such, we asked what role the cholinergic system plays in cognition and cognitive decline in both humans and rodents.
Methods: To investigate the relationship between cholinergic system integrity and cognition in vivo, in humans, we use [18F] VAT Positron Emission Tomography as a measure of cholinergic synaptic integrity. To better interpret the human findings and examine mechanism, in rodents, we use higher-resolution methods including post-mortem imaging of cholinergic axonal

arbors and in vivo electrophysiology. Both are coupled with cognitive measures to understand how alterations to the cholinergic system can alter cortical function.
Results: In a pilot cohort, we find a strong positive relationship between cholinergic synapse density in the entorhinal cortex (EC; a region vulnerable in aging) and cognition in humans. In age-accelerated mice, high resolution investigation revealed lower cholinergic axonal density in the EC and altered EC baseline activity.
Conclusions: We applied high-resolution techniques in both humans and rodents to better understand the organization of the cholinergic system. Our studies suggest cholinergic integrity is important for normal cognition and is affected early on in pathological aging conditions. Future experiments will help determine whether changes to cholinergic EC circuits can be regarded as a marker of early cognitive impairment.
Supported By: Alzheimer's Foundation of America
Keywords: Human PET/MR Imaging, Animal Models, Cognitive Impairment, Translational Research

S4. Age Differences in Hippocampal Glutamate Modulation During Object-Location Encoding: Evidence From Proton Functional Magnetic Resonance Spectroscopy (^{1}H-FMRS)

Chaitali Anand[1], Dalal Khatib[2], Cheryl Dahle[3], Naftali Raz[3], and Jeffrey Stanley[2]

[1]Wayne State University, [2]Wayne State University, School of Medicine, [3]Institute of Gerontology, Wayne State University

Background: Hippocampal glutamate activity mediates learning and memory, and glutamatergic dysfunction may contribute to age-related cognitive decline. We hypothesized altered hippocampal glutamate modulation during memory encoding in the elderly compared to the young.
Methods: ^{1}H fMRS data were acquired from unilateral hippocampi (side randomized across subjects) of seventeen young (age 24±2.7; M=8; F=9) and seven old (65±3.7; M=2; F=5) healthy adults during an associative learning and memory task, which involved encoding and cued retrieval of 12 object-location pairs. To foil rehearsal, the twelve encoding-retrieval cycles were interspersed with epochs of counting backwards. Consecutive epoch-pairs were averaged to increase the signal-to-noise ratio. Glutamate levels across 6 epoch-pairs were quantified using LCModel. Associative learning data were modeled using the Gompertz function. Outcome variables included learning proficiency over time (slope, asymptote, inflection-point) and glutamate levels acquired during a neutral condition, and across the encoding and retrieval epochs.
Results: Older participants tended to show a lower asymptote [$t(23)=1.07$, $p=.05$] and a later inflection-point of learning [$t(23) = 1.14$, $p=.07$], compared to the young. During memory encoding, glutamate evidenced distinct patterns of change across epochs between groups: age-group × epoch: $F(5,104)=3.81$, $p=.012$. Post-hoc analyses demonstrated that compared to the young, older adults evidenced lower glutamate, during the 3rd ($p=0.05$), 4th ($p=0.07$), and 6th ($p=0.03$) epoch-pairs.
Conclusions: Altered hippocampal glutamate modulation was observed during memory encoding concomitant with the poorer learning proficiency in old adults. The results suggest a functional role of glutamate in age-related memory decline, without the confounding effects of hemodynamics that limit validity of fMRI inference.
Supported By: 1 F31 AG058420 - 01, 1 R21 AG059160 - 01
Keywords: MR Spectroscopy, Glutamate, Aging And Memory

S5. Epigenetics of Delirium and Aging: Potential Role of DNA Methylation Change on Cytokine Genes in Glia and Blood Along With Aging

Gen Shinozaki[1], Patricia Braun[2], Benjamin Hing[3], Andrew Ratanatharathorn[4], Mason Klisares[3], Gabrielle Duncan[3], Sydney Jellison[3], Jonathan Heinzman[3], Yasunori Nagahama[3], Liesl Close[3], Sayeh Sabbagh[3], Brian Dlouhy[3], Matthew Howard[3], Hiroto Kawasaki[3], and Ryan Cho[5]

[1]University of Iowa Hospitals and Clinics, [2]Johns Hopkins University, [3]University of Iowa, [4]Columbia University, [5]University of Iowa, College of Public Health

Background: Delirium in elderly patients is common and dangerous. Major risk factors include aging and exogenous insults, such as infection or surgery. In animal models, aging enhances pro-inflammatory cytokine release from microglia in response to exogenous insults. The epigenetic mechanism DNA methylation (DNAm) regulates gene expression and changes with age. Older individuals may have methylation changes that influence the increased cytokine upon insult, but the degree to which aging affects DNAm of cytokine genes is not fully understood.
Methods: The relationship between DNAm and aging of pro-inflammatory cytokine genes (TNF-alpha, IL1-beta, IL-6) was investigated using methylation array data in two cohorts. Brain and blood samples were collected from a neurosurgery cohort (NSG) of 21 subjects who underwent brain resection. A second cohort, the Grady Trauma Project (GTP), included blood samples from 265 subjects.
Results: In the NSG cohort, a significant negative correlation between age and DNAm in brain was found at a CpG in IL-6. With the GTP dataset, significant negative correlations between age and DNAm were seen at most of the CpGs in TNF-alpha. Also, TNF-Alpha expression increases with age. These GTP DNAm correlations were also nominally significant in NSG blood samples. In neuronal negative NSG brain tissue, a similar negative trend was observed.
Conclusions: With aging, a decrease in DNAm of cytokines gene CpGs in glia and blood was seen. As this can affect their expression, additional research is needed to fully elucidate the role of DNAm in aging and how it may influence the pathogenesis of delirium.
Supported By: K23MH107654
Keywords: Epigenetics, DNA Methylation, Aging, Inflammatory Cytokines, Microglial Activation

S6. Digital Cognitive Assessment in Psychiatry Research

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Background: Measuring cognitive functions is complex and requires the use of expensive and inconvenient in-lab neuropsychological assessments. We will discuss the use of smartphones to assess cognitive performance "in the wild," using cognitive functioning among older persons living with HIV (PLHIV) as a use-case example.
Methods: Ninety-one persons with and without HIV (aged 50-74) completed an in-person neuropsychological assessment and 14 days of a smartphone-based mobile color-word interference test (mCWIT). Different versions of the mCWIT were completed daily. Acceptability, feasibility and validity of the mCWIT were examined.
Results: Adherence to the mCWIT was excellent (85%). Aggregate means of the mCWIT number correct, number errors, and time to completion were calculated. PLHIV took longer (M=23.68 seconds, SD=6.01) to complete the mCWIT compared to participants without HIV (M=21.04 seconds, SD=4.70; p=0.03). PLHIV with neurocognitive impairment made significantly more errors on the mCWIT than PLHIV without neurocognitive impairment or HIV- participants with or without neurocognitive impairment (p=0.02). Controlling for HIV status and demographics, both in-person color-word interference time (p=0.019) and average mCWIT time (p=0.041) predicted neurocognitive impairment.
Conclusions: Our preliminary findings indicate mobile cognitive testing is feasible and valid among PLHIV and comparison participants with and without cognitive impairment. While we do not view mobile cognitive testing as a replacement for traditional in-person neuropsychological testing, this methodology has several exciting implications for psychiatry, including monitoring subtle changes in real-world cognitive abilities over time, examining the relationship between real-world variability in cognition, symptoms and mood, and monitoring outcomes for clinical trials or pharmacological interventions.
Supported By: NIMH K23 MH107260
Keywords: Mobile Cognitive Testing, Digital Health, Ecological Momentary Assessment, Executive Functioning, Long-Term Measurement

S7. General Functional Connectivity: Shared Features of Resting State and Task fMRI Drive Reliable and Heritable Individual Differences in Functional Brain Networks

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Background: Intrinsic connectivity, measured using resting-state fMRI, has emerged as a fundamental tool in the study of the human brain. However, due to practical limitations, many studies do not collect enough resting-state data to generate reliable measures of intrinsic connectivity necessary for studying individual differences.
Methods: After preprocessing, time series from task and resting-state fMRI were combined across a variety of scan lengths and used to derive intrinsic functional connectivity. Test-retest reliability, heritability and predictive utility were investigated.
Results: Here we present general functional connectivity (GFC) as a method for leveraging shared features across resting-state and task fMRI and demonstrate in the Human Connectome Project and the Dunedin Study that GFC offers better test-retest reliability than intrinsic connectivity estimated from the same amount of resting-state data alone. Furthermore, at equivalent scan lengths, GFC displays higher heritability on average than resting-state functional connectivity. We also show that predictions of cognitive ability from GFC generalize across datasets, performing as well or better than resting-state or task data alone.
Conclusions: Collectively, our work suggests that GFC can improve the reliability of intrinsic connectivity estimates in existing datasets and, subsequently, the opportunity to identify meaningful correlates of individual differences in behavior. Given that task and resting-state data are often collected together, many researchers can immediately derive more reliable measures of intrinsic connectivity through the adoption of GFC rather than solely using resting-state data. Moreover, by better capturing heritable variation in intrinsic connectivity, GFC represents a novel endophenotype with broad applications in clinical neuroscience and biomarker discovery.
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Keywords: Test-Retest Reliability, Intrinsic Connectivity Networks, Heritability, Prediction, General Cognitive Ability

S8. Increased Locus Coeruleus Volume in Humans With Pathological Anxiety: An Ultra-High Field 7-Tesla MRI Study

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Background: The locus coeruleus (LC), a small set of bilateral norepinephrine -neuron containing nuclei located in the brainstem pons, has an established role in the normal attentional and arousal responses to threat and has long been

implicated in the emergence of pathological anxiety and hyperarousal in pre-clinical models. However, human evidence of links between LC dysfunction and pathological anxiety has been restricted by limitations in discerning LC with current neuroimaging techniques.

Methods: We combined ultra-high field 7-Tesla 0.4mm isotropic magnetization-transfer MRI with a novel computational LC localization and segmentation algorithm to delineate the LC in 23 subjects including 14 patients with an anxiety or stress-related disorders and 9 non-psychiatric healthy controls.

Results: Our automated, data-driven LC segmentation algorithm provided LC delineations with good homology with previous post-mortem histological definitions of the LC. Increased LC volume was observed in patients compared to controls ($p=0.037$), controlling for gender, an expected mediator of LC size. Higher LC volume was associated with higher anxious arousal symptoms ($R=0.37$, $p=0.039$) and lower attentional control ($R=-0.56$, $p=0.003$) trans-diagnostically across the full sample.

Conclusions: Our methods provide high-resolution structural quantification of the LC in psychiatric patients, permitting in vivo LC localization and structural characterization and indicating that pathological anxiety is trans-diagnostically related to LC structure.

Supported By: Support was provided by the Friedman Brain Institute and by the Ehrenkranz Laboratory for Human Resilience, both components of the Icahn School of Medicine at Mount Sinai.

Keywords: Locus Coeruleus, Anxiety Disorders, Ultra-High Field 7-Tesla MRI

S9. Effects of Bergen 4-Day Treatment on Resting-State Graph Features in Obsessive-Compulsive Disorder

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Background: Abnormal topology of cortico-striato-thalamo-cortical, fronto-limbic and fronto-parietal circuits has been found in obsessive-compulsive disorder (OCD). The Bergen-4-Day-Treatment concentrates exposure-in-vivo with response prevention (ERP) over four consecutive days. We investigated treatment-related changes in static and dynamic graph measures.

Methods: Thirty-four OCD patients (25 unmedicated) and 28 controls were included for pre-post treatment assessments. Twenty-eight patients and 19 controls were included in longitudinal analyses. Resting-state functional MRI was performed on 3T-MRI. Scans were motion corrected (6 regressors and ICA-AROMA), smoothed, and nuisance signals were regressed out. Two-hundred-and-twenty-six nodes were defined. Wavelet coherence was used to construct the connectivity matrices. We calculated static (efficiency, clustering coefficient, modularity, strength, and betweenness centrality) and dynamic (flexibility, promiscuity, temporal correlation coefficient, and temporal variation in efficiency and clustering coefficient) graph measures, at the global, subnetwork, and regional level. Non-parametric tests in R were used for group, time, and group-x-time effects (reported after false discovery rate correction).

Results: We found significant group-$\times$-time effects in frontoparietal-limbic connectivity ($p=.03$) and flexibility in the right subgenual anterior cingulate cortex ($p=.03$), where unmedicated patients showed significant decreases while controls showed no significant changes. Controls also showed increases in global and subnetwork efficiency and clustering coefficient, particularly in the somatomotor subnetwork.

Conclusions: Concentrated ERP for OCD over four days leads to decreases in frontoparietal-limbic connectivity and flexibility in the subgenual anterior cingulate cortex, suggesting more independent subnetworks and stable network state. In line with previous studies, we found that medicated OCD patients showed less limbic abnormalities and changes.

Supported By: Helse Vest Health Authority (No. 911754 and 911880)

Keywords: Obsessive Compulsive Disorder (OCD), Exposure Therapy, Graph Analysis, Frontoparietal Network, Resting State Functional Connectivity

S10. Frontoparietal and Salience Network Alterations in Obsessive-Compulsive Disorder: Insights From Independent Component and Sliding Time Window Analyses

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Background: Resting-state functional magnetic resonance (fMRI) studies commonly report alterations in three core networks in obsessive-compulsive disorder (OCD): Frontoparietal network (FPN), default mode network (DMN) and salience network (SAL), defined by functionally connected infra-slow oscillations in ongoing brain activity. However, most of these studies observe static functional connectivity in the brain of OCD patients.

Methods: In order to investigate dynamic functional connectivity alterations and to widen the evidence towards the triple network model in OCD, we performed group based independent component and sliding time window analyses in 49 OCD patients and 41 healthy controls.

Results: The traditional independent component analysis showed disturbances within the left FPN, as well as between the left and right FPN in OCD patients compared to healthy controls. Concerning the dynamic functional connectivity, the sliding time window approach revealed peak dysconnectivity between left and right FPN and between left FPN and SAL.

Conclusions: Our results suggest that disrupted modulation of these intrinsic brain networks may contribute to OCD

pathophysiology and underline the importance of connectivity of frontoparietal regions.
Supported By: TUM Graduate School of Medicine
Keywords: OCD, Brain Imaging, fMRI, Independent Component Analysis, Functional Connectivity, Resting State fMRI

S11. The Structural Neural Correlates of Negative Self-Focused Thought in Women With PTSD

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Background: A core feature of posttraumatic stress disorder (PTSD) is increased negative self-focus. Previous neuroimaging research has identified abnormal activity in brain regions involved in negative self-focus, including the default mode network (DMN) and affective network (AN), in PTSD. However, no studies to our knowledge have used a language analysis of impact statements and structural neuroimaging to examine the relationship between negative self-focus and cortical thickness and volume in DMN and AN regions in PTSD.
Methods: In the present study, women with PTSD due to interpersonal trauma ($n = 32$) underwent structural magnetic resonance imaging and completed a written impact statement (i.e., description of how the trauma has affected their lives) prior to beginning therapy.
Results: Statistical associations between cortical thickness/volume in major regions of the DMN and AN and negative self-focus from the impact statements were analyzed using linear regression models. After covarying for depression severity and age, negative self-focus was a predictor of thickness in DMN and AN regions including the left precuneus ($t(30) = -2.13$, $p = .042$), right inferior parietal ($t(30) = -2.51$, $p = .018$), left insula ($t(30) = -2.14$, $p = .042$) and volume in both the left ($t(30) = 2.45$, $p = .021$) and right amygdala ($t(30) = 2.17$, $p = .039$) of the AN.
Conclusions: These results suggest that network dysfunction within the DMN and AN may contribute to negative self-related thought in individuals with PTSD. Future research will be necessary to determine whether AN and DMN dysfunction predict changes in negative self-focus after successful treatment.
Supported By: National Institutes of Health: grant K23 MH090366-01 and RC1 MH089704-01
Keywords: PTSD - Posttraumatic Stress Disorder, Default Mode Network, Negative Self-Focus

S12. Dimensions of Psychopathology are Dissociably Linked to Brain Structure in Youth

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Background: High comorbidity among psychiatric disorders suggests that they may share underlying neurobiological deficits. Abnormalities in cortical thickness and volume have been demonstrated in clinical samples of adults, but less is known when these structural differences emerge in youth. The purpose of this study was to examine the association between dimensions of psychopathology and brain structure.
Methods: We studied 1,394 youth imaged as part of the Philadelphia Neurodevelopmental Cohort. Dimensions of psychopathology were constructed using a bifactor model of symptoms. Cortical thickness and volume were quantified using high-resolution MRI at 3T. Structural covariance networks were derived using non-negative matrix factorization and analyzed using generalized additive models with penalized splines to capture both linear and nonlinear developmental effects.
Results: Fear symptoms were associated with reduced cortical thickness in the anterior and posterior cingulate cortex, temporal-parietal junction, anterior insula, as well as orbitofrontal and temporal cortex ($p \leq .045$). Overall psychopathology was associated with globally reduced gray matter volume across all networks ($p \leq .002$). Lastly, structural covariance networks predicted psychopathology symptoms above and beyond demographic characteristics and cognitive performance ($p \leq .023$).
Conclusions: Our results suggest a dissociable relationship whereby fear is most strongly linked to reduced cortical thickness and overall psychopathology is most strongly linked to global reductions in gray matter volume. Such results have implications for understanding how abnormalities of brain development may be associated with divergent dimensions of psychopathology, and suggest potential biomarkers that could be used to enhance personalized interventions for psychiatric disorders in youth.
Supported By: This work was supported by grants from the National Institute of Mental Health (NIMH; grant numbers: K99MH117274 to ANK, R01MH107703 and R01MH113550 to TDS, R01NS085211 to RTS, R01MH112847 to RTS and TDS, R01MH107235 to RCG, and R01MH112070 to CD); the Dowshen Program for Neuroscience, and the Lifespan Brain Institute at the Children's Hospital of Philadelphia and Penn Medicine. The PNC was funded by RC2 grants MH089983 and MH089924 to REG from the NIMH. Support for developing statistical analyses (RTS & TDS) was provided by a seed grant by the Center for Biomedical Computing and Image Analysis (CBICA) at Penn. Support for developing multivariate pattern analysis software (AS & TDS) was provided by a seed grant by the Center for Biomedical Computing and Image Analysis (CBICA) at Penn. Support was also provided by a NARSAD Young Investigator Award (ANK) as well as a Penn PROMOTES Research on Sex and Gender in Health grant (ANK) awarded as part of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) grant (K12 HD085848) at the University of Pennsylvania.
Keywords: Psychopathology, NEUROANATOMY, Brain Imaging

S13. The PPM1F Gene Influences the Association Between PTSD and Cortical Thickness

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Background: Recent work has shown that the PPM1F gene is associated with posttraumatic stress disorder (PTSD) as well as PPM1F expression in post-mortem brain tissue and human blood. This study investigated the influence of PPM1F on PTSD-related brain processes in vivo, specifically on the association between PTSD and cortical thickness.
Methods: In a sample of 240 white, non-Hispanic trauma-exposed veterans, 18 single nucleotide polymorphisms (SNPs) spanning the PPM1F gene were investigated, alone and in interaction with PTSD, in models predicting 68 cortical thickness parcellations, controlling for multiple testing across both SNPs and phenotypes.
Results: After correction for multiple testing, six SNPs in PPM1F in perfect linkage disequilibrium (LD) with one another, moderated associations between PTSD symptom severity and reduced cortical thickness of bilateral superior frontal and orbitofrontal regions as well as the right pars triangularis (all corrected ps$<$0.05). A whole-cortex vertex-wise analysis with the most significant SNP (rs9610608) revealed this effect to be localized to a cluster in the right superior frontal gyrus that survived multiple comparison correction (cluster-corrected p$<$0.02).
Conclusions: These results extend prior work demonstrating a role for PPM1F in PTSD by suggesting that PPM1F influences the association between PTSD and reduced cortical thickness in the prefrontal cortex.
Supported By: VA Clinical Science Research and Development Career Development Award (VA CSR&D CDA-2, 1IK2CX001772-01); National Institutes of Mental Health (NIMH) training grant (T32MH019836-01)
Keywords: PTSD - Posttraumatic Stress Disorder, Cortical Thickness, Imaging Genetics, MRI, Trauma

S14. Intrinsic Brain Connectivity Moderators of Psychotherapy Response and Changes in PTSD: A Combined Connectomic, Network Level, and Seeded Connectivity Approach

To see this abstract, please see Oral Abstract #O15.

S15. A Mindfulness Interoception Task Engages Distributed Brain Networks That are Dysregulated in Posttraumatic Stress Disorder (PTSD)

To see this abstract, please see Oral Abstract #O2.

S16. PTSD as a Threat Mood: Insights From a Reinforcement Learning Model

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Background: Posttraumatic stress disorder (PTSD) is often modeled as intense Pavlovian learning, leading to subjective distress and changes in subsequent learning. We present a generative model of how a learner estimates threats independent of specific associations.
Methods: Bayesian model: Events occur according to a modified binomial model defined by rate of attack and lethality of attack for n=10000 generated samples. The probability distribution of parameters is estimated via Markov Chain Monte Carlo sampling.

Reinforcement learning (RL) momentum model: Following Eldar et al 2016, threat prediction errors shared across associational contexts due to a momentum term. Parameters are derived from freezing in n=16 mice undergoing stress-enhanced fear learning (SEFL), then compared with the Bayesian model on simulated data.
Results: A Bayesian observer can estimate attack rates precisely (dispersion 0.0014), unlike the lethality of attacks (dispersion 0.1171). If events occur in early life, this leads to persistent overestimates of the attack rate (estimated attack rate 0.0110 ELS vs 0.0041 random traumatic events, p$<$1e-6). Parameters from SEFL define a previously unknown behavior in the RL momentum model that resembles the optimal Bayesian learner.
Conclusions: A Bayesian estimator of attack rate provides a parsimonious model of the long duration of symptoms and sensitivity to ELS in PTSD. Comparison with a RL momentum model suggests that this more biologically plausible approach can reconcile non-specific sensitization to threat in PTSD with enhanced associability. Measuring neural correlates of threat momentum and may yield insights into the biological mechanisms of PTSD that are distinct from those of associative learning parameters.
Supported By: NARSAD YI (Kaye); VA National Center for PTSD (Kaye)
Keywords: PTSD, Computational Psychiatry, Reinforcement Learning, Bayesian Modeling, Threat Sensitivity

S17. Pre-Deployment Risk Factors for PTSD in Afghanistan Veterans: A Machine Learning Approach for Analyzing Multivariate Predictors

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Posttraumatic Stress and Traumatic Brain Injury, NYU School of Medicine, [3]Harvard University, [4]NYU School of Medicine, [5]U.S. Army Center for Environmental Health Research, [6]Harvard Medical School, McLean Hospital, [7]New York University, [8]Stanford University

Background: Active duty Army personnel have an increased risk for Post-traumatic Stress Disorder (PTSD) due to the higher rate of exposure to traumatic and stressful warzone events. Despite that PTSD leads to high individual and societal costs in veterans, predictive markers to guide preemptive risk mitigation before deployment are not yet well understood. The Fort Campbell Cohort study, a prospective longitudinal naturalistic cohort study, examined the predictive value of a clinical predictive model of PTSD risk using a large multidimensional data set collected prior to deployment to Afghanistan that consists of polygenic, epigenetic, metabolomic, endocrine, and inflammatory markers, neurocognitive and symptom self-report measures. The talk will highlight the potential of using pre-deployment data to predict the development of PTSD and also discuss potentials challenges.
Methods: Data of active duty Army personnel (N=473) was collected prior to deployment to Afghanistan (phase 1), three days after a 10-month deployment (phase 2) and 90-180 days post-deployment (phase 3).
Results: Random forests were predictive of symptom-trajectory identified with Latent Growth Mixture Modeling (AUC=.85; 95%CI of .75-.94) and provisional PTSD diagnosis at 90-180 days after deployment (AUC=.78; 95%CI of .67-.89). The most important predictors included pre-deployment sleep, anxiety, depression, cognitive flexibility and sustained attention, demographic characteristics such as age and blood-based biomarkers such as metabolites, epigenomic, immune, inflammatory and liver functioning markers.
Conclusions: The clinical prediction of PTSD symptoms after deployment is achieved with good accuracy from pre-deployment data incorporating biological, clinical and neurocognitive factors. Machine learning predictive analytics is promising for identifying warfighters at increased risk for PTSD.
Supported By: German Research Foundation: (SCHU 3259/1-1); grants from Steven A. and Alexandra M. Cohen Foundation, Inc. and Cohen Veterans Bioscience, Inc. (CVB) and U.S Army Medical Research and Material Command (USAMRMC)
Keywords: Post-Traumatic Stress Disorder, Military Deployment, Early Risk Detection, Predictors, Machine Learning

S18. Computational Modeling of Threat Learning: Associations With Anxiety, Age, and Brain Structure

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Background: Major theories link early-life aberrations in threat learning to pathological anxiety. However, across the lifespan, most research finds normal threat learning in anxiety patients. This may reflect challenges in quantifying dynamic, associative learning processes. We implement computational modeling to quantify threat conditioning and extinction learning rates, and examine developmental associations among threat learning, anxiety, and brain structure.
Methods: Participants were 351 individuals (209 females, ages 8-50 years; 195 healthy, 156 anxious) who completed a threat-conditioning and extinction task. Associative learning models were fitted to individual trial-by-trial skin conductance data indexing physiological responses to conditioned and aversive stimuli, yielding one learning rate per task phase. Whole-brain structural images were available for a subset (n=253). Learning rates were analyzed using GLM to: 1) compare threat learning between healthy and anxious individuals; 2) examine moderating effects of age on associations between threat learning and anxiety; 3) examine links between brain structure, threat learning, and anxiety across age.
Results: Relative to healthy individuals, anxiety patients exhibited faster acquisition of threat associations, $F(1,348)=4.51$, $p=0.03$, regardless of age; extinction learning rate did not differ by anxiety, $p=0.57$. Learning rates diminished with age for conditioning, $F(1,348)=13.67$, $p<0.001$, and extinction, $F(1,348)=4.38$, $p=0.04$. Developmental links between anxiety and extinction learning manifested on hippocampus gray-matter volume, $p<0.05$ (FWE-corrected). No sex effects were noted.
Conclusions: Results support a role for rapid acquisition of threat associations in anxiety and highlight hippocampus in developmental effects on extinction learning in anxiety. These findings inform our understanding of anxiety from a threat-learning perspective and bear potential treatment implications.
Supported By: Intramural Research Program at the National Institute of Mental Health
Keywords: Anxiety Disorders, Threat, Fear Learning, Associative Learning, Hippocampus

S19. Neural and Behavioral Evidence of Estradiol Modulating Fear Learning and Extinction Among Women With PTSD

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Background: Fear expression in posttraumatic stress disorder (PTSD) and anxious psychopathology is sexually dimorphic and varies with fluctuations in estrogen throughout a menstrual cycle. While estrogen is hypothesized as a mechanism of increased PTSD among women, there is a dearth of research on modulatory effects of estrogen on fear responding among women with PTSD specifically, and no data on neural outcome measures in women with PTSD.
Methods: Forty adult women with PTSD underwent a fear conditioning and extinction paradigm. Saliva samples were

assayed to determine estradiol concentration. Both skin conductance responses (SCR) and whole-brain activation during fMRI were analyzed as outcome variables using linear mixed effects modeling with estradiol level, PTSD severity, and task contrasts as predictors. Whole-brain analyses were corrected with voxelwise p=.001 and k>=18.
Results: We observed an estradiol x PTSD severity x habituation (run1 vs run2) interaction in SCR (t=4.340, p<.001), such that PTSD severity was inversely related to habituation among women with low estradiol (t=-5.249, p<.001) but not high estradiol (t=0.811, p=0.417). This finding was corroborated with the same three-way interaction (t=4.340, p<.001) in left hippocampus and left insula activation.
Conclusions: These results demonstrate a moderating role of estrogen in the relationship between PTSD severity and fear responding during fear conditioning and extinction, such that high estradiol protected against the impact of high PTSD symptoms on less habituation. We observed this effect across both SCR and neural measures. These findings suggest consideration of estrogen levels during extinction-based therapies such as exposure therapy.
Supported By: R21
Keywords: PTSD, Fear Extinction, Brain Imaging, fMRI, Estrogen, Skin Conductance Responses

S20. Depletion of CD4+CD25+ Regulatory T Cells Inhibits the Anxiolytic Effects of Lactobacillus Rhamnosus (JB-1)

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Background: We have previously demonstrated that Lactobacillus rhamnosus JB-1 (JB-1) has anxiolytic and antidepressant-like effects in mice. The behavioral changes induced by JB-1 occur alongside immunomodulatory effects of the bacteria, characterized by increased systemic regulatory T cells. In the current study we addressed a potential causal relationship between the anxiolytic effects of JB-1 and the induction of regulatory T cells.
Methods: BALB/c mice were treated orally with JB-1 (1x10^9 cfu/day) or vehicle for 28 days (n=24 per group). Within each treatment group, mice were depleted of CD4+CD25+ regulatory T cells through injection with anti-CD25 antibody (n=12) or received isotype IgG (n=12). Depletion of T regulatory (CD4+CD25+Foxp3+) cells was confirmed by flow cytometry. Following treatments, mice underwent a series of behavior tests, including elevated plus maze (EPM), open field test (OFT) and light-dark test (LDT), to analyze anxiety-like behavior.
Results: JB-1 treatment lead to a significant decrease in anxiety-like behavior as determined by increased open arm entries in the EPM and greater time and distance travelled in the light zone of LDT. Depletion of Treg cells alone had no significant effect on behavior in the EPM or LDT but abolished the anxiolytic effects of JB-1 in these tests. In the OFT depletion of Tregs alone lead to a significant reduction in entries and time spent in the center area.
Conclusions: These results suggest that T regulatory cells can influence certain behaviors in mice and play a role in the gut-brain axis, contributing to the anxiolytic effects of L.rhamousus JB-1.
Supported By: Office of Naval Research
Keywords: T Regulatory Cells, Gut-Brain Axis, Anxiety

S21. Identification of a Novel T-Lymphocyte Inflammatory Protein in Psychological Stress-Induced Hypertension

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Background: Post-Traumatic Stress Disorder (PTSD) dysregulates physiological systems leading to elevated sympathetic tone and norepinephrine (NE) outflow, pronounced inflammation, and a >50% increased risk in developing comorbid cardiovascular diseases like hypertension (HTN). We hypothesized that NE increases T-lymphocyte-driven inflammation leading to HTN after trauma exposure.
Methods: A mouse model of psychological trauma known as repeated social defeat stress was utilized for animal experiments. Human studies were performed on age/sex matched plasma from 30 PTSD and 30 PTSD+HTN patients.
Results: Stressed animals demonstrated increased sympathetic tone (NE, +2.5 fold; p<0.001) and T-lymphocyte pro-inflammatory cytokines (IL-17A, +4.4 fold; IL-6, +3.1 fold; IL-2, +3.0 fold; p<0.01). Blood pressure was elevated during stress induction (+19.5 mmHg, p<0.05) with an even greater (+39.8 mmHg, p<0.01) rise after contextual stress re-exposure. Mice devoid of mature lymphocytes were utilized to investigate the causal contribution of T-lymphocytes, and showed a blunted blood pressure response upon context re-exposure (+8.8 mmHg, p<0.01). Single cell RNAseq analysis of T-lymphocytes from stressed wild-type animals demonstrated a significant increase (p=8.6x10-19) in the inflammatory protein calprotectin (S100a8 and S100a9) mRNA levels. Additionally, circulating levels of calprotectin protein correlated with severity of the behavioral changes and hypertension in mice (p<0.01). Last, an approximate 2-fold increase (p<0.05) in circulating calprotectin was found in human patients with PTSD with comorbid hypertension compared to PTSD alone.
Conclusions: Our data suggest a new role for T-lymphocytes in the regulation of stress-induced inflammation and hypertension, and present an undescribed protein target for future investigation and potential therapeutic intervention.
Supported By: NIH R00HL123471
Keywords: PTSD - Posttraumatic Stress Disorder, Lymphocytes, Inflammation, Hypertension, Biomarkers

S22. Effects of Providing Additional Lesions to Single-Shot Gamma Ventral Capsulotomy for Obsessive Compulsive Disorder

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Background: A subset of refractory obsessive-compulsive disorder (OCD) patients may respond to neurosurgical procedures, such as Gamma Ventral Capsulotomy (GVC). Although most studies have employed bilateral double-shot (ds) targets, one study found that single-shot (ss) lesions were also efficacious in a small sample. Our aim was to replicate these findings with ss lesions and later include additional dorsal shots, in case of low efficacy.
Methods: Bilateral ssGVC (radiation dose of 150 Gy; target at the ventral anterior limb of the internal capsule) was offered to five refractory OCD patients. After a minimum of 12 months of follow-up, in case of non-response to treatment, patients received additional dorsal shots. Subjects were assessed pre and post-operatively with psychopathological, global status, and neuropsychological scales and neuroimaging.
Results: After 12 months of follow-up, no ssGVC patients responded to treatment, with mean [SD] reductions of only 6.6% [14.6] on their Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores. Later, in a median follow-up of 20 months, symptom reductions were even smaller (5.7% [18.9]). After additional dorsal lesions were made, their mean Y-BOCS scores decreased 21.9% [7.4]. However, only one patient (in the ssGVC phase), or two patients (dsGVC phase) were deemed partial responders.
Conclusions: Our study suggests that ssGVC is not efficacious for treating OCD. Moreover, adding a second dorsal shot, more than one year after the original lesions, resulted in higher reductions of Y-BOCS scores, but the total number of responders remained small. Factors that might have contributed to these findings will be discussed.
Supported By: FAPESP (Foundation for the Support of Research in the State of São Paulo), #2005/55628-08, #2008/10257-0, #2009/09949-8, and #2011/21357-9 and from CNPq (National Council for Scientific and Technological Development), #480196/2009-5 and # 302463/2011-9
Keywords: Obsessive Compulsive Disorder (OCD), Radiosurgery, Capsulotomy

S23. The Neurobiological Substrates of Uncertain and Certain Threat

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Background: When extreme, anxiety—a sustained state of elevated apprehension, arousal, and vigilance in response to uncertain threat—can be debilitating. Anxiety disorders are common and challenging to treat, yet the underlying neurobiology remains poorly understood. Although considerable progress has been made using animal models, the translational significance of these discoveries remains unclear. Existing human neuroimaging work is limited by small samples and paradigms that do not permit distinct dissociations of neural responses to different types of threat.
Methods: A total of 99 subjects were selectively recruited from a pool of >2,000 phenotyped individuals to capture a wide range of risk for internalizing disorders. A novel Multi-Threat countdown task was used to rigorously dissect regions sensitive to the anticipation of uncertain and certain threat. Multiband fMRI and other 'best-practices' maximized spatial and temporal resolution.
Results: Subjects reported elevated fear and anxiety during threat anticipation (ps<.001), confirming task validity. Neuroimaging results revealed several cortical regions showing elevated activity during the anticipation of uncertain threat, including the mid-cingulate cortex and anterior insula (qs<.05, corrected). In contrast, a number of subcortical regions exhibited greater activity during the anticipation of certain threat, including the extended amygdala, hippocampus, putamen, and caudate (qs<.05, corrected). The hemodynamic time courses of key regions were further examined using a finite impulse response basis function analysis.
Conclusions: These findings provide new insights into the neural systems most responsive to different types of threat in humans, setting the stage for refining animal models and ultimately developing improved interventions for pathological anxiety.
Supported By: R01
Keywords: Fear And Anxiety, Uncertainty, Central Extended Amygdala, Affective Neuroscience, Functional MRI

S24. Characterizing the Association of Mobile Skin Conductance and Ambulatory Heart Rate on PTSD Symptom Clusters

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Background: Increased psychophysiological reactivity to stress is a defining feature of Post-Traumatic Stress Disorder (PTSD). While various stress-inducing tasks are available, they can be time-consuming and difficult to implement in the resource-constrained settings often found in low-and middle-income countries. Thus, the aim of this study was to evaluate the feasibility of using ambulatory heart rate (HR) and mobile skin conductance level (SCL) during a standard trauma interview (STI) in predicting PTSD symptom severity among Vietnamese young men who have sex with men (YMSM).
Methods: YMSM were recruited at out-patient clinics and community-based organizations in Hanoi, Vietnam, using venue-based sampling. In total, N=199 individuals (aged 18-29) were recruited. Participants completed surveys assessing lifetime trauma exposure and current PTSD symptoms. At the start of their visit (baseline) and during the STI, participants' SCL and HR were measured using the Mindfield eSense Skin

Response mobile app and the ActiGraph wGT3X-BT watch, respectively, worn in tandem with a Polar H7 Bluetooth Heart Rate Monitor.
Results: SCL and HR were significantly higher during the STI compared to baseline ($p < .001$). Controlling for demographic characteristics and lifetime trauma exposure, regression analyses revealed that baseline SCL, but not SC response, was associated with intrusive ($\beta = .25$, $p < .01$) and avoidance/numbing ($\beta = .18$, $p < .05$) symptom severity, while heart rate response to the STI was uniquely associated with hyperarousal symptoms ($\beta = -.18$, $p < .05$).
Conclusions: Findings provide support for the integration of low-cost, mobile assessments of physiological indicators into psychiatric research in challenging environments.
Supported By: NIH Fogarty International Center Grant #D43TW009340
Keywords: Assessment, PTSD - Posttraumatic Stress Disorder, Psychophysiology, Trauma

S25. Longitudinal Neurocognitive Performance Post-Trauma Exposure: Design and Initial Validation of Neurocognitive Measures for the NIMH Aurora Study

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Background: The Aurora Study (Longitudinal Assessment of Post-Traumatic Syndromes) is a large-scale NIMH funded initiative which aims to characterize how trauma-related disorders develop and generate tools that will help clinicians identify high-risk individuals in the early aftermath of trauma.
Methods: An initial sample of 1,042 individuals presenting in 12 emergency departments (EDs) across the country have been enrolled (M age = 35.32, SD = 12.94; 64% female). Neurocognitive data obtained via web-connected devices during the ED visit, at 48 hours, and in weeks 1-8 post ED are presented. Tasks include measures of processing speed, sustained attention, cognitive control, verbal reasoning, working memory, episodic memory, decision-making, social cognition, reward learning, and threat bias.
Results: Tests were identified that had good psychometric properties when administered in naturalistic settings, longitudinally. Other tests (e.g. threat biases) did not have sufficient reliability for continued inclusion. In the ED/48 hours, internal reliabilities ranged from .01 (Threat Dot Probe) to .98 (simple reaction time), with comparable reliabilities at subsequent time points. Test-retest reliabilities ranged from -.05 (Threat Dot Probe) to .69 (gradCPT). The Threat Dot Probe was dropped from ED assessment due to poor internal reliability.
Conclusions: Aurora is the largest longitudinal study of the effects of trauma that has ever been conducted. Neurocognitive data collected in Aurora were generally high quality, with notable exceptions that will be discussed. We provide information on the relationship of this data to existing data collection efforts, data-sharing, follow-up, and recommended future studies.
Supported By: U01MH110925; Dorris Family Fellowship Award, McLean Hospital
Keywords: Neurocognition, PTSD - Posttraumatic Stress Disorder, Digital Devices, Longitudinal Study

S26. Transcranial Direct Current Stimulation in Obsessive-Compulsive Disorder: Electric Field Models and Considerations for the Optimal Montage of Electrodes

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Background: Transcranial Direct Current Stimulation (tDCS) is a non-invasive transcranial brain stimulation (NTBS) approach. It has been studied as a treatment for Obsessive-Compulsive Disorder (OCD). As there are several candidate regions for targeting OCD relevant networks by NTBS, previous studies considerably vary in terms of electrode montages used. For guiding research on tDCS for OCD, we critically review the current evidence for different montages and their mechanistic actions hypothesized based on computational models of electric fields (EFs).
Methods: A literature search for articles with keywords "tDCS", "Transcranial Direct Current Stimulation" and "Obsessive Compulsive Disorder" was conducted to identify relevant publications. Based on criteria selection, we selected 13 articles. For comparing electrode montages, EF models were computed using SimNIBS (modeling software for NTBS).
Results: Most studies showed an improvement in OCD symptoms, whereas the cathode and anode montages differ among them. Two patterns of stimulus were revealed by the computer simulation: a diffused one, with global cortical regions being stimulated and a focused one, specifically stimulating the prefrontal cortex (PFC). Rationale for stimulating the PFC is based on the hypothesis that there is an increased frontostriatal activity observed in OCD patients compared to healthy controls. There are no placebo-controlled randomized clinical trials (RCT) that clarify its efficacy in OCD, and it is not possible to define which type of montage is most advantageous.
Conclusions: Computational modeling could be used to estimate EF over cortical regions and define optimal montages to ameliorate OCD symptoms. RCT may clarify which types of montages may be advantageous.
Supported By: FAPESP
Keywords: Neuromodulation, Transcranial Direct Current Stimulation (tDCS), Obsessive Compulsive Disorder (OCD)

S27. Investigating Anxiety-Related Behavior in Young Primates: A Novel, Computer-Automated Approach

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Background: Anxiety disorders affect millions of people worldwide, are more common in females, and often develop early in life (Bandelow & Michaelis, 2015; Rice & Miller, 1995). Our group examines the neurobiology of early life anxiety using a well-validated rhesus-monkey model (Macaca mulatta). The scalability of this approach, however, is limited by the need for human experts to score primates' behavior.
Methods: Here, we validated a computer-automated approach to quantify primate activity and freezing in a stratified sample of 20/98 females aged 2-3 years (mean age = 2.75 years; SD = 0.47) based on early life inhibited-temperament scores (Golub, Hogrefe, Capitanio, & Widaman, 2009). Reliable video of subjects' responses to a human intruder presenting their profile was collected and analyzed for 18/20 animals. We used frame-by-frame correlations, one-dimensional Gaussian mixture modeling, and Bayesian modeling to score subjects' behavior. We then correlated these data with neuroimaging and longitudinal measures.
Results: Our computer-automated method recorded an intraclass correlation coefficient of .978 and achieved 95.9% correspondence with four human raters (sensitivity: 92%, specificity: 100%) across a randomized sample of 100 3-second video segments. Subjects' activity was associated with increased motor cortex metabolism in voxelwise tests ($p < .05$, two-tailed, uncorrected). Subjects' freezing duration was associated with early life nervousness ($r = .50$, $p < .05$, two-tailed, uncorrected).
Conclusions: We validated and demonstrated the utility of a computer-automated behavioral-coding method. Our findings highlight the potential for computer-automated methods to augment the study of anxiety-related behavior. These and other machine-learning approaches will be explored.
Supported By: California National Primate Research Center: P51-OD011107
Keywords: Machine Learning, Anxiety Disorders, Nonhuman Primates, Translational Research

S28. Acute Inflammation and Attentional Bias for Threat Following Salmonella Typhi Vaccine

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Background: In animal models, acute inflammation elicits behaviors related to psychiatric symptoms, including exaggerated threat sensitivity. Less is known about the effects of acute inflammation on the brain and behavior in humans. The polysaccharide form of the Salmonella Typhi vaccine elicits an acute inflammatory response and may provide a useful tool for clinical psychiatry research. Here, we examined the effects of typhoid vaccine on immune cells, cytokines, and attentional bias towards threat.
Methods: Twenty-four healthy males (Mean age = 38.1±13.4; Range = 20-60) were randomized to typhoid vaccine or placebo. Blood was drawn immediately before and at 2 and 4.5 hours after vaccine/placebo. At approximately 3 hours post-vaccine, we administered a probe detection task to assess attentional bias towards threat.
Results: Participants who received the typhoid vaccine showed increases in interleukin-6 at 4.5 hours, $F(1,20)=6.85$, $p=.02$, and tumor necrosis factor-á at 2 hours, $F(1,21)=7.38$, $p=.01$, as well as increases in the number of white blood cells, $F(1,19)=7.80$, $p=.01$, and neutrophils, $F(1,19)= 7.23$, $p=.02$, and a trend towards greater increases in monocytes, $F(1,19)= 4.04$, $p=.059$, at 4.5 hours. There were no differences between groups in lymphocytes, platelets or high-sensitivity C-reactive protein. Within participants who received the typhoid vaccine, higher increases in numbers of white blood cells, eosinophils, and monocytes were associated with greater attentional bias towards threatening faces.
Conclusions: The typhoid vaccine elicits an immune response that may be associated with increases in threat sensitivity. Typhoid vaccine is a safe and useful tool for clinical psychiatry research.
Supported By: K01MH109871
Keywords: Inflammation, Attentional Bias, Endotoxin, Threat Sensitivity, Vaccine

S29. Long Term Evolution of Panic Disorder Patients: A Naturalistic Study

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Background: Panic disorder (PD) affects 1.5% of the general population. In spite of his clinical relevance, high comorbidity and socioeconomical burden for patients few studies have been published to know his prognosis.
Methods: We studied 150 PD patients (DSM-IV) in a naturalistic follow up study. Patients were evaluated with the HAMD, HAMD, CGI, SCL-90 scales.
Results: Patients recruited were 84 (56%) male, 116 (77%) had agoraphobia. Mean (SD) age was 34. (9.2) years old, start age of PD was 27.4 (9.6) years, evolution time 75.5 (87.1) months and they suffered 25.5 (41.3) panic attacks per month. Patients without comorbid psychiatric disorders were 81/150 (54%), 27 (18%) with major depression. No differences were found in any of variables studied between patients with or without agoraphobia. Patients were followed up (N=90, 60%) for a mean of 12 months. Treatment was related with a statistical reduction ($p<.05$) in HAMD, HAMA, SCL-90 and CGI scores. While near 50% of patients suspended treatment due to improvement, 23% continue with moderate to severe PD in spite adequate pharmacological treatment.

Conclusions: This naturalistic follow up study results are in agreement with those published in previous similar studies. However, we did not find prognostic differences between patients with or without agoraphobia.
Supported By: INFOSAME
Keywords: Anxiety Disorders, Panic Disorder, Evolution, Prediction of Treatment Outcome, Psychopharmacological Treatment

S30. Perception of Abilities and the Effect of Treatment on Neurocognitive Performance in a Treatment Seeking Sample of Individuals With Hoarding Disorder

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Background: Individuals with Hoarding Disorder (HD) frequently complain of problems with attention and memory. Neurocognitive (NC) deficits in visual memory, information processing speed, visual detection, and visual categorization are associated with HD in previous work. In this study, we examine 1) the impact of hoarding-specific treatment on NC functioning, 2) whether self-reported problems with memory and attention predict actual performance on NC tests, and 3) how task performance relates to psychopathology in individuals with HD.
Methods: 323 individuals were randomized for behavioral treatment of HD in San Francisco. 242 participants completed pre- and post-NC testing. MANOVA and post-hoc t-tests were conducted on pre- and post-treatment for NC tests. Multiple regression was used to assess prediction of task performance based on self-report measures with age, education, psychopathology severity as covariates.
Results: Participants were older (60 $\pm$ 10.4) and majority female (77%). There was significant change with treatment in information processing speed, visual memory, visual detection and visual categorization ($p \leq 0.01$). Visual categorization time increased post treatment; there was not a comparable increase in time to complete a block task or in information processing speed. Self-reported memory and attention difficulties were not related to memory performance or attention. Self-reported anxiety predicted visual memory performance ($p < .04$), and HD severity, anxiety and depression all predicted attention performance ($p < .05$).
Conclusions: Targeted treatment for HD produces significant change in NC performance in key domains. These changes occurred without treatment targeted to these domains, and predictors of performance had stronger relationships to psychopathology than to individual perception of cognitive ability.
Supported By: PCORI Grant CE-1304-6000
Keywords: Hoarding Disorder, Treatment Study, Neurocognition, Memory, Attention

S31. Beneficial Effects of FAAH Inhibition on Fear- and Stress-Related Behaviors in Healthy Humans

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Background: The endocannabinoid (eCB) system is proposed to act as a "stress buffer" and thus represents a novel therapeutic target for stress-related psychiatric disorders. Preclinical data suggests that inhibition of fatty acid amide hydrolase (FAAH), the main degradative enzyme of the eCB anandamide (AEA), facilitates fear extinction and protects against the anxiogenic effects of stress. However, no studies have yet assessed whether pharmacological inhibition of FAAH would produce similar effects in humans.
Methods: Healthy adults (N = 60) were randomized to receive Pfizer compound PF-04457845 (N=30) or placebo (N =30) for 10 days. On days 9 and 10, participants complete a 2-day behavioral and psychophysiological laboratory paradigm assessing various components of fear learning, as well as emotional reactivity before and after a standardized stress (or control) task.
Results: An intent-to-treat analysis revealed that FAAH inhibition produced enhanced recall of fear extinction and attenuated stress-induced negative affect. However, analysis of circulating eCBs revealed significant variation in the biochemical response to the drug, revealing two distinct groups ("responders" and "non-responders"). A re-analysis of the behavioral data found that responders drive the effects of FAAH inhibition on fear extinction recall and stress-induced negative affect. Moreover, they also show an attenuated autonomic and subjective stress response. Analyses are currently underway to pinpoint the cause of this apparent variation in drug response.
Conclusions: We report the first evidence of the ability of pharmacological inhibition of FAAH to influence stress- and fear-related behaviors in humans, suggesting it may represent a novel pharmacotherapeutic target for the treatment of stress-related disorders.
Supported By: Swedish Research Council
Keywords: Endocannabinoids, Stress, Emotional Reactivity, Fear Conditioning and Extinction, FAAH

S32. Therapeutic Potential of Nociceptin/Orphanin Fq (NOP) Receptor Antagonists in a Rodent Model of Traumatic Stress

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Background: Current FDA-approved pharmacotherapies for the treatment of post-traumatic stress disorder (PTSD) are limited in number and efficacy. Recent evidence implicates the nociceptin/orphanin FQ (NOP) receptor system in PTSD.

Therefore, NOP antagonists may have therapeutic potential for the treatment of PTSD. Here, we evaluate the efficacy of NOP antagonists to remediate the effects of traumatic stress exposure using preclinical rodent models of traumatic stress exposure and conditioned fear.
Methods: The NOP antagonists J-113397 and SB-612111 were tested at a range of doses to determine effects on pain sensitivity, exploratory and anxiety-like behaviors in male rats under basal conditions and following a single-day sequential exposure to three predator species (snake, ferret and cat) to model traumatic stress. SB-612111 was also evaluated to determine effects on extinction of conditioned fear memories.
Results: We found that neither NOP antagonist tested had significant effects on baseline measures in the hot plate, open field, elevated plus maze and acoustic startle tests. Importantly, we did not observe adverse effects in the selected dose ranges. Preliminary data suggests that SB-612111 may have efficacy in reducing behavioral reactivity to conditioned fear cues and enhancing extinction of conditioned fear memories.
Conclusions: Together, these data suggest that NOP antagonists may have therapeutic efficacy for mitigating intrusive fear memories, a common feature of PTSD. Further NOP antagonists may have clinical utility as adjunctive medication to support extinction-based psychotherapies like Prolonged Exposure Therapy.
Supported By: Medical Research and Materiel Command's Military Operational Medicine Research Program
Keywords: Post-Traumatic Stress Disorder, Nociceptin, Fear Extinction

S33. Angiotensin Type 1 Receptor (AT1R) Inhibition Disrupts Reconsolidation of Conditioned Auditory Fear

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Background: Recent studies demonstrate that consolidated memories temporarily return to a labile state following retrieval. This window of reconsolidation presents a potential therapeutic target for treatment of psychiatric disorders such as PTSD. The renin-angiotensin system contributes to memory consolidation processes in rodent models of Pavlovian conditioning; however, its role in reconsolidation of auditory fear conditioning has not been investigated.
Methods: Twenty-four hours after fear conditioning, C57Bl/6 mice were subjected to a single cue retrieval to initiate memory reconsolidation. Retrieval was followed by intraperitoneal injection of the AT1R antagonist losartan (10mg/kg) or saline. Freezing responses to the conditioned stimulus were assessed 24hr and 1wk post-retrieval. Additionally, cue-dependent mean arterial pressure (MAP) and heart rate (HR) responses were measured using radiotelemetry.
Results: 24 hrs following retrieval, a significant reduction in freezing behavior was observed in the losartan group versus control ($F(1, 22) = 5.756$, $p = 0.025$, n=12), as well as a trend for sustained reduction at 1wk ($F(1, 21) = 2.883$, $p = 0.104$ n=12). Cue presentation in the home cage elicited similar MAP and HR increases between groups 24hr after retrieval (Saline: ΔMAP= 24mmHg $\pm$ 7, ΔHR= 140bpm $\pm$ 54, n=4; losartan: ΔMAP= 20mmHg $\pm$ 8, ΔHR= 131bpm $\pm$ 3, n=3).
Conclusions: These findings suggest that peripheral AT1R inhibition disrupts the reconsolidation of conditioned fear and identify renin-angiotensin signaling as a contributor to memory restabilization. Furthermore, AT1R antagonism following memory retrieval may result in modified behavioral reactions to previously consolidated memories independent of alterations in conditioned MAP or HR responses.
Supported By: NIH1R01HL137103-01A1 and American Heart Association 15CSA24340001
Keywords: PTSD - Posttraumatic Stress Disorder, Reconsolidation, Pavlovian Conditioning, Angiotensin, Fear Memory

S34. Central Amygdala Angiotensin Type 2 Receptor (AT2R) Activation Reduces Fear-Related Behavior

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Background: Previous clinical studies identify the renin-angiotensin system (RAS) as a potential therapeutic target in post-traumatic stress disorder (PTSD), however the mechanism(s) are unknown.
Methods: Immunohistochemistry studies conducted in AT2R-eGFP reporter mice crossed with GAD-mCherry mice were used to observe the expression and phenotype of AT2R-eGFP+ cells. Cue- and context-dependent fear conditionings were used to examine the behavioral role of AT2R in fear memory. Twenty-four hours after fear conditioning, the AT2R agonist C21 (0.06ug/ul) was administered bilaterally via intra-CeA injection and fear expression was quantified by percentage of time spent freezing during cue stimuli or context exposure.
Results: AT2R-eGFP+ neurons were present in the amygdala, an important structure in the expression and extinction of fear memory. These neurons were predominately observed in the medial amygdala (203.8 $\pm$ 39.4 cells/mm2) and the medial division of the central amygdala (CeM) (224.7 $\pm$ 9.4 cells/mm2). Within the CeM, 96% of the AT2R-eGFP+ neurons expressed the GABAergic marker GAD and the majority of these were determined to be projection neurons. Compared to vehicle controls, mice receiving intra-CeA C21 displayed decreased freezing in response to both the first 5 CS tone presentations (74.6% $\pm$ 5.1 vehicle vs 54.7 $\pm$ 6.8 C21, $p<0.05$), and the first 10 minutes of context exposure (64.6% $\pm$ 4.4 vehicle vs 48.3% $\pm$ 3.7 C21, $p<0.05$), both indices of a reduction in fear expression.
Conclusions: These findings suggest that CeM AT2R-expressing neurons can modulate fear expression and provide

evidence for a novel angiotensinergic circuit in the regulation of fear.
Supported By: NIH 1R01HL137103-01A1
Keywords: Pavlovian Conditioning, Angiotensin, PTSD, Fear Expression, Amygdala

S35. Using Machine Learning to Characterize Circuit-Based Subtypes in Mood and Anxiety Disorders

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Background: Although computational approaches applied to imaging measures of resting-state functional connectivity show promise for identifying brain circuit-based subtypes for mood and anxiety disorders, these approaches have not yet been applied to measures of task-evoked functional connectivity. Our objective was to deploy a machine-learning approach to determine if there are coherent and clinically interpretable subtypes defined by distinct disruptions in functional connectivity across four tasks relevant to systems of emotion valence and cognition.
Methods: A multidiagnostic sample of 174 adults (18-71 years) comprising mood and anxiety disorders were scanned during facial emotion viewing (conscious, non-conscious), Go/No-Go inhibition and n-back working memory tasks. Participants also completed a comprehensive battery of symptom questionnaires. Functional connectivity between all brain region pairs was quantified with generalized psychophysiological interaction analysis. Machine-learning approaches that included convolutional neural network and random forest analyses were used to identify coherent subtypes based on both functional connectivity and symptom data.
Results: We identified four subgroups with distinct functional connectivity profiles and unique characterizations on 10 clinical items. Results were cross-validated with no significant difference between training and testing (K-S: all Ds>0.2, ps>.758). Subgroups were distinguished by their symptom profiles. For example, subgroup 2 was characterized by low levels of worry and a higher propensity to keep emotions to themselves, while subgroup 3 showed high worry and health dissatisfaction.
Conclusions: This study leveraged novel machine-learning methodologies with task-evoked functional connectivity to identify circuit-based subtypes of mood and anxiety that correspond to clinical profiles, which may be useful for advancing precision psychiatry.
Supported By: NIMH R01MH101496
Keywords: Task fMRI, Mood/Anxiety, Machine Learning, Biotypes, Functional Connectivity

S36. Interrelationships Between Hyperarousal, Nightmares and Parasympathetic Activity in REM Among Recently Traumatized Individuals

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Background: Hyperarousal, sleep disturbances, and autonomic dysfunction are core manifestations of PTSD. We examined associations of hyperarousal, nightmares, and REM-sleep parasympathetic activity in traumatized adults.
Methods: Individuals exposed to a PTSD Criterion-A trauma within the past 2-years (N=70, 45 females) completed the Clinician-Administered PTSD Scale (range=0-50, mean=21.4, SD=12.8; 32 meeting DSM-IV-TR PTSD criteria). They also completed questionnaires measuring hyperarousal (Composite Hyperarousal Index; CHI), general psychopathology (Composite Psychopathology Index; CPI), and 12-27 nights of sleep diaries (mean=14.8, SD=2.45) asking if recalled dreams were nightmares (caused waking) or bad dreams and their resemblance to trauma. A subset of 56 (35 females) underwent a night of ambulatory polysomnography. ECG recordings during REM-sleep periods of at least 5-minutes were analyzed using Kubios software. Each participant's average Root Mean Square of Successive Differences (RMSSD) and High Frequency (0.15-0.4Hz) power (HF) were calculated.
Results: CHI significantly predicted nightmares (R=0.32, p=0.008), bad-dreams (R=0.33, p=0.006), and their combined rates (R=0.411, p=0.0007), but not trauma-related-nightmares (p=0.15). Relationships of CPI with these rates were weaker: nightmares (p=0.52), bad-dreams (p=0.013), bad dreams/nightmares (p=0.049), and trauma-related-nightmares (p=0.68). REM% predicted combined (R=0.481, p=0.0006) and trauma-related-nightmare rates (R=0.385; p=0.008). Across all participants, CHI correlated negatively with both RMSSD (R=-0.31, p=0.023) and HF (R=-0.28, p=0.035). CPI did not significantly predict either RMSSD (p=0.13) or HF (p=0.11).
Conclusions: Hyperarousal, but not psychopathology, predicted bad dream/nightmare rates and decreased parasympathetic activity in REM. Greater REM% predicted higher rates of bad dreams/nightmares and trauma-related-nightmares. Interventions focusing on features of hyperarousal and REM may assist in treating trauma-related nightmares.
Supported By: R01MH109638
Keywords: Hyperarousal, REM Sleep, PTSD, Nightmares, Heart Rate Variability

S37. Chemogenetic Excitation of Parabrachial Nucleus Neurons That Project to Perifornical Hypothalamus Induces Panic-Associated Behaviors and Autonomic Responses in Rats

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Background: It is well established that exciting the perifornical hypothalamus (PeF) region elicits panic-associated

behavior and cardiovascular responses in rodents and in recent human studies it also induces self-reports of panic attacks and fear of dying. Yet the panic on and off inputs to the PeF are largely unknown. Here we utilized retrograde tracing then intersectional genetic approaches to investigate potential panic-on inputs to the PeF. One of the strongest inputs from an initial PeF tracing study arose from the parabrachial nucleus (PBN) which contains predominantly excitatory glutamatergic neurons. Here we hypothesized that PeF projecting glutamatergic neurons in the PBN represent a panic-on pathway.
Methods: To test this hypothesis we injected a retrogradely transported CAV-CMV-Cre into the PeF to induce expression of Cre-recombinase in the PeF-projecting sites and a Cre-dependent AAV into the PBN to induce expression of the excitatory human muscarinic 3 Designer Gq Receptor (hM3Dq) exclusively Activated by the Designer Drug (DREADD) clozapine-n-oxide (CNO).
Results: We first determined that the 3mg/kg intraperitoneal injection of CNO did not alter panic-associated behaviors or cardiovascular responses in naïve animals. We then injected CNO or vehicle into rats and determined that chemogenetic excitation of PeF-projecting PBN neurons induced robust flight and avoidance behaviors that were accompanied by robust cardioexcitation.
Conclusions: Our results suggest that the parabrachial input to the PeF region represents a panic-on pathway.
Supported By: 1K01AG044466; R01MH52619; R01MH65702
Keywords: Perifornical Hypothalamus, Parabrachial Nucleus, Panic On, Chemogenetics

S38. Dissecting the Functional Heterogeneity of Serotonergic Systems That Regulate Fear and Panic

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Background: Central serotonin systems are major target for treating anxiety disorders with the use of selective serotonin (5-HT) reuptake inhibitors (SSRIs). Yet SSRIs tend to increase anxiety initially having their anxiolytic properties 2-3 weeks after daily treatment. There is pharmacological/electrophysiological evidence that 5-HT is largely excitatory in pro-fear regions such as the basolateral amygdala (BLA), but inhibitory on pro-panic orexin neurons in the perifornical hypothalamus (PeF). Using retrograde tracing we determined that the BLA and PeF are innervated by distinct serotonergic networks in the dorsal (DR) and median (MR) raphe with BLA projections outnumbering PeF projections 2:1. Here we sought to elucidate the role of these serotonergic networks on learned fear and innate panic responses.
Methods: In order to excite serotonergic pathways, we first injected the retrogradely transported CAV-CMV-Cre into BLA or PeF to induce the expression of Cre-recombinase in serotonergic neurons in the DR/MR followed by an AAV injection into DR/MR to induce the expression of a Cre-dependent channelrhodopsin. In a second series of experiments, we injected saporin toxin conjugated to 5-HT transporter into the BLA or PeF to lesion these 5-HT pathways.
Results: LED excitation or lesioning of BLA projecting 5-HT system respectively enhanced and impaired fear conditioned freezing. Conversely, LED excitation or lesioning of PeF projecting 5-HT system respectively attenuated and enhanced panic associated escape/flight behaviors and cardioexcitation following a 7.5 and 20% CO2 challenge.
Conclusions: Collectively these studies show that BLA and PeF projecting 5-HT neurons from midbrain respectively represents pro-fear and anti-panic networks.
Supported By: 1K01AG044466; R01MH52619; R01MH65702
Keywords: Panic And Fear, Basolateral Amygdala, Perifornical Hypothalamus, Dorsal And Median Raphe, Optotgenetics

S39. Effects of Childhood Threat and Deprivation on Stria Terminalis and Medial Forebrain Bundle White Matter

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Background: Childhood threat and deprivation (adversity) are associated with broad differences in the structural integrity of large white matter bundles (e.g., cingulum or uncinate). While stress may be a potential mechanism by which childhood adversity influences mental health, few studies have considered stress-related white matter pathways, such as the stria terminalis (ST) and medial forebrain bundle (MFB).
Methods: Participants included adults (n=96, mean age=27.34, SD=3.97) with a full range of maltreatment and affective symptom severity. The Trauma History Questionnaire (age 0-11) and maximum parental education (before age 18) provided assessments of repeated traumatic events (threat) and childhood socioeconomic status (deprivation), respectively. The BDI and PCL-C assessed depressive and post-traumatic stress symptoms, respectively. Participants underwent diffusion spectrum imaging (271 directions). Human Connectome Project data were used to perform ST and MFB tractography (n=488), which were used as ROIs to extract generalized fractional anisotropy (gFA) from the voxelwise reconstructed spin distribution functions.
Results: Threat (Beta, p: -.332, .001) and deprivation (-.271, .011) had significant negative effects on ST gFA. Additionally, threat (-.271, .011) had significant negative effects on MFB gFA. MFB gFA was associated with depressive (-.247, .029) and post-traumatic stress symptoms (-.270, .018).

Conclusions: Our results suggest that greater childhood threat is associated with less, while greater deprivation is associated with greater ST structural integrity. Further, greater threat is associated with less MFB structural integrity, while greater MFB structural integrity is associated with lower affective symptom severity. Thus, childhood adversity-related influences on stress-related white matter may modulate the risk of affective psychopathology in young adults.
Supported By: K01 MH102406
Keywords: Childhood Adversity, Childhood Trauma, Socioeconomic Status, Stria Terminalis, Medial Forebrain Bundle

S40. Tinnitus Severity in Posttraumatic Stress Disorder (PTSD) is Directly Correlated With Hyperarousal and Inversely Correlated With Rapid Eye Movement (REM) Sleep Percentage and Duration

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Background: Tinnitus has been studied primarily in war veterans and refugees with PTSD, often exposed to head injury. A 50% tinnitus prevalence is reported in PTSD (versus a 10%-15% general population prevalence). Tinnitus is associated with both cochlear and central nervous pathologies including limbic activation. Overnight polysomnography of non-psychiatric tinnitus patients has revealed lower %REM (6.4%±4.9%) in tinnitus patients versus controls (21.5%±3.6%)(Attanasio G, 2013). To my knowledge, there are no polysomnographic studies of PTSD patients with tinnitus.
Methods: 57 consenting civilian PTSD patients (52 female; mean±SD age: 46.91±13.09 years), with no head trauma history, underwent ≥1 nights of Level 3 polysomnography (WatchPAT200; Itamar Medical, Israel) and completed a battery of instruments including the Tinnitus Functional Index (TFI), a 25-item instrument that measures both severity and negative impact of tinnitus, the Pennebaker Inventory of Limbic Languidness (PILL), and PTSD Checklist for DSM-5(PCL-5).
Results: 33/57(57.9%) endorsed experiencing tinnitus. TFI scores correlated directly (Pearson r=0.520, p<0.002) with PCL-5 scores (mean±SD PCL-5 score: 37.82±19.02). Multiple regression analysis using TFI score as dependent variable and PCL-5 clusters, PILL scores and age as independent variables revealed that only PCL-5 Cluster E(hyperarousal) (β=0.524,t=3.372,p=0.002) remained a significant predictor of TFI. Both %REM (r= -0.390, p=0.025) and REM duration (r=-0.430, p=0.012) were significantly inversely correlated with TFI.
Conclusions: Tinnitus was associated with PTSD severity, especially the hyperarousal cluster, in civilian PTSD patients with no head trauma histories. Higher baseline REM sleep has been associated with reduced fear conditioning, therefore decreased REM sleep in tinnitus patients may be an indication of increased PTSD severity.
Keywords: PTSD - Posttraumatic Stress Disorder, Hyperarousal, REM Sleep, Tinnitus, Rapid Eye Movement Sleep

S41. Poster Withdrawn

S42. Functional Connectivity of the Locus Coeruleus Identifies Individuals at Familial Risk for Alzheimer's Disease

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Background: Prevention and early treatment strategies for Alzheimer's Disease (AD) are hampered by the lack of risk biomarkers. Neuropathological changes in the Locus Coeruleus (LC) are detected early in AD, and noradrenaline plays a neuroprotective role in LC projecting areas. We assessed functional connectivity (FC) of the brainstem in asymptomatic individuals at familial risk for AD hypothesizing that FC of the LC will be decreased in relation to not-at-risk individuals.
Methods: Thirty-one offspring of patients with late-onset AD (O-LOAD) (22 females; mean age±SD=50.36±8.32) and 28 controls (20 females; mean age±SD=53.90±8.44) underwent a neuropsychological evaluation and a resting-state functional MRI acquisition. In FC analyses we evaluated whole-brain global connectivity of the brainstem area, and subsequently assessed seed-to-voxel FC patterns from regions showing between-group differences.
Results: O-LOAD individuals scored worse in the MMSE and RAVLT verbal recognition and delayed recall (pFDR<0.05). In imaging analyses, we identified a cluster encompassing the left LC (peak=-4,-34,-32, PTFCE<0.05) showing decreased global connectivity and a positive correlation with verbal delayed recall scores in O-LOAD subjects (r=0.441; p=0.035). Seed-to-voxel analyses revealed that above findings were largely explained by decreased LC-cerebellar connectivity. Specifically, FC between the LC and left Crus 1 correlated positively with verbal delayed recall in the O-LOAD group (r=0.464; p=0.022).
Conclusions: FC between the LC and the cerebellar cortex is decreased in the healthy offspring of patients with LOAD, such connectivity measurements being associated with verbal memory scores. FC between the LC and the cerebellum may eventually enable the development of prevention and early treatment strategies in AD.
Supported By: Agencia de Promoción MINCYT (Argentina) grant PICT-2014-0633
Keywords: Alzheimer's Disease, Locus Coeruleus, Resting State Functional Connectivity MRI (fcMRI), Early Risk Detection, Biomarkers

S43. Structural Brain Differences Between Cognitively Impaired Patients With and Without Apathy

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Background: Apathy is associated with cognitive deficits and worse outcomes in patients with cognitive impairment. Disruptions of frontostriatal circuits and frontotemporal association areas are strongly associated with apathy. We sought to examine structural brain differences between patients with and without apathy who exhibit with similar levels of cognitive impairment.
Methods: Demographic, Neuropsychiatric Inventory, and structural MRI data from cognitively impaired patients in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were cross-tabulated. Patients with apathy were matched to those without apathy by age, sex, apolipoprotein 4 allele number, Mini-Mental State Exam score, and mild cognitive impairment or AD diagnosis in matched strata by coarsened exact matching. Differences in cortical thickness and subcortical volume from the aforementioned regions were tested with a total intracranial volume-controlled and false discovery rate-corrected ($q = 0.10$) mixed-effects MANCOVA analysis.
Results: 71 patients with apathy and 165 patients without apathy were compared in 39 matched strata. Relative to patients without apathy, the bilateral medial orbitofrontal cortex and left rostral anterior cingulate were smaller in patients with apathy, whereas the left superior temporal cortex, left banks of the superior temporal sulcus, and right putamen were larger.
Conclusions: Patients with cognitive impairment and apathy exhibit larger left lateral temporal association areas and smaller bilateral medial frontal areas compared to patients without apathy. Our results confirm that frontostriatal circuit disruptions are associated with apathy in cognitively impaired patients. Structural differences suggest that distinct neuropathologies may produce similar levels of cognitive impairment.
Supported By: Canadian Institute of Health Research (CIHR)
Keywords: Alzheimer's Disease, Structural Neuroimaging, Apathy, Case Control Studies, Frontostriatal Circuits

S44. Using Acoustic and Linguistic Markers From Spontaneous Speech to Predict Scores on the Montreal Cognitive Assessment (MoCA)

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Background: Recent clinical trials in Alzheimer's disease have been overwhelmingly negative. This has spurred development of composite metrics and novel biomarkers with the intent of more accurately capturing changes in cognitive function. Computational analysis of speech and language represents one such group of biomarkers. The objective of this study was to examine the construct validity of speech and language markers by using them to predict scores on the MoCA.
Methods: 94 individuals, aged 55-95, were recruited from the community and senior care facilities. A picture description task and a MoCA were administered by a trained psychometrist. Audio samples and transcripts were analyzed to generate markers pertaining to acoustics, syntax and grammar (among others). Feature selection and linear regression with 10-fold cross validation were used to generate an estimated MoCA score (total and subscales).
Results: Numerous speech and language markers relating to complexity, coherence and level of detail reported in picture descriptions were significantly correlated with MoCA scores. Feature selection identified 55 variables which were most predictive of total MoCA score. Regression produced a MoCA estimate with a mean error of 3.4 points (11% of total score) which explained 18.4% (R^2) of the variance. Regression to MoCA subscales produced estimates with 6.5% (Orientation) to 34.7% (Delayed Recall) error.
Conclusions: The low error in total score prediction suggests that speech and language variables map to the constructs measured by the MoCA. This supports the further development of novel, speech based markers, and composite metrics for assessing cognitive status.
Keywords: Computational Neuroscience, Machine Learning, Cognition, MOCA, Psychometrics

S45. Working Memory Mediates the Association Between Dorsolateral Prefrontal Cortex Plasticity and Global Cognition in Alzheimer's Dementia and Healthy Comparison Individuals

Adetunji Oremakinde[1], Sanjeev Kumar[1], Pushpal Desarkar[1], Reza Zomorrodi[1], Michelle S. Goodman[1], Daniel M. Blumberger[1], Corinne E. Fischer[2], Zafiris J. Daskalakis[1], Bruce G. Pollock[1], Benoit H. Mulsant[1], and Tarek K. Rajji[1]

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Background: Dorsolateral prefrontal cortex (DLPFC) plasticity — measured using Paired Associative Stimulation (PAS)-induced Long Term Potentiation-like activity (PAS-LTP) — is associated with working memory in a combined sample of early Alzheimer's dementia (AD) and healthy comparison (HC) individuals. Still, its relationship with global cognition is yet to be established. In this same sample, we predicted that DLPFC PAS-LTP will be associated with global cognition and that this association will be mediated by working memory.
Methods: In 32 AD (Mean Age = 76.3, SD = 6.3) and 20 HC (Mean Age = 75.7, SD = 5.8) participants, global cognition was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and working memory was assessed with the N-back task. PAS-LTP was measured by delivering PAS to the left DLPFC and combining PAS with electroencephalography (EEG).

Results: As predicted, PAS-LTP in the DLPFC was associated with both global cognition (B [SE] = 21.65 [9.08]; β = 0.30; p = .02) and working memory (B [SE] = 0.40 [0.14]; β = 0.38; p = .008). Working memory was also associated with global cognition (B [SE] = 49.44 [6.53]; β = 0.78; p < .001) and mediated the association between DLPFC plasticity and global cognition (β = 21.45 (SE = 7.30), 95% CI, [8.67, 36.93]).
Conclusions: This study demonstrates the relationship between DLPFC plasticity and global cognition in healthy individuals and patients with AD. It also suggests that enhancing DLPFC plasticity could not only enhance working memory but also global cognition.
Supported By: This study was supported by grant RR120070 from Weston Brain Institute (Dr Rajji); in part by the Canada Research Chairs program (Dr Rajji); research support from Canada Foundation for Innovation (Dr Rajji); a fellowship award from the Centre for Addiction and Mental Health (CAMH) (Dr Kumar); and in-kind support from Temerty Centre for Therapeutic Brain Intervention at CAMH.
Keywords: Paired Associative Stimulation, Alzheimer's Disease, Transcranial Magnetic Stimulation, Working Memory, Cognition

S46. A Systematic Review of Case-Control Human Studies of Lead (Pb) in Alzheimer's Dementia

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Background: Chronic lead exposure (Pb) from the environment is associated with cognitive impairment and has been described as a potential contributing factor in the pathogenesis of Alzheimer's dementia (AD). Animal models link Pb exposure with AD-related pathology. As AD is a major public health concern with no available disease-modifying treatment, we sought to review the literature of human studies of Pb in AD to better understand the possible connection.
Methods: In a scoping review and series of systematic reviews, we identified case-control studies comparing AD to controls on Pb accumulation in blood, bone, cerebrospinal fluid, hair/nail, postmortem pathology, and urine. We completed meta-analyses of blood Pb studies.
Results: We identified the following case-control studies comparing AD to controls by measurement method: blood—15, bone—0, cerebrospinal fluid—5, hair/nail—3, postmortem—3, urine—1. Meta-analyses of whole blood and serum Pb levels did not demonstrate significant group differences between AD and controls. Pb levels were lower in the cerebrospinal fluid of AD patients in the largest study, and lower Pb levels were found in hair of AD patients.
Conclusions: Acutely, Pb is not elevated in AD. Measurement of Pb in bone is most closely reflective of chronic exposure, yet there has not been a case-control study in AD using this method. The methods that have been used do not capture earlier-life exposure covering the period of AD pathogenesis. Measuring bone Pb in future case-control studies, with other biomarkers (e.g. amyloid and tau imaging, cerebrovascular markers) may clarify the role of Pb in AD in future research.
Supported By: CIHR Canadian Graduate Scholarships; Ontario Graduate Scholarship, University of Toronto Clinician Scientist Program
Keywords: Alzheimer's Disease, Lead, Environmental Factors, Amyloid, Systematic Review

S47. Deficit in Executive Abilities Can Predict the Delay in the Development of Grammar Understanding in Children

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Background: Children with specific language impairment have difficulties producing and understanding language (Bishop, 1997). Specifically, these children have deficit in grammar understanding. The goal of this research was to examine the hypothesis that children at the age of 5 with deficit in executive abilities have a risk for emerging weakness in grammar understanding at the age of 9.
Methods: 125 children at the age of 5 were assessed using 5 subtests from NEPSY (Tower, Auditory Attention and Response Set, Visual Attention, Statue, Design Fluency), which are designed to assess executive abilities in children. We have revealed 28 children with deficit in executive abilities. These children were included in the experimental group. The control group included 28 children with no deficit in executive abilities. In the framework of longitudinal research children at the age of 9 from both groups were assessed by Grammar Understanding Test from Luria's neuropsychological assessment technique.
Results: One-way ANOVA has revealed significant differences [F(1,48)=5,06; p=0,03] between groups for scores in Grammar Understanding Test. Children from experimental group had low level of grammar understanding.
Conclusions: This research has shown that deficit in executive abilities can predict the delay in development of grammar understanding in children. The received results provided insight into cognitive mechanisms in typically developing and the underlying nature of specific language impairments, helping to elucidate the nature of impaired mechanism in this disorder. It can be assumed that deficit in executive abilities is one of the risk factors for emerging weakness in grammar understanding in children.
Supported By: Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.
Keywords: Executive Abilities, Language Development, Longitudinal Research

S48. Relations Among Socioeconomic Status, Brain Connectivity at Birth, and Psychiatric Symptoms at Age 2

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Background: Low socioeconomic status (SES) during childhood has been linked to the development of both externalizing and internalizing disorders. The brain mechanisms by which low SES at birth relates to behavioral outcomes are not well known. This study investigated whether neonatal resting state functional connectivity (rsfc) mediated the relationship between SES at birth and both externalizing symptoms and internalizing symptoms at age 2.
Methods: In a sample of 112 newborns, seed-based voxel-wise linear regressions related whole-brain functional connectivity of five regions of interest to insurance type (public/private) and neighborhood level disadvantage. Mediation analysis was employed to ascertain brain connections that mediate the relationships between insurance type and symptoms at age 2.
Results: Public health insurance at birth was associated with increased externalizing symptoms and decreased behavioral inhibition, one form of internalizing behavior, at age 2. Public health insurance was correlated with differences in left striatum and right ventrolateral prefrontal cortex connectivity (VLPFC). Left striatum connectivity mediated the relationship between insurance type and both externalizing symptoms and behavioral inhibition.
Conclusions: These results show that differences in socioeconomic status are correlated with variation in neonatal striatum and VLPFC rsfc. Further, they suggest that neurodevelopmental trajectories linking poverty and psychopathology may have begun as early as birth.
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Keywords: Socioeconomic Status, Neonatal Imaging, Externalizing, Internalizing, Striatum, Prenatal Stress

S49. Mapping Patterns of Network Dysconnectivity in the Developing Brain to Psychopathology Across Clinical Diagnostic Categories

Cedric Huchuan Xia[1], Zongming Ma[2], Rastko Ciric[1], Shi Gu[1], Richard Betzel[1], Antonia Kaczkurkin[1], Monica E. Calkins[1], Phillip Cook[1], Angel Garcia de La Garza[1], Simon Vandekar[3], Zaixu Cui[1], Tyler Moore[1], David Roalf[1], Kosha Ruparel[1], Daniel Wolf[1], Christos Davatzikos[1], Ruben Gur[1], Raquel Gur[3], Russell Shinohara[3], Danielle Bassett[1], and Theodore D. Satterthwaite[3]

[1]University of Pennsylvania, [2]The Wharton School, University of Pennsylvania, [3]University of Pennsylvania School of Medicine

Background: Neurobiological abnormalities associated with mental illnesses do not map cleanly to diagnostic categories. This mismatch suggests common mechanisms of circuit-level abnormalities. Here we sought to identify brain-based dimensions of psychopathology using a multivariate machine learning method in a large sample of youths.
Methods: We studied 999 subjects (age 8-22) as part of the Philadelphia Neurodevelopmental Cohort, who completed resting-state fMRI scans and comprehensive psychiatric evaluations. We constructed whole-brain functional connectivity matrices using an a priori brain parcellation. To find relationships between functional networks and item-wise symptoms, we used sparse canonical correlation analysis (sCCA), which seeks linear combinations of variables in each dataset that are maximally correlated. We assessed the significance of each linked dimension using regularization, permutation testing, resampling, and validation in a hold-out sample.
Results: sCCA revealed four dimensions of psychopathology – mood, psychosis, fear, and externalizing behavior - that were highly correlated with specific brain connectivity patterns. While each dimension exhibited a unique connectivity pattern, a common feature was shared across the dimensions. Notably, there was a loss of segregation between the default mode network and fronto-parietal network, two networks that usually become increasingly distinct during adolescence.
Conclusions: Using a data-driven method, we discovered four linked dimensions of psychopathology and connectivity in a large sample of youth. These dimensions were clinically interpretable, had both common and dissociable patterns of dysconnectivity, and spanned traditional diagnostic boundaries.
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Keywords: Connectivity, Default Mode Network, Psychopathology, Machine Learning, Brain Development

S50. The Relation Between Tanner Stage and Age is Moderated by Trauma in Youth With Depression and Obesity

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Background: Previous literature suggests that female youth with a history of sexual abuse reach menarche younger than non-abused females, indicating a relation between trauma exposure and the pituitary-gonadal axis. Additionally, repeated and chronic stress, such as that imparted by childhood trauma, leads to physiologic adaptations in the hypothalamic-pituitary-gonadal axis. To date, no human studies have examined the relation between age of pubertal development and overall trauma exposure in both male and female youth. This study aimed to investigate the role of trauma exposure and sex on age of pubertal development.
Methods: Sixty-nine youth aged 9-17 with depression and obesity were comprehensively assessed on psychometrics, metabolic parameters including clinician evaluated Tanner stage, and childhood trauma as measured by the childhood trauma questionnaire (CTQ).
Results: Tanner stage was significantly associated with age, sex, and overall CTQ score ($p<.05$). There was not a significant correlation between BMI and Tanner stage. The model examining moderation of the relation between Tanner stage and age by CTQ score was significant ($p<.0001$). There was a significant interaction between childhood trauma exposure and age ($p=.015$) such that youth with higher trauma reached post-pubertal Tanner stages at a younger age. There was not a significant interaction between sex, CTQ score, and age on Tanner stage.
Conclusions: Trauma appears to accelerate secondary sex characteristic development in both sexes. This apparent acceleration of sexual development after trauma exposure may reflect implementation of a compensatory mechanism to counter known deleterious neurobiological effects of trauma in these youth.
Supported By: National Institute of Mental Health (R01MH106581; Dr. Singh)
Keywords: Neuroendocrinology, Puberty, Childhood Trauma, Adolescents, Sex Differences

S51. The Effect of Childhood Adversity Exposure and Recent Stressful Life Events on Longitudinal Inflammatory Response

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Background: Childhood adversity is an independent risk factor for physical and psychiatric illnesses. Elevated inflammatory activity has been identified as one possible mechanism for the biological translation of childhood adversity exposure. However, limited research has investigated the combined effect of childhood adversity exposure and recent life stress on inflammatory biomarkers over time.
Methods: We performed multi-level linear regression analyses to assess whether the interaction of childhood adversity and recent life stress exposure predicted change in cytokine levels between two blood draws (BD1-BD2) in a diverse, urban sample of adolescents ($n=134$, 50.0% female; mean age at baseline=12.5years; 54.5% African American). Participants completed a measure of childhood adversity, an interview assessing recent stress exposure and two annual BDs with no current serious illnesses (i.e. diabetes, autoimmune disease).
Results: The interaction of childhood adversity exposure and recent life stress prior to BD1 was found to significantly predict the change in proinflammatory cytokine interleukin (IL)-6 from BD1 to BD2 ($\beta=.181$, SE=.001, $p=.035$), when controlling for gender, medications affecting inflammation, and the time between assessments. Johnson-Neyman analyses indicated that adolescents with greater childhood adversity exposure and fewer recent stressors showed significantly decreasing levels of IL-6. Those with higher childhood adversity and more recent stressors tended to have increasing levels of IL-6 although it did not attain statistical significance ($p<.10$).
Conclusions: This study indicates that recent stress in adolescence may worsen the proinflammatory effects of childhood adversity exposure, whereas a more benign environment may help to ameliorate the negative trajectory and health risk initiated by childhood exposure to adverse events.
Supported By: Supported by The Temple Mood and Cognition Lab: Risk for Adolescent Depression: Stress, Cognitive Vulnerability, & Inflammation (NIMH # 5R01 MH101168) and Marin Kautz was supported by National Science Foundation Graduate Research Fellowship (2018263024).
Keywords: Childhood Adversity, Inflammation, Adolescence, Stressful Life Events

S52. Poster Withdrawn

S53. The Effects of a Prebiotic Supplementation on Reading and Cognitive Performance in Elementary School Children: A Randomised Placebo-Controlled Study

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Background: Childhood is a developmental period characterised by substantial changes in cognitive abilities. There has been an emerging interest in how manipulating gut microbiota can enrich the developing brain with improved emotional and cognitive functions, but to date this has not been tested in children. In this study, we investigate whether the daily intake of a prebiotic supplement (galacto-oligosaccharides, Bimuno®, B-GOS) by children influenced their reading and cognitive abilities.

Methods: 35 children aged 7-9 with below-average reading scores received a 12-week treatment with the prebiotic or a matched placebo in this randomised, double-blind, between-subjects, placebo-controlled study. Reading and working memory (British Ability Scales) and broader cognition (CogTrackTMSystem) were assessed. As a secondary aim, the effects of the prebiotic on sleep (actigraphy and questionnaire), behaviour, mood, anxiety and cortisol (saliva samples) were also evaluated using mixed-design ANOVAs.
Results: Daily intake of the B-GOS prebiotic did not affect reading ($p=.536$), cognition ($p>.148$), or any of the secondary measures assessed, compared to placebo. Both treatment groups improved over time in reading and memory retrieval speed. In addition, both groups displayed a decline in actual sleep time and immobile minutes.
Conclusions: In this sample, the prebiotic did not influence any of the outcome measures. It is possible that at this age-range, behaviour, immunity and diets are erratic and could potentially confound the effects of the supplement; or that the influence of gut bacteria on the brain is not fully established in early-life. Future studies should explore the relationship between the gut microbiome and cognition across development.
Supported By: Sponsor: University of Oxford; Funding: Clasado BioSciences Ltd
Keywords: Prebiotics, Cognition, Children

S54. Circuit Models of Social Dysfunction: Applications for Drug Discovery

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[1]F. Hoffman-La Roche

Background: Impaired social behavior is a major symptom in neurodevelopmental diseases such as autism spectrum disorders and schizophrenia. Previous studies show that the medial prefrontal cortex (PFC) is critically involved in governing social behavior. However, the cellular and circuit mechanisms that might be responsible for long-term social dysfunction remain poorly understood.
Methods: We hypothesized that perturbing PFC circuit homeostasis over longer timescales would lead to social impairments in rats. To test the effect of chronic increase in PFC excitability on social behavior, we expressed the activatory DREADD hM3D in the PFC and treated the rats chronically with CNO. Sociability was assessed in a 3-chamber task while in a set of parallel experiments, fMRI or electrophysiological recordings were performed.
Results: Our data shows that chronic PFC hyperactivity leads to a persistent decrease in social interaction and a characteristic functional magnetic resonance imaging (fMRI) signature. Field potential recordings in PFC slices revealed persistent alterations in synaptic transmission. Whole-cell patch clamp recordings from retrogradely-identified cortico-thalamic projection neurons demonstrated that the excitability of these neurons is altered. Further, to address the effect of Oxytocin agonist in this circuit model, we treated rats undergoing chronic PFC activation with a selective peptidic oxytocin agonist. Data from social behavior experiments and physiological characterization reveal a corrective effect on the circuit and behavioral dysfunction caused by the disruption of the PFC network.
Conclusions: Taken together this study highlights the role of the PFC network in dysfunctional social behavior and points to a circuit mode of action for the pro-social effects of oxytocin.
Supported By: F. Hoffman-La Roche
Keywords: Prefrontal Cortex, Chemogenetics, Oxytocin, Brain Magnetic Resonance Imaging (MRI), Social Behavior

S55. Human Monocyte- Derived-Neuronal-Like Cells (MDNCs) Replicate Dynamic Structural Changes Present During Brain Development

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Background: Despite intense research, the pathophysiology of neurodevelopmental illnesses such as autism and schizophrenia remains obscure. Among the main obstacles is the lack of adequate models able to replicate essential neurodevelopmental processes. One of these essential processes is neurons ability to constantly modify their shape to explore the environment and establish proper connections. We have previously proposed a deficit in neurostructural dynamics as a core feature of the pathophysiology of schizophrenia. But this hypothesis has not been tested yet.
Methods: We have developed a protocol to transdifferentiate blood circulating monocytes into neuronal-like cells in only 20 days. Unlike other models such as Induced Pluripotent Stem cells (IPSCs), the cell's genome is not altered with viral insertion which can become a confounder in illnesses with a strong but still misunderstood genetic component such as schizophrenia and autism.
Results: We have transdifferentiated monocytes into neuronal-like cells from over 70 individuals and established that Monocyte-Derived-Neuronal-like cells (MDNCs) resemble human neurons early in development, express several neuronal markers and conduct electrical activity. Moreover, MDNCs deliver reproducible results in serial samples from the same individuals. In addition, we recently established that MDNCs as well as human neuroblastoma cells present similar structural dynamic changes as those described during brain development. We also found a correlation between increased structural complexity and increased dynamics in the neuronal shape.

Conclusions: MDNCs are a practical, inexpensive and reliable model to study dynamic structural changes directly in cells from patients with neurodevelopmental disorders such as autism and schizophrenia.
Keywords: Stem Cell, Schizophrenia, Autism Spectrum Disorders, Dendritic Arborization

S56. The Relation Between Hippocampal Volume and Allostatic Load is Moderated by Tanner Stage, Sex, and Adversity in Youth With Depression and Obesity

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Background: Stress and sex hormones impact hippocampal volume; imparting risk for neuropsychiatric disorders. Repetitive, chronic stress, such as that imparted by adverse childhood experience (ACE) exposure, can lead to systemic physiologic adaptations increasing disease risk, defined as allostatic load (AL). No human studies have examined the relation between hippocampal volume and AL as related to ACEs and sex in youth. Our work investigated the role of ACEs, sex, and pubertal development in the relation between hippocampal volume and AL.
Methods: Sixty-nine youth aged 9-17 with depression and obesity were comprehensively assessed on psychometrics, systemic markers of AL, including dimensions from metabolic and inflammatory pathways, and hippocampal volumetric data acquired by magnetic resonance imaging and analyzed using FreeSurfer.
Results: Tanner stage significantly moderated the relation between hippocampal volume and AL ($p=.0015$). Pre-pubertal youth showed a negative relation between hippocampus volume and AL, while post-pubertal youth showed a positive relation. In post-pubertal youth ($N=47$), there was a significant three-way interaction between sex, ACE score and hippocampal volume ($p = .0005$). Females with low ACE scores exhibited smaller hippocampal volumes predicting higher AL, while famels with high ACE scores exhibited larger hippocampal volumes predicting higher AL. The opposite effects were observed in males.
Conclusions: These findings describe, for the first time, a high risk for hippocampal sensitivity to changes in AL in youth with depression and obesity, and a role of stress and sex in moderating this relation. Future work should explore how allostatic mechanisms impact hippocampal neurogenesis contextualized by sex-specific hormonal signaling.
Supported By: National Institute of Mental Health (R01MH106581; Dr. Singh)
Keywords: Allostatic Load, Adverse Childhood Experiences, Sex Differences, Puberty, Neurodevelopment

S57. Does the Acquisition of Social Cognitive Skills Over Adolescence Coincide With Neurophysiological Metric of Brain Maturation? A Cross-Sectional Analysis of the NAPLS-II Consortium Sample

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Background: Schizophrenia is conceptualized as a neurodevelopmental disorder, including a prodromal period during which biological vulnerability is expressed before the emergence of formal symptoms. Individuals at clinical high-risk for psychosis (CHR) are characterized by prodromal features resembling attenuated symptoms of psychosis and were previously found to show a blunted developmental trajectory for attaining theory of mind (ToM). Analysis of the NAPLS-II consortium sample was undertaken to determine whether ToM ability corresponds to neurophysiological metrics of brain maturation, and whether this relationship is altered in CHR.
Methods: Participants included 764 CHR and 279 community comparison (CC) subjects aged 12-35. ToM was measured using the TASIT sarcasm scale. Brain maturation was indexed by auditory P300b (target) amplitude. Amplitude values in CHR were referenced to normal age-expected values obtained in CC and statistically adjusted by study site. Analyses examined whether age moderated relationships (1) between P300 and group status, and (2) between P300 and ToM within group.

Results: CHR showed steeper age-related decline in P300 than CC (group*age p=.039), with significant deficits emerging around age 17. P300 and ToM were modestly positively related in community participants older than 19 (r=.219, p=.005; age*P300 p=.012) but unrelated among CHR participants of any age.
Conclusions: While small, observed effects are consistent with previous findings regarding abnormally accelerated brain maturation in CHR. The lack of a normative developmental relationship between P300 and ToM in the CHR group may suggest that multivariate approaches, reflecting the interaction of neurodevelopment and age-expected achievement, could further enhance classification of at-risk status.
Supported By: NIMH: U01 MH081984, U01 MH081928, P50 MH080272, R01 MH60720, U01 MH082022, K24 MH78191, U01 MH081902, P50 MH066286, U01 MH082004, U01 MH081988, U)1 MH082022, U01 MH081857-05.
Commonwealth of Massachusetts: SCDMH82101008006.
Keywords: Clinical High Risk For Psychosis, Electrophysiology, P300, Theory Of Mind, Neurodevelopmental Trajectories

S58. Fetal Antidepressant Exposure and Outcomes

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Background: The current study examined the impact of fetal exposure to individual antidepressants as measured via in vivo cord blood concentrations on outcomes. These novel analyses may serve to optimize treatment guidelines.
Methods: Paired maternal and umbilical cord samples were collected at delivery. Placental passage is the ratio of umbilical cord to maternal plasma drug concentrations. We examined the association between cord drug concentrations and obstetrical and neonatal outcomes, and explored the determinants of higher cord drug concentrations.
Results: A total of 346 umbilical cord blood and maternal plasma pairs met study inclusion criteria (psychotropic monotherapy, single gestation) for analyses. Individual cord/maternal pairs included: sertraline n=119, fluoxetine n=89, paroxetine n=57, bupropion n=26, citalopram n=25, venlafaxine n=22, escitalopram n=8. Median placental passage was highly variable with the highest estimated for venlafaxine (0.78; 95% CI: 0.47-5.84) and bupropion (0.79; 95% CI: 0.5-1.06); while the lowest was with sertraline (0.52; 95% CI: 0.41-0.62). Among the fluoxetine exposed neonates, those admitted to the NICU (N=11) had a higher median cord concentrations (p=0.04). Aggregated cord drug concentration data for the primary metabolite(s) of each medication was associated with an increased rate of NICU admissions (p=0.045).
Conclusions: Higher cord drug concentrations are associated with adverse outcomes. It is feasible that fetal exposure contributes to the outcome or possible factors associated with the adverse outcome influences fetal medication exposure. The determination of fractional monoamine transporter occupancy (analyses in progress) for medications and metabolites may serve to further clarify the relationship between fetal exposure and outcome.
Supported By: National Institutes of Health, National Institute of Mental Health, award number P50 MH 68036
Keywords: Women's Mental Health, Pharmacology, Placenta, Antidepressant, Pregnancy

S59. Digital Cognitive Assessment: Results From the Testmybrain NIMH RDoC Field Test Battery Report

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Background: Digital technology has become a major target area for the development of assessments that can be deployed through mobile devices, across large cohorts, and in naturalistic environments. Here, we summarize the results of a report commissioned by the NIMH to evaluate mobile assessments of cognition and their appropriateness for deployment in a field test battery.
Methods: Using data from over 100,000 participants tested through our digital research platform, TestMyBrain.org, we analyze 25 standard tests of cognition for field test battery use. Measures are evaluated in terms of their psychometric properties, validity, engagement, and sensitivity to variations in device hardware and software. We also define a minimum duration for acceptable reliability (minDAR) across all tests, operationalized as the test duration required to achieve an internal reliability of at least 0.7 for primary outcomes.
Results: We note that many tests adapted from experimental approaches, particularly those involving aspects of positive and negative valence, need further development to achieve acceptable length and reliability (based on very high minDAR values, e.g. 180 minutes vs 3 minutes for threat biases in memory vs. memory alone). Device variability also presents a confound for reaction time tests (e.g. iOS vs Android Cohen's $d = 0.4$ for simple reaction time, $p < 0.001$). Areas of focus for development of such measures are described.
Conclusions: Digital tools can quickly assess a range of psychological functions in large samples at low cost. Consequently, this approach has great potential for phenotyping at scale.
Supported By: This project was supported by NIH / NIMH contract HHSN271201700776P.
Keywords: Behavior, Neurocognition, Digital Phenotyping, Digital Devices, Cognition

S60. Sex Differences in Placental Epigenetic Aging

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Background: Placental DNA methylation has been used to calculate the "epigenetic age" of the placenta, and placental epigenetic aging has been associated with preeclamptic pregnancies. However, this method of assessing epigenetic age in the placenta has not been tested in other samples, and sex differences in placental epigenetic aging need to be examined. The current study assessed the association between placental epigenetic aging and gestational age at birth in two independent samples and examined sex differences in epigenetic aging of the placenta.
Methods: Healthy pregnant women (N=184), ages 18–45, were recruited through the Department of Obstetrics and Gynecology at Columbia University Medical Center from 2011-2016 and (N=192), ages 18–40, were recruited through eight clinical research sites and 12 sub sites around the country from the NICHD nuMoM2b study. Gestational age was obtained from medical records. Methylation of placental tissue was analyzed using 450K Beadchips and bisulfite sequencing (Illumina). DNA methylation in 62 previously identified CpG sites was estimated to calculate epigenetic age.
Results: In these two studies of healthy pregnant women, DNA-methylation age was correlated with chronological gestational age. Female versus male fetuses had stronger associations between placenta DNA-methylation age and chronological gestational age (r =.21 versus .11 in the first sample and .39 versus .01 in the second sample).
Conclusions: Consistent with male vulnerability to preterm birth and early-appearing neurodevelopmental disorders, these data indicate that for women carrying male fetuses, epigenetic age of the placenta is accelerated or decelerated, relative to birth age, with possible implications for health outcomes.
Supported By: NIMH grant R01 MH092580, NIMH grant T32 MH096724
Keywords: Placenta, Sex Differences, Epigenetic Aging

S61. Corticohippocampal Activity Patterns Modulate the Impact of Safety Signals During Adolescence

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Background: Evidence from both humans and animals has indicated that adolescents are sensitive to threat, and that fear is easily generalized and retained during this developmental stage. Moreover, although the emergence of anxiety disorders is highly prevalent in developing populations, conventional behavioral treatments are ineffective for a notable percentage of adolescents. Many treatments rely on enhancing safety learning, making it critical to understand the development of this form of learning.
Methods: Mice were trained to discriminate between a fear stimulus (CS-F; tone paired with mild footshock) and a safety stimulus (i.e., 'safety signal'; CS-S; unpaired tone). Using in-vivo calcium imaging techniques (fiber photometry) targeted to PL-projecting ventral hippocampal neurons (VH-PL) we recorded neural activity during presentations of CS-F, CS-S, or a compound presentation of both (CS-C).
Results: Our data shows age differences in how the 'safe' properties of a safety signal are formed and maintained. In addition, exposure to safety signals can augment the rate of extinction learning in adolescents. These results are paralleled by age differences in the relative activity of VH-PL neurons during CS-F, CS-S, and CS-C stimuli. Moreover, heightened signaling in these neurons during adolescence may enhance fear regulation.
Conclusions: Safety signals can be used to effectively attenuate conditioned fear during adolescence, and differential signaling patterns in cortico-hippocampal networks during development may provide a unique 'sensitive window' for the efficacy of fear regulation. Together, our findings highlight the potential for safety learning to augment traditional therapies for fear and anxiety disorders that are less effective during adolescence.
Supported By: NIH NCATS, NIMH P50, Pritzker Neuropsychiatric Disorders Research Consortium Award
Keywords: Adolescence, Safety, Fear, Ventral Hippocampus, Prelimbic Cortex

S62. Symptom Improvement Following Cognitive Behavioral Therapy in Obsessive-Compulsive Disorder is Associated With Cingulo-Opercular Activation

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Background: Cognitive behavioral therapy with exposure and response prevention (CBT-ERP) is the gold standard psychotherapeutic treatment method for obsessive compulsive disorder (OCD). Recent meta-analytic evidence points to cingulo-opercular network underactivation during inhibitory/interference control but hyperactivation during error processing in OCD relative to controls. However, whether these neural abnormalities are associated with response to CBT-ERP is unknown.
Methods: Thirty-four patients with OCD (age range 12-45, 22 female, 19 medicated) completed a functional magnetic resonance imaging version of the incentive flanker task, before receiving 12-weeks of CBT-ERP treatment. Symptoms were assessed at baseline and post-treatment using the (Children's)

Yale-Brown Obsessive Compulsive Scale ((C)Y-BOCS). Whole-brain multiple regression analyses examined whether symptom change following treatment in CBT-ERP was associated with brain activation during inhibitory/interference control and error processing.
Results: Following CBT-ERP, patients showed a significant decrease in (C)YBOCS scores ($t(33)=11.37$, $p<0.001$, T1mean=24.8, T1SD=5.19, T2mean=12.22, T2SD=6.79). Symptom change scores ranged from -24.5 to +1.5, and greater improvement correlated with greater activation during inhibitory/interference control in bilateral inferior frontal gyrus (extending into anterior insula on the right side) and dorsomedial prefrontal cortex.
Conclusions: The current findings suggest that intact cingulo-opercular functioning may allow patients to engage more effectively with CBT-ERP treatment, perhaps due to a greater capacity for inhibiting maladaptive responses to symptom triggers during exposure.
Supported By: NIMH ROI1
Keywords: Obsessive Compulsive Disorder (OCD), Anxiety Disorder, Cognitive Behavior Therapy, Brain Imaging, Performance Monitoring

S63. Effects of Prenatal Drug Exposure on Amygdala-mPFC Connectivity During the First Year of Life

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Background: Studying the effects of prenatal drug exposures (PDE) on baby brain and cognitive development has become increasingly more important given the recent drug epidemic. Our previous studies revealed hyper-connectivity between the amygdala and medial prefrontal cortices (mPFC) in newborns with PDE (1), however independent validations are lacking. Moreover, whether alterations persist, grow, or become normalized with age remains unknown. In this study, amygdala-mPFC connectivity was investigated using an independent longitudinal sample of infants (gestational age between 294 days and 722 days) to answer both questions.
Methods: Infants (N = 32 (15 M); 25 with PDE) were retrospectively identified from an on-going longitudinal study of PDE effects on baby brain/cognitive development. Baby connectome protocols were used for imaging. Resting-state functional connectivity between the amygdala and a priori region in the mPFC, previously detected to show PDE-related hyper-connectivity, was evaluated.
Results: Controlling for multiple other participant characteristics (i.e., birth age/weight, sex, scan age, maternal education, and subject motion), highly convergent hyper amygdala-mPFC connectivity in infants with PDE ($t = 2.89$, $P = 0.0067$) was detected. When the longitudinal pattern was examined, no significant change was detected, indicating persistent hyper-connectivity during the first year of life.
Conclusions: Based on an independent data-set obtained using a different scanner and new imaging parameters, our preliminary results confirmed hyper amygdala-mPFC connectivity in neonates with PDE. More importantly, such hyper-connectivity seemed to persist suggesting long-lasting PDE effects on early brain development.

Reference: (1) Salzwedel et al. Prenatal Drug Exposure Affects Neonatal Brain Functional Connectivity. The Journal of Neuroscience. 2015;35(14):5860-9.
Supported By: 1R01DA042988-01A1
Keywords: Amygdala, Infants, Resting State Functional Connectivity MRI (fcMRI), Prenatal Drug Exposure, Developmental Trajectories

S64. White Matter Abnormalities in the Anterior Section of the Left Cingulum Bundle Correlates With a Severe Course of Illness in Adults With Bipolar Disorder Who Have Been Prospectively Characterized Since Childhood for up to 18 Years of Illness

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Background: Different courses of Bipolar Disorder (BD) have important implications for psychosocial functioning and morbidity, yet neural correlates of these trajectories remain unclear. The Course and Outcome of Bipolar Youth (COBY) study has identified important demographic/clinical factors predicting different trajectories of BD course.
Methods: Based on weekly assessments of depressive/manic symptoms for up to 18 years, latent class analysis was used to derive different BD courses. Fifty-four BD adults (M/F=25/29; R/L=43/9) were classified in distinct class-trajectories (persistently euthymic, N=19; moderately ill, N=22; persistently ill, N=13). To identify diffusion imaging correlates of these class-trajectories, we used global probabilistic tractography and a tract-profile approach of the cingulum bundle (CB), primarily involved in emotional regulation and reward. Fractional anisotropy (FA; indirect index of fiber collinearity) was estimated. Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) were used to account for severity of symptoms at scan. Two (for HDRS or YMRS) repeated measure analyses were used to model the 'class-trajectory' (3 class-trajectories) effect upon 'tract-profile' of FA (99 segments along CB). Data from 43 healthy controls served as reference.
Results: Covering for HDRS or YMRS, class-trajectory showed a main effect (HDRS: $F=3.4$,$p=0.042$; YMRS: $F=4.6$,$p=0.015$) on the left CB. Further analyses revealed that abnormality (lower FA) in the left anterior CB (K=10 segments) distinguished BD adults with a persistently ill course from those with a less severe course (and controls).
Conclusions: Lower fiber collinearity in anterior portion of the left CB, which connects the anterior cingulate with

ventromedial/ventrolateral prefrontal cortex, might represent a BD-marker of chronic illness.
Supported By: R01MH059929
Keywords: Neuroimaging, Mood Disorders, Child and Adolescent Psychiatry

S65. Assessing the Developmental Taxonomy of Antisocial Behavior: Structural Neural Correlates of Life-Course Persistent vs. Adolescence-Limited Subtypes in a Longitudinal Birth Cohort

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Background: Conduct Disorder (CD) is characterized by persistent antisocial behavior, typically emerging before adulthood. Developmental Taxonomic Theory suggests that there are two etiological pathways of antisocial behavior: 'life-course persistent' (LCP), beginning in childhood and persisting into adulthood, and 'adolescence-limited' (AL), beginning in adolescence and limited to this developmental window. AL antisocial behavior is common and influenced by a normative gap between biological and social maturity, whereas the LCP subtype is less-common and exhibits more severe offending and neurocognitive deficits. Neuroimaging research into CD subtypes is limited. Structural and functional findings have been mixed; some studies have differentiated the LCP and AL groups, whilst others have not. Inconsistent findings could arise because these CD subtypes are inadequately defined in small cross-sectional samples.
Methods: We compared 609 individuals from the longitudinal Dunedin Study who were classified by CD subtype using 8 waves of data (LCP=73, AL=138, Low=398) on age-45 grey matter volume with voxel-based morphometry.
Results: Whole-brain ANOVA ($p<0.001$ cluster-wise correction; $k=240$) showed reduced volume in CD vs. the low group bilaterally in premotor cortex, dorsomedial and ventrolateral PFC, as well as thalamus and right OFC. Reductions in thalamus, right VLPFC and bilateral dmPFC differentiated AL and LCP.
Conclusions: These findings support that CD is associated with structural abnormalities in prefrontal-thalamic cognitive control regions that, in some instances, distinguish AL and LCP subgroups. These results provide insight into the respective neurocognitive profiles of LCP and AL CD phenotypes based on rich, multi-source longitudinal measures, with implications for prevention and treatment of severe antisocial behavior.
Supported By: Wellcome Trust, NIMH, ESRC
Keywords: Voxel-Based Morphometry, Conduct Disorder, Antisocial Behavior, Longitudinal study, Adolescence

S66. Morphometric Changes Associated With Math Deficits in Adolescent Marijuana Users

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Background: An estimated 1.6 million adolescents are current users of marijuana (MJ). Previous research on cognition in MJ using adolescents has generally shown reduced executive function. However, few studies have focused on mathematic performance in this population. Investigations into the neuroanatomical architecture underlying math performance have suggested parietal regions play a key role. The current study examines the association between reduced math performance, attention, and potential changes in parietal morphometry.
Methods: Twenty-seven adolescent chronic MJ users (mean age = 17.35) and 35 non-using controls completed a battery of cognitive and clinical measures including drug use history. Math performance was measured using the Wide-Range Achievement Test (WRAT). Participants also completed magnetic resonance imaging (MRI) on a 3T Verio scanner and data were analyzed using FreeSurfer to obtain regional brain volumes.
Results: MJ-using adolescents showed deficits on math performance ($p=0.003$) but not on estimated IQ or measures of attention compared to non-using controls. Reduced math performance in MJ users negatively correlated with right parietal volume ($p=0.033$) and left inferior parietal thickness ($p=0.029$).
Conclusions: Lower math performance in MJ users was associated with reduced thickness and volume in parietal regions. Results suggest reduced mathematics performance in adolescent MJ users is unrelated to attentional capacity or estimated IQ. Future research should examine onset of math performance deficits compared to onset of MJ use to clarify potential causal effects.
Supported By: ABCD (RFA-DA-15-015)
Keywords: Marijuana, Adolescence, Academics, Brain Magnetic Resonance Imaging (MRI)

S67. Suicidal Behavior is Associated With Greater Medial Prefrontal and Fusiform Activation During Risky Decision Making in Youth With Disruptive Behavior Disorders

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Background: Suicide rates among youth are increasing; while research on adults has identified endophenotypes characterized by deficits in decision-making in risk for suicidality, less is known regarding neurobiological markers of suicide risk among youth. Understanding of neural mechanisms characteristic of youth with a history of suicidal ideation or attempts may inform screening, prevention, and intervention. We examined neural mechanisms underlying decision-making among 11-12 year-olds with and without suicidality.
Methods: N=57 youth who met DSM-5 diagnostic criteria for disruptive behavior disorders and ADHD were assessed for

history of suicidal behavior using items from the K-SADS. Youth were assigned to either the suicidality or non-suicidality group based on parent and self-report. Youth were considered having a history of suicidality/self-harm if parent or youth endorsed lifetime history of recurrent thoughts about killing oneself or plan to kill oneself, actual attempts, or history of recurrent non-suicidal self-harm behaviors. After psychiatric evaluation, youth completed the BART (Balloon Analog Risk Task), a decision-making task, during fMRI scanning. We examined neural activity during the choice and outcome phases of decision-making.
Results: N=22 (38%) reported lifetime history of suicidality. Examining neural activity during the BART performance, youth with suicidality showed greater activation in the medial prefrontal cortex when making "safer" decisions (choosing win vs. inflate; $p<.01$). During the outcome phase, youth with suicidality showed greater activation in the fusiform gyrus (59 voxels) in response to explosions vs. inflations ($p<.01$).
Conclusions: Results suggest youth with a history of suicidality show greater sensitivity to punishment, based on activation in the fusiform gyrus.
Supported By: NIDA: R01DA039764
Keywords: Suicidal Behavior, Disruptive Behavior Disorders, Decision Making, Adolescence

S68. Robotic TMS Motor Map Changes After rTMS Intervention in Children With Tourette's Syndrome

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Background: Tourette's syndrome (TS) is a disabling disorder with limited treatments. Repetitive transcranial magnetic stimulation (rTMS) is a promising non-invasive neuromodulation approach — but the mechanisms are not known. Single pulse TMS can quantify cortical motor map neurophysiology. We hypothesized that motor map metrics would decrease following the 3-week rTMS trial in children with TS.
Methods: Children (6-18 years) with severe TS participated. At baseline, surface electromyography was recorded from the first dorsal interosseous muscle (FDI) of the dominant hand. Using neuronavigated robotic TMS, a 10x10 grid was placed over the primary motor area (M1) of the dominant hand. Motor maps were generated at 120% RMT with mean motor evoked potential (MEP) values used to calculate map volume, ellipse properties, and spatial entropy. rTMS then targeted the supplementary motor area (SMA) for 15 weekdays (1 Hz, 1800 stimulations). Motor map metrics, tic severity, and secondary clinical outcomes were repeated.
Results: The first nine participants are presented (2 female). Average dominant FDI motor map volume, ellipse area, ellipse length, and spatial entropy all demonstrated a decrease (-7.7%, -26.7%, -22.1%, -10.9% from pre to post respectively). Accurate maps were unobtainable in 2 subjects. Tic severity decreased was not strongly associated with motor map change. Procedures were well tolerated with no serious adverse events.
Conclusions: Robot-driven, personalized, neuro-navigated TMS motor mapping is feasible within a clinical trial of children with TS. Hand muscle motor maps may decrease in size following rTMS interventions. Future motor map reliability studies and larger samples are required to demonstrate efficacy and mechanisms.
Supported By: Canadian Institute for Health Research
Keywords: Tourette's Syndrome, Gilles De La Tourette Syndrome, Transcranial Magnetic Stimulation (TMS), Children And Adolescents, Robot

S69. Glycine Transporter Inhibition Improves Conspecific-Provoked Immobility in Balb/c Mice, an Effect Unrelated to Peripheral Corticosterone Response or Glucocorticoid Gene Expression in Cortex and Hippocampus

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Background: Comorbid anxiety often presents with autism spectrum disorder (ASD). Alterations in stress and glucocorticoid signaling are also implicated in ASD. D-Cycloserine, a partial glycineB agonist of the NMDA receptor (NMDAR), and VU0410120, a novel glycine type-1 transporter inhibitor, improved sociability in Balb/c mice, suggesting that NMDAR activation regulates sociability, and the endogenous tone of NMDAR-mediated neurotransmission is altered in this strain.
Methods: Conspecific-provoked immobility (CPI) of Balb/c mice in the presence of enclosed and freely-behaving stimulus mice was investigated using a 3-chambered sociability apparatus. We explored the relationship between CPI and serum corticosterone (CORT) response (ELISA) and also determined effects of a prosocial dose of VU0410120 in Balb/c mice on these measures. A targeted expression profiling of 88 genes implicated in the social stress and anxiety phenotypes was explored in cortex and hippocampus (Affymetrix GeneChip).
Results: Balb/c mice were more immobile than comparator Swiss-Webster mice. There were no differences in CORT levels between vehicle-treated Balb/c and Swiss-Webster mice or between vehicle-treated Balb/c mice with high (>73s; N=8) or low (<73s; N=9) immobility scores. VU0410120-treated Balb/c mice (N=21) showed significantly less immobility and higher CORT levels compared to vehicle-treated mice. Regardless of high (N=11) or low (N=8) immobility, CORT levels of VU0410120-treated Balb/c mice did not differ. Glucocorticoid gene expression did not differ between Balb/c and Swiss-Webster mice.
Conclusions: The "anxiolytic" effect of VU0410120 was unrelated to conspecific-provoked CORT response in Balb/c

mice. Social stress alone may not determine increased immobility in Balb/c mice; this strain may also display an element of social "disinterest".
Keywords: BALB/C Mice, Autism Spectrum Disorder, Psychosocial Stress, Immobility, Corticosterone

S70. Neural Structure and Function as Transdiagnostic Predictors of Psychopathology Among Institutionally-Reared Children

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Background: Psychosocial neglect due to institutional deprivation is a transdiagnostic vulnerability factor for psychopathology. Previous studies also suggest that cortical maturity and the structure and function of the insula are shared neural substrates for multiple psychiatric disorders. We used data from a longitudinal randomized controlled trial to examine the relation between cortical thickness of the insula and resting EEG alpha power and general psychopathology in a sample of institutionally-reared children.
Methods: Children reared in Romanian institutions (N = 136) were randomly assigned to either care as usual or foster care at an average age of 22 months. A group of non-institutionalized children served as a comparison group. At age 8, EEG and structural MRI were acquired, and psychopathology was assessed from teacher ratings.
Results: A similar pattern was observed for both resting EEG alpha power (an index of cortical maturity) and thickness of the insula, with greater alpha power and greater thickness of the insula associated with lower general psychopathology at age 8. These relations were strongest among those with a history of institutional deprivation, and especially among those assigned to foster care. In contrast, psychopathology was relatively low in the non-institutionalized group, with no relation between either alpha power or insula thickness and psychopathology.
Conclusions: These results suggest that both resting alpha power and insula thickness may be transdiagnostic markers of psychopathology among children who have experienced severe early neglect. Furthermore, removal from depriving environments and placement into high-quality care may augment the positive effect of neural development on children's psychological health.
Supported By: John D. and Catherine T. MacArthur Foundation, the Binder Family Foundation, NIMH (R01MH091363), and a CIHR Banting Postdoctoral Fellowship.
Keywords: General Psychopathology, Electroencephalography (EEG), MRI, Abuse and Neglect, Foster Care

S71. Meal Related Interoceptive Dysfunction in Anorexia Nervosa

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Background: Individuals with eating disorders exhibit abnormal interoception during meal anticipation, yet it is unclear to what extent this is driven by the presence of comorbid affective psychopathology. The current study investigated the degree to which cardiorespiratory interoception differs in anorexia nervosa versus mood and anxiety disorders.
Methods: Individuals with anorexia nervosa (AN, n=11) mood/anxiety disorders (MA, n=19), and healthy comparisons (HC, n=25) received randomized double-blinded bolus infusions of isoproterenol (0.5, 2 micrograms) and saline during BOLD fMRI scanning at 3 Tesla. Throughout each infusion scan participants rated the intensity of perceived cardiorespiratory sensations by rotating a dial. To target meal anticipation all participants were informed they would be asked to eat a 1000 Calorie meal upon scan completion. Since data collection is ongoing to accrue adequate statistical power for the neuroimaging analysis, we report only the behavioral analysis using linear mixed effects models.
Results: There were no significant differences in age, sex, BMI, or heart rate response between the three groups. AN and MA exhibited heightened anxiety sensitivity relative to HC but did not differ from each other (HC=7.9+/-4.5, AN=24.8+/-15, MA=27.1+/-12.0). AN and MA reported greater levels of cardiorespiratory sensation during the 0.5 mcg infusions ($p<0.0004$ and $p<0.0005$ respectively), whereas during the 2-mcg dose only the AN group reported significantly elevated levels of cardiorespiratory sensation ($p<0.0001$).
Conclusions: Top-down fear-related stimuli exaggerate aversive interoceptive sensation, which may sustain anxiety in AN further leading to the avoidance of food. Development of interventions to reduce meal related interoceptive dysfunction in AN may be warranted.
Supported By: NIMH K23; NIGMS CoBRE; The William K. Warren Foundation
Keywords: Anxiety, Interoceptive Awareness, Anorexia Nervosa, Depression, Autonomic Nervous System

S72. Longitudinal Assessment of Impairments in Goal-Directed Reinforcement Learning for Money and Food in Anorexia Nervosa

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Background: Although anorexia nervosa (AN) appears to be characterized by extreme goal-directedness, the goal-directed vs. habitual nature of maladaptive behavior in AN remains unclear. This question has not been examined using computational approaches, which provide tools to distinguish between these possibilities.
Methods: We tested individuals with AN (n=41) and healthy comparison (HC, n=53) participants on a two-stage decision

task designed to measure the contribution of model-based and model-free learning, which are thought to underlie goal-directed vs. habitual behavior, respectively. Because food is at the core of AN psychopathology, model-based behavior is most relevant for outcomes related to food and we administered tasks with both monetary and food outcomes. Further, we tested individuals with AN while acutely ill and again after weight restoration, and HC at two time points.
Results: AN and HC did not differ significantly in their model-free learning (Estimate: 0.09, SE = 0.06, z = 1.36, p = 0.17). In contrast, model-based learning was significantly worse in the AN group relative to the HC group (Estimate: 0.15, SE = 0.06, z = 2.27, p = 0.023). This pattern was invariant to whether food or monetary outcomes were used (Estimate: -0.08, SE = 0.07, z = -1.11, p = 0.27) and to whether AN were acutely ill or weight restored (Estimate: 0.02, SE = 0.08, z = 0.27, p = 0.79).
Conclusions: AN show a deficit in goal-directed learning across domains and illness state. This persistent deficit may contribute to difficulty changing behavior in response to treatment and to poor long-term prognoses.
Supported By: NIMH R01 MH105452
Keywords: Anorexia Nervosa, Computational Psychiatry, Goal-Directed Behaviour, Habitual Behavior, Reinforcement Learning

S73. Characterizing Approach and Avoidance Learning in Anorexia Nervosa

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Background: Individuals with Anorexia Nervosa (AN) show aberrant response patterns to appetitive and aversive cues, which may relate to differences in behavioral and neural sensitivity to reward and punishment. This ongoing study used a probabilistic instrumental learning task to examine approach and avoidance learning through manipulation of outcome valence and feedback type in AN relative to HC. We hypothesized that learning from aversive stimuli relative to rewarding stimuli would be increased in AN compared with HC.
Methods: To date, females with AN (n=15) and HC (n=17) completed the task. The learning phase presents four cue pairs corresponding to four context conditions (Reward/Partial, Reward/Complete, Punishment/Partial, Punishment/Complete). One cue in each pair has a higher probability of a 'good' outcome (Gain75%, Loss25%) than the other (Gain25%, Loss75%). Participants are instructed to learn which cues are associated with highest probability of reward, or the lower probability of loss. A post-learning test measures cue value retrieval and transfer.
Results: Both AN and HC show evidence of instrumental learning (i.e. participants seek reward and avoid punishment) ($p<0.001$). Relative to HC, AN show increased contextual learning of the intermediate cue options, choosing the Loss25 cue (less punishing option in the punishment condition) more often than Gain25 cue (less rewarding option in the reward condition) ($F[1,30] = 5.6$, $p=0.024$).
Conclusions: Preliminary results suggest significant differences related to contextual learning of approach and avoidance cues in AN. Characterizing approach and avoidance learning in AN is a fundamental step towards elucidating the decision-making processes underlying maladaptive dietary choice.
Supported By: Hilda and Preston Davis Foundation
Keywords: Anorexia Nervosa, Approach/Avoidance, Instrumental Learning

S74. Identifying Valuation Disturbances in Anorexia Nervosa Using a Translational Decision-Making Paradigm

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Background: Anorexia nervosa (AN) is a disorder characterized by aberrant decision-making surrounding consummatory behavior leading to inadequate intake and severe weight loss. Prominent theoretical models hypothesize that AN is maintained through insufficient responsivity to rewards (including palatable foods) or over-reliance on habitual, as opposed to deliberative, learning. In this study, we used a translational foraging paradigm to parse valuation abnormalities associated with distinct neural signatures in AN.
Methods: AN (n=17) and healthy control (HC; n=17) participants completed the Web Surf task, in which they chose to stay with or skip offers to watch videos from four categories with delays ranging from 3-30 seconds. Preference is reflected through video stay/skip threshold (delay participants will tolerate to access videos) and enjoyment ratings.
Results: AN and HC groups did not differ in video thresholds (p=.64) or ratings (p=.31), suggesting intact reward responsivity in AN. Both groups exhibited deliberation, whereby decision times were slower for offers closest to the stay/skip threshold. AN participants demonstrated quicker decision times for low value choices (p=.006) and completing enjoyment ratings (p=.01). NC enjoyment decreased (B=-0.31, p=.006) whereas AN enjoyment increased (B=0.40, p< .001) over time. Greater enjoyment led to slower subsequent decisions for the NC (B=.04, p=.004), but not AN (B=-.006, p=.69) group.
Conclusions: AN participants displayed intact reward responsivity and deliberation. However, their decision-making appeared to follow a self-reinforcing pattern of rule-following behavior, whereby value-based choices were more quickly and reliably automated, leading to increasing pleasure from selections, and continued automaticity. Rule-based decision-making may represent a unique intervention target for AN.
Keywords: Anorexia Nervosa, Eating Disorders, Translational Research, Reward Valuation, Reward Learning

S75. Maladaptive Food Choice and Neural Correlates Persist After Weight Restoration in Anorexia Nervosa

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Background: Anorexia nervosa (AN) is characterized, in part, by persistent dietary restriction leading to starvation. Eating patterns are associated with longer-term outcome. We have demonstrated that among AN, but not healthy controls (HC), active decision-making around food choice was related to neural activation in the dorsal striatum. We hypothesized that these measures would begin to normalize with weight restoration.
Methods: We administered a computer-based Food Choice Task with functional MRI to women with AN (n=38) before and after weight restoration and to HC (n=36) at two time-points. The next day, a laboratory multi-item meal was administered. Proportion of high-fat foods selected in the Choice block of the task was compared before and after treatment using repeated measures ANOVA. Parametric analyses were used to measure neural activation associated with choice.
Results: Despite improvement in mood, anxiety, and eating disorder severity scores (p's <0.01), there was persistent disturbance and no significant change (p=0.30) with weight restoration in task-based food choices [Est.=-0.40, z=-5.1, $p<0.0001$], or in the laboratory meal (Group: F1,51=12.3, p=0.01; Time: F1,51=0.42, p=0.51). Preliminary fMRI analyses indicated that AN engage dorsal striatum during food choice, while HC did not ($p<0.001$, uncorrected), and this pattern persisted after weight restoration ($p<0.05$, uncorrected).
Conclusions: Maladaptive restrictive food choice is highly persistent in AN, with no significant change after weight restoration treatment, in behavior or in associated neural activity. The absence of meaningful change with weight restoration highlights the need for new mechanism-based treatment interventions.
Supported By: R01 MH105452
Keywords: Anorexia Nervosa, Decision Making, Cognitive Neuroscience, Eating Disorders, Brain Imaging, fMRI

S76. Omega-3 Fatty Acid Deficiency Augments C-Reactive Protein Biosynthesis in Response to Repeated Lipopolysaccharide Administration in Rats

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Background: The pathoetiology of major depressive disorder (MDD) is associated with elevated biomarkers of systemic inflammation, including C-reactive protein (CRP), and lower red blood cell (RBC) omega-3 polyunsaturated fatty acid (n-3 PUFA) levels. The present study investigated the effects of dietary-induced alterations in n-3 PUFA biostatus on basal and stimulated CRP levels in rats.
Methods: Male rats were fed a diet with no n-3 fatty acids (Deficient, DEF, n=16), preformed n-3 PUFA (fish oil, FO, n=16), or a control diet fortified with alpha-linolenic acid (CON, n=16) from P21-P90. On P86, half of each diet group received five daily injections of lipopolysaccharide (LPS, 500 ug/kg) or saline (SAL). Plasma CRP concentrations were measured by Luminex and RBC membrane n-3 PUFA composition by gas chromatography.
Results: Compared with CON rats, RBC n-3 PUFA levels were lower in DEF rats ($p<0.0001$) and higher in FO rats ($p<0.0001$). LPS did not alter RBC n-3 PUFA levels. CRP levels did not differ between diet groups after acute LPS or SAL treatment. Following chronic LPS treatment, CRP levels were significantly greater in DEF rats compared with CON (p=0.01) and FO (p=0.004) rats. Within diet groups, chronic LPS treatment significantly increased CRP levels in DEF rats (+16%, p=0.02), but not in CON (-2%, p=0.82) or FO (-13%, p=0.11) rats.
Conclusions: These findings suggest that low n-3 PUFA biostatus augments the biosynthesis of CRP in response to repeated LPS treatment and may therefore represent a modifiable risk factor for inflammation-induced depression.
Supported By: NIMH R01 MH107378
Keywords: Inflammation, N-3 Fatty Acids, Infection, Developing Brain

S77. Reductions of Myelination and Connexin 43 by Glucocorticoids are Prevented by Mifepristone in Mixed Central Nervous System Cell Cultures

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Background: Repeated stress induces systemic elevations in glucocorticoid levels. Stress is also associated with alterations in astrocytes and oligodendrocytes in the central nervous system involving connexins and myelin proteins. Corticosteroid elevation seems a major factor in stress-induced neuropathology. Changes in astrocyte connexins and myelin components may be important mediators for the neurological effects of corticosteroid elevations.
Methods: Two primary cell culture models, myelination culture from rat embryonic spinal cord (SC) or cerebral cortex (CC) consisting of neurons and glial cells (oligodendrocytes, microglia and astrocytes), and mixed astrocyte-and-oligodendrocyte culture prepared from postnatal rat CC, were used in this study. Cell cultures were treated with either vehicle, corticosterone (CORT) with or without glucocorticoid receptor antagonist mifepristone, or dexamethasone (DEX) during the period of in vitro myelination. Immunoreactivity of astrocyte connexin 43 (Cx43) and oligodendrocyte myelin basic protein (MBP), or the myelination index (co-localization of MBP and phosphorylated neurofilament) were determined by double immunofluorescent labeling. Oligodendrocyte morphology was evaluated by Sholl analysis

Results: Prolonged exposure to CORT or DEX induced dose-dependent reduction of the myelination index, and immunostaining for MBP and Cx43 in SC and CC myelination cultures, which was prevented by mifepristone. In glial cultures, single CORT or DEX exposure caused shrinkage and simplification in MBP- or CNPase positive oligodendrocyte processes.
Conclusions: The results support that concurrent effects of glucocorticoids on myelination and astrocyte Cx43 immunoreactivity are mediated by glucocorticoid receptors and may partially account for the involvement of central nervous system glia in the pathological effects of prolonged stress.
Supported By: NIMH/NIH R56MH113828; IRSP University of Mississippi Medical Center
Keywords: Astrocytes, Glucocorticoids, Dexamethasone, Oligodendrocytes, Chronic Stress

S78. Towards Precision Medicine for Mood Disorders: New Diagnostics and Therapeutics for Depression and Mania

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Background: Currently there are no diagnostic blood tests for mood disorders used in clinical practice. Early pilot studies by us to discover blood biomarkers for mood disorders were promising (Le-Niculescu et al. Molecular Psychiatry 2009) and validated by others (Keri et al. Journal of Affective Disorders 2014).
Methods: Recent comprehensive work by our group has identified blood gene expression biomarkers that track suicidality, a tragic behavioral outcome of mood disorders (Niculescu et al. Molecular Psychiatry 2013, 2015, 2017). We endeavored to use a similar comprehensive approach to identify more definitive biomarkers for mood disorders.
Results: First, we used a longitudinal within-subject design and whole-genome gene expression approach to discover biomarkers which track mood in subjects who had diametric changes in mood state from low to high and vice-versa, from visit to visit. Second, we prioritized these biomarkers using a convergent functional genomics approach encompassing using prior evidence in the field. Third, we validated the biomarkers in an independent cohort of subjects with clinically severe depression and with clinically severe mania. Fourth, we tested in another independent cohort of psychiatric patients the ability of the top biomarkers to predict depression state (as measured by HAMD), and trait (future hospitalizations for depression). We also studied the ability of the biomarkers to predict mania state (as measured by YMRS), and future hospitalizations for mania. Finally, we used the biomarker signatures to bioinformatically repurpose candidate drugs.
Conclusions: Overall, our studies provide leads for new diagnostics and targeted therapeutics that enable precision medicine for mood disorders.
Supported By: NIH, VA
Keywords: Depression, Bipolar, Biomarkers, Gene Expression, Blood

S79. Predicting Venlafaxine Remission in Late-Life Depression Using Genome-Wide and Clinical Data

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Background: In late-life depression, antidepressant treatment response is often slow and incomplete. While our previous GWAS has implicated PDE9A and ERBB4 in remission on venlafaxine-treatment, here we used a machine learning approach to build integrated clinical and genetic models to predict remission status.
Methods: Our sample included 350 older adults ($\geq$60 years) with MDD and genome-wide data for 4.7 million gene variants, treated with venlafaxine XR for 12 weeks. Based on end-of-treatment symptom dimensions, k-means clustering was used to extract two bootstrap-validated clusters showing high concordance with clinically-defined remission status ($p<2.2e-16$). Based on the defined classes (robust remitters, n=108; non-remitters, n=122), we evaluated predictive models built using (1) clinical data only, (2) genetic data only, and (3) integrated clinical and genetic data. Using a nested 5-fold cross-validation framework, the top 25 variables with non-zero coefficients were selected using elastic net. We evaluated seven classifiers, tuned using 10-times-repeated 5-fold cross-validation. Our models were tested in a 30% holdout test set, as well as an external sample (STAR*D, n=707).
Results: Our best performing clinical model using support vector machines to predict remission included baseline symptoms for depressive mood, guilt, anhedonia, gastrointestinal problems, and lack of insight (holdout, AUROC=0.58, sensitivity=0.61, specificity=0.47, $p>0.05$; STAR*D, AUROC=0.60, sensitivity=0.70, specificity=0.47, $p<0.01$). None of the genetic models or integrated models were significant in the holdout or external tests sets.
Conclusions: Baseline clinical models show some promising performance in predicting antidepressant treatment response. However, clinically-significant model performance may be achieved, model optimization is required for the integration of both clinical and genetic data.
Supported By: Ontario Mental Health Foundation (OMHF), Canadian Institutes for Health Research (CIHR)

Keywords: Antidepressant, Venlafaxine, Geriatric Depression, Pharmacogenetics, Machine Learning

S80. The TRKB rs2289656 Genetic Polymorphism is Associated With Acute Suicide Attempts in Depressed Patients: A Transversal Case Control Study

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Background: Suicide Attempts (SA) are the main complications of Major Depressive Episodes (MDE) and are difficult to predict. Suicide is associated with the expression of Receptor Tyrosin-Kinase B (TRKB), the receptor of the Brain Derived Neurotrophic Factor (BDNF) involved in MDE. However, the impact of its genetic polymorphisms as predictive factors of SA should be clarified. Our main aim is to assess the association of 8 TRKB genetic polymorphisms and SA in depressed patients.
Methods: In 624 patients currently experiencing an MDE in the context of Major Depressive Disorder (MDD) (METADAP study), we assessed the association between 8 TRKB genetic polymorphisms (rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and rs1439050) and acute (previous month) or past (older than one month) SA. Bonferroni corrections and multivariate analysis adjusted for age, sex, level of education, marital status, Hamilton Depression Rating Scale score and previous MDE were used.
Results: Only rs2289656 was associated with acute SA (CC genotype=28.5%, CT genotype=15.0% and TT genotype=11.5%, p=0.0008). Patients with the CC genotype had a higher rate of acute SA (28.5%) as compared to T carriers (14.6%) (adjusted OR=2.2, CI95% [1.4; 3.5], p<0.0001).
Conclusions: The TRKB rs2289656 CC genotype is associated with a 2.2 fold higher risk of acute SA in depressed patients. If this result could be confirmed, this TRKB SNP may be assessed to contribute to the prediction of SA in depressed patients.
Supported By: National grant (PHRC) of the French Ministry of Health (AOM06022 – E Corruble)
Keywords: Suicide Attempts, Major Depression, TRKB Genetic Polymorphism, rs2289656

S81. Hippocampal Epigenetic Aging in Bipolar Disorder

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Background: Evidence suggests accelerated aging mechanisms in bipolar disorder (BD), with reports of DNA methylation (DNAm) aging in blood. It is unknown whether such mechanisms are also evident in the brain, in particular in association with other biological clocks.
Methods: Genome-wide DNA methylation was interrogated in postmortem hippocampus from 32 BD-I patients and 32 age-, sex-, and race-matched non-psychiatric controls from the NIMH Human Brain Collection Core. DNAm age and epigenetic aging acceleration were estimated using the Horvath method. Telomere length (TL) and mitochondrial DNA (mtDNA) copy number were quantified by quantitative real-time PCR. Between-group differences were assessed by linear regression and univariate general linear models with age, sex, race, postmortem interval, tissue pH, smoking, and body mass index included as covariates.
Results: Groups did not differ for epigenetic aging acceleration when considering the entire sample. However, after splitting the sample by the median age, an epigenetic aging acceleration was detected in patients compared to controls among older subjects ($p = 0.042$). While TL did not differ between groups, patients showed a reduction in mtDNA copy number compared to controls ($p = 0.047$). Significant correlations were observed between epigenetic aging acceleration and TL ($r = -0.337$, $p = 0.006$), and between TL and mtDNA copy number ($r = 0.274$, $p = 0.028$).
Conclusions: Hippocampal epigenetic aging acceleration is present in older BD patients, which may underlie neurocognitive dysfunctions seen in this population. A complex cross-talk between biological clocks in hippocampus may underlie clinical manifestations of premature aging in BD.
Keywords: Bipolar Disorder, DNA Methylation, Accelerated Aging, Epigenetic Aging, Telomere Length

S82. Greater Depression Severity is Associated With Lower Frontal Brain Gaba in Women

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Background: Major Depressive Disorder (MDD) is a debilitating disorder that interferes with successful daily life and functioning, particularly in women, who have a greater prevalence of MDD compared to men. Gamma-amino butyric acid (GABA), the main inhibitory neurotransmitter in brain has been implicated in the pathophysiology of mood disorders. As prior studies have documented GABAergic alterations associated with MDD, the objective of this study was to investigate brain chemistry, using magnetic resonance spectroscopy (MRS), in women across a clinical spectrum of MDD.
Methods: Fifteen women ranging from without/past MDD (Beck Depression Inventory (BDI) score < 10) to current MDD (BDI > 10), underwent proton MRS at 3 Tesla. MEGAPRESS, optimized to detect GABA, was employed to acquire

metabolite data from separate voxels placed in the anterior cingulate cortex (ACC) region of the frontal lobe and in the mesial temporal lobe (MTL), which is functionally integrated with hippocampus. Metabolite levels were quantified using LCModel and normalized to creatine (Cr) levels.
Results: Women with a current diagnosis of MDD had significantly lower GABA/Cr levels in the ACC than women without/past MDD ($p = .044$). Higher BDI scores also were significantly negatively correlated with lower GABA/Cr levels ($p = .039$). These patterns were not evident for the MTL.
Conclusions: These data showing a relationship between greater depression severity and brain GABA are consistent with prior reports. As low GABA has been implicated in depression, these data may help elucidate underlying neurobiology of MDD in women, and potentially, responsiveness to pharmacological GABA-targeted interventions.
Supported By: NARSAD Young Investigator Grant (Sneider)
Keywords: Major Depressive Disorder, Women, GABA, ACC

S83. Mood and Anxiety Disorders Affect Brain Temporal Dynamics Evidence From EEG Microstates

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Background: EEG microstates (EEG-ms) reflect spatio-temporal dynamic brain neuronal activity, with quasi-stationary EEG global field power topographies that are typically classified into four distinct classes (coined EEG-ms A through D). EEG-ms classes have been associated with large-scale fMRI brain networks, suggesting that examining how EEG-ms characteristics relate to mental disorders may reveal how mental disorders affect brain function and dynamics.
Methods: 52 healthy controls (HC, 28 females) and 61 mood and anxiety disorder subjects (MA, un-medicated, 38 females) completed one resting-state EEG scan (8 min). EEG-ms was extracted for MA and HC and then several EEG-ms dynamic properties were examined within both groups.
Results: We did not find EEG-ms (A through D) topographic differences among HC and MA groups, nor any significant EEG-ms changes in the duration or occurrence frequency between groups. However, EEG-ms dynamic characteristics differed. Specifically, there were significant differences between groups in regards to the following transition probabilities (Tr) among EEG-ms: Tr (D → B), Tr (B → D), Tr (A → D) and Tr (B → C) (both one direction transition, $p < 0.05$, Bonferroni corrected).
Conclusions: The presence of four EEG-ms classes regardless of mood and anxiety symptoms suggests a lack of large structural cortical abnormalities. However, the lower switching frequency between EEG-ms B and D in patients suggests that mood and anxiety disorders are characterized by disruptions in the neural dynamics of signaling within the brain, especially between the Visual Network (microstate B) and Dorsal Attention Network (microstate D).
Supported By: This work has been supported by Laureate Institute for Brain Research, the William K. Warren Foundation, and by National Institute of General Medical Sciences, National Institutes of Health Award 1P20GM121312.
Keywords: EEG Microstate Analysis, Mood Disorders, Anxiety Disorders

S84. PET Quantification of Serotonin Transporter Binding in Major Depressive Disorder

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Background: We previously used PET imaging with [11C] DASB to quantify serotonin transporter (5-HTT) binding in patients with major depressive disorder (MDD) and healthy volunteers (HV), and did not observe differences as a function of MDD diagnosis. In the present study we examined this relationship in an independent cohort.
Methods: 22 healthy volunteers (HV) and 35 unmedicated patients with current MDD underwent PET imaging with [11C]DASB and T1-weighted structural MRI. We applied a hybrid deconvolution approach, and likelihood estimation in graphical analysis, in combination with an arbitrarily scaled and noninvasively-derived input function, to quantify the binding potential BPND without having to assume any reference region, an approach validated for [11C]DASB. We examined the following regions of interest (ROIs): caudate, putamen, amygdala, midbrain, thalamus, and ventral striatum, based on our earlier work and meta-analyses of 5-HTT binding in MDD. Linear mixed effects models were computed with region and diagnostic group as fixed effects and subject as the random effect; age and sex were included as covariates.
Results: [11C]DASB BPND did not differ between MDD and HV groups considering the a priori ROIs simultaneously ($p = 0.84$). [11C]DASB BPND did not differ between antidepressant-naïve and antidepressant-exposed MDD participants ($p = 0.52$).
Conclusions: We did not observe altered 5-HTT binding in our a priori ROIs in current MDD, consistent with our prior publication using the same radiotracer, despite using different modeling approaches. Future work will examine baseline clinical characteristics that may relate to [11C]DASB BPND, as well as the relationship between baseline [11C]DASB BPND and future clinical course.
Supported By: 1R01MH109326
Keywords: Depression, Serotonin Transporter, PET Imaging

S85. Individual Functional Abnormalities in the Default-Mode Network Predict Symptom Severity in Bipolar Disorder

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Background: Bipolar Disorder (BD) is characterized by episodes of mania and depression interspersed with periods of remission. This study tests the hypothesis that these clinical states are associated with alterations in dynamic connectivity of the resting-state networks (RSNs).
Methods: We collected resting-state fMRI data from 73 patients with BD, type I (35 symptomatic and 38 remitted) and 41 demographically matched healthy individuals (HI). We used the Matlab Adjusted Local Connectivity toolbox to quantify the average and the variance in dynamic regional synchrony of 13 major RSNs' BOLD signal. The data from healthy individuals were used to determine the normative mean for each measure. For each patient, we computed the degree of their individual deviation from the normative mean for the average and the variance in signal coherence of each RSN. Clustering was then applied to these data to test their relevance to clinical states in patients.
Results: Individual-patient deviation in signal coherence variance was able to separate symptomatic and remitted patients with high accuracy (74% of patients well-classified; Chi-square test: p=3.1x10-5). Further receiver operating characteristic curves analysis showed that this clustering solution predicted symptom severity with high accuracy (AUC=0.81). Separate regression analyses showed that individual-patient deviation in signal coherence variance in the posterior default-mode network (pDMN) was the best predictor, explaining 29% of the variance in overall symptom severity.
Conclusions: This study demonstrates state-related changes in dynamic functional connectivity and suggests that patient's deviation in signal coherence variance in the pDMN from normals may assist in the early detection of symptomatic relapse.
Supported By: R01
Keywords: Resting State fMRI, Bipolar Disorder-I, Cluster Analysis, Remission

S86. Dissociating PTSD and Depression Structural Neuroimaging Profiles in Veterans With Mild Traumatic Brain Injury

To see this abstract, please see Oral Abstract #O1.

S87. Depression During Pregnancy is Associated With an Altered Gut Microbiome

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Background: Antenatal depression is common among minority women and confers significant risks to mother and child (e.g., preterm birth). Despite increasing evidence linking depression to the gut microbiome, this research has not been extended to the perinatal period. Our aim was to examine gut microbial structure and composition in pregnant women with and without depression.
Methods: Sixty pregnant women (80% under-represented minorities) provided rectal swabs to assess the gut microbiome and completed the Computerized Adaptive Diagnostic Test for Major Depression Disorder (MDD) diagnostic screening tool (CAD-MDD) during the first and second trimesters. 16S rRNA amplicon sequence analysis of fecal DNA identified exact sequence variants (ESVs) that were correlated against MDD using Generalized Linear Models, corrected for false discovery rate.
Results: Rates of MDD during the first and second trimester were 15.6% and 12.2%, respectively. No significant difference in the overall microbial community composition of women with or without MDD was observed, but 55 ESVs were significantly enriched in the first trimester and 30 in the second trimester as a function of MDD (p-value<0.001). Parabacteroides and Bifidobacterium were significantly enriched in MDD patients overall, while Gardnerella was only enriched in MDD patients during the 1st trimester. Similarly, Prevotella was enriched in non-MDD patients overall, and Lactobacillus was only enriched in non-MDD patients in the first trimester
Conclusions: Our results provide new evidence that antenatal depression is associated with an altered gut microbial composition and varies with trimester. Maternal gut microbiota could serve as a future assay to detect antenatal depression in clinical settings.
Supported By: Mabel and Arnold Beckman Fundation; 1 R03 HD095056-01
Keywords: Pregnancy, Microbiome-Gut-Brain Axis, Major Depressive Disorder (MDD), Systems Biology

S88. Longitudinal Plasma GABAergic Neuroactive Steroid Concentrations in Postpartum Depression

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Background: The peripartum period involves changes in neuroactive steroids (NAS) which may be associated with postpartum depression (PPD). We previously demonstrated that women at-risk for PPD, compared to healthy peripartum women, have altered NAS profiles suggesting a shift towards 5β- reduction of progesterone to pregnanolone. In this study, we measured plasma pregnane steroid precursors and NAS in healthy comparison peripartum women (HCPW) and women with PPD with/without anxiety.

Methods: A prospective observational cohort study evaluated 53 medication-free peripartum adult women (HCPW, n=28; PPD, n=25). Hamilton Depression Rating Scale (HAM-D17), State Trait Anxiety Inventory (STAI-S) and blood assessments were completed across 5 visits. Plasma pregnenolone, progesterone, 5α- and 5β-dihydroprogesterone, pregnanolone, allopregnanolone, deoxycorticosterone and tetrahydroxycorticosterone were quantified by liquid chromatography-tandem mass spectrometry. We analyzed the longitudinal relationship between symptoms and NAS concentrations across visits using generalized estimating equation methods to control for repeated measures correlation.
Results: Peripartum 5α-dihydroprogesterone, allopregnanolone, deoxycorticosterone, and tetrahydroxycorticosterone concentrations were higher in women with PPD than HCPW (β=1.87±1.08, p=0.09; β=0.97±0.42, p=0.03; β=0.14±0.07, p=0.04; and β=0.03±0.01, p=0.01 respectively) and were weakly positively correlated with total HAM-D17 (β=0.13±0.06, p=0.05; β=0.05±0.02, p=0.07; β=0.007±0.004, p=0.09; β=0.001±0.001, p=0.02). Postpartum 5α-dihydroprogesterone, allopregnanolone and deoxycorticosterone were weakly inversely correlated with STAI-S (β=-0.012±0.005, p=0.03; β=-0.009±0.004, p=0.04 and β=-0.001±0.0003, p=0.04). No between-group differences in peripartum progesterone, 5β-dihydroprogesterone or pregnanolone were identified.
Conclusions: Between-group differences in NAS concentrations could represent differential metabolism within the progesterone-based biosynthetic pathway. Data suggest a shift towards 5α- reduction of progesterone to 5α-dihydroprogesterone, allopregnanolone, deoxycorticosterone and tetrahydroxycorticosterone in women with PPD.
Supported By: NIH 5K23MH097794-01
Keywords: GABAergic Neurosteroid, Postpartum Depression, Peripartum Depression, Mass Spectrometry, Liquid Chromatography

S89. Antenatal Depressive Symptoms are Associated With the Trajectory of Hair Cortisol Concentration Across Pregnancy

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Background: Major Depressive Disorder (MDD) is associated with altered cortisol production; however, the association between MDD and cortisol levels during pregnancy, when cortisol levels normatively increase, is less clear. The present study examines the association of MDD history and current depressive symptomatology with the trajectory of hair cortisol concentration (HCC) across pregnancy.
Methods: 57 women (M age[SD]=32.52 years[4.88]) provided hair samples in mid-pregnancy (M gestational weeks[SD]=24.55[6.02]) and/or at 4-6 weeks postpartum. During pregnancy, the CES-D and SCID were administered to assess current depressive symptoms and history of MDD, respectively. We used linear mixed modeling to examine the trajectory of HCC across pregnancy.
Results: HCC increased linearly across pregnancy (beta=.26, B=0.03, SE=0.01, t(106.64)=4.44, p<.001). The severity of depressive symptoms during pregnancy interacted with gestational week (beta=.25, B=1.61, SE=0.001, t(46.66)=2.40, p=.020), indicating the trajectory of HCC across pregnancy depended on the severity of depressive symptoms. Specifically, HCC increased more steeply across pregnancy in mothers with higher depressive symptoms (beta=0.37, B=3.88, SE=0.01, t(70.04)=4.94, p<.001) than in mothers with lower symptoms (beta=0.14, B=1.47, SE=0.01, t(76.04)=1.88, p=.063); in contrast, past MDD diagnosis was not associated with trajectory of HCC (beta=-.04, B=-0.003, SE=0.01, t(51.86)=-0.34, p=.735).
Conclusions: Our findings suggest that current depressive symptoms are more predictive of changes in cortisol production across pregnancy than is history of MDD. High levels of maternal cortisol during pregnancy may have downstream consequences for fetal brain development, indicating that antenatal depressive symptoms may affect risk for children through increased exposure to glucocorticoids in utero.
Supported By: NIMH R21; NICHD R21
Keywords: Pregnancy, Cortisol, Depression, Child Development

S90. Association of Autoimmunity With Dysfunctional Th2-Mediated Immune Response in Major Depressive Disorder

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Background: Dysfunctional T-helper 2 (Th2) cell mediated immune response, characterized by reduced interleukin 4 (IL-4), was reported recently in patients with major depressive disorder (MDD) who were enrolled in the Predicting Response to Depression Treatment study. Similarly, we found reduced levels of IL-4 in a separate sample of adolescents with MDD and recent suicide behavior as compared to healthy controls. However, the functional consequence of reduced IL-4 in patients with MDD remains unclear.
Methods: Concentration of IL-4 was measured using the Bioplex Pro™ human cytokine multiplex kit in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (n=166). Autoantibodies (immunoglobulin G) against 128 autoantigens were assayed in the same samples using a previously validated microarray panel by the Genomics and Microarray Core Facility at UT Southwestern. Spearman's correlation coefficients (rs) were calculated to test the association between IL-4 and autoantibodies.
Results: Thirty four out of 128 autoantibodies were significantly and negatively correlated (Bonferroni adjusted p <0.05) with IL-4, suggesting reduced levels of IL-4 were associated with increased levels of these autoantibodies. No

autoantibody had a significant positive correlation with IL-4. Of the 34 autoantibodies with negative correlations, β2 microglobulin (a component of major histocompatibility complex class 1 molecule) was the strongest (rs= -0.45) and aquaporin 4 was the weakest (rs= -0.27). Autoantibodies against extracellular self-antigens mostly targeted innate immune response with 12/34 autoantibodies targeting complement pathway.

Conclusions: Reduced IL-4 in patients with MDD may be associated with autoimmunity against mediators of innate immune response. Future studies should characterize aberrant adaptive-innate immune interactions in MDD.

Supported By: NIMH N01 MH-90003; Center for Depression Research and Clinical Care at UT Southwestern, Hersh Foundation,

Keywords: Autoimmunity, Interleukin-4, Major Depressive Disorder (MDD), Complement System

S91. P. Gingivalis and Cardinal Symptoms of Depression

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Background: Strong evidence implicates periodontal disease in cardiovascular and metabolic disease. Given associations between inflammation and periodontal disease, and the increasing evidence for immune-neuropsychiatric links we hypothesize that periodontal disease can also contribute to onset, exacerbation and perpetuation of mood disorders. As Porphyromonas gingivalis (P. gingivalis) is the bacteria with the highest etiological implication in periodontal disease, we hypothesized that we will identify an association between the titers for P gingivalis and clinical estimates of depression. We performed the study in the Old Order Amish, considering the poor dental health estimates, the virtual absence of smoking (a strong confounder in periodontitis) and being generally less heterogeneous in lifestyle.

Methods: We studied 642 Adult Old Order Amish participating in the Amish Wellness Study with self-reported current and ever anhedonia and dysphoria (modified PHQ2) and with plasma analyzed for with ELISAs for seven serotypes of P. gingivalis. We used logistic regression models with adjustment for age and sex.

Results: The titers for the K6 serotype were significantly associated with current dysphoria ($p<0.05$), anhedonia ($p<0.01$), current both (p,0.05) and current either ($p<0.01$). The titers for K7 serotype were significantly associated with current anhedonia ($p<0.01$), current either ($p<0.01$) , and ever either anhedonia or dysphoria ($p=0.05$). All other serotypes were not significantly related to anhedonia or dysphoria.

Conclusions: Certain P. gingivalis serotypes are significantly associated with estimates of dysphoria and anhedonia. Future studies should include longitudinal designs, clinical examinations and inflammation markers, and ideally interventions.

Supported By: Intramural

Keywords: Periodontal Disease, P Gingivalis, Anhedonia, Dysphoria, Amish

S92. Exploring the Association of BDNF, GDNF, IL-6 and IL-1β From Periphery to CNS: Relevance to Psychiatric Disorders

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Background: Brain-derived neurotrophic factor (BDNF) and glial derived neurotrophic factor (GDNF) are proteins involved in neuronal survival and plasticity of dopaminergic, serotonergic neurons in the central nervous system and in the peripheral region. Latest research evidence reveals the involvement of pro-inflammatory cytokines like IL-6, and IL-1β are implicated in the pathophysiology of psychiatric disorders. In the current study, we are screening for IL-6, BDNF, GDNF and IL-1β and in both CNS and periphery in subtypes of Psychiatric disorders.

Methods: Plasma and brain tissue from Brodmann's area 10 were collected from postmortem donations from the same individual. Normal Control (NC) (n=8, 13), Mood (MDD) (N=15, 10), MDD + SUD (N=8, 6), substance/alcohol use disorder (SUD/AUD) (N=10, 8). Samples were subjected to multiplex assay using a customized 4-plex cytokine (GDNF, BDNF, IL-6 and IL-1β) human acute phase based on xMAP technology platform. Data were collected and analyzed using a Luminex 200 instrument equipped with Milliplex-analyzing software. Spearman Rho(R) method was used to identify significant correlations $P<0.05$.

Results: We found the following correlations in Brain and Plasma subjects of NC, MDD and MDD with SUD. We found clinically significant correlations in NC, Brain-Brain IL-1; Brain BDNF to Brain IL-1β; Brain-BDNF to Plasma IL6. However, In MDD+SUD, Brain IL6- Brain IL-1, Brain GDNF-Brain BDNF; Plasma IL1β to Plasma-GDNF. In addition, MDD, Brain IL6- BrainIL1β; SUD/AUD, Brain IL6-Brain IL-1β are significant.

Conclusions: Overall we found BDNF and IL-6 were clinically significant correlations between Brain and Plasma. Both of the inflammatory markers are important in the psychoimmunology of mood disorders.

Supported By: Other-

Keywords: GDNF, BDNF, Psychiatry Disorders, Neuroinflammation, Inflammatory Cytokines

S93. Ketamine Treatment Modulates the Kynurenine and Arginine Pathways in Depressed Unipolar and Bipolar Patients

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Background: Glutamatergic and immune dysregulation are involved in pathophysiology of depression. One potential confluence of these relevant systems includes kynurenine (KP) and arginine pathways (AP). Pathological activation of the KP via the indoleamine-2,3-dioxygenase (IDO) induces microglial activation and production of exitotoxic byproducts such as quinolinic acid, thereby decreasing formation of kynurenic acid (KynA) and altering glutamate release/reuptake. In addition, two components of the AP—arginine and citrulline—are critical substrates for protein synthesis, serve as precursor to nitric oxide, shown to be downregulated in depressed patients. We explore the impact of ketamine on key components of the KP and AP in subjects with MDD, bipolar depression (BD) and healthy controls (HCs).
Methods: Data from randomized trials assessing the efficacy of single-dose ketamine (0.5 mg/kg IV) in treatment-resistant subjects with MDD, BD or HCs were included. Specific ELISA and LC-MS-based metabolomics were used to characterize components of the KP and AP at baseline, 230-min, Day-1, and Day-3 post-ketamine.
Results: Ketamine decreased IDO levels and increased kynurenine and KynA levels in BD. Lower circulating levels of citrulline and ARG were observed in MDD patients relative to HCs. Interestingly, in the MDD group, ARG levels increased significantly in ketamine responders; specifically, MDD subjects who previously responded to ketamine compared to non-responders' counterpart at 230min.
Conclusions: These results demonstrate that ketamine affects the KP and AP, both altered in patients with MDD and BD. Ketamine also modulated the bioavailability of ARG in ketamine responders, indicating that ketamine may affect the nitric oxide cycle in subjects who respond to ketamine treatment.
Supported By: Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA MH002857), by a NARSAD Independent Investigator Award to Dr. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Dr. Zarate.
Keywords: Ketamine, Treatment Resistant Depression, Kynurenine, Arginine Pathway, Bipolar Disorder, Major Depressive Disorder (MDD)

S94. Tumor Necrosis Factor Alpha in Major Depressive Disorder: Effects of Anti-Depressant Treatments

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Background: The comorbid, bidirectional relationship between mood disorders and immune system dysfunction is well documented. Many investigative efforts have sought to identify and validate a reliable biomarker for depression. This study examined TNF-α's role as a potential biomarker in depression and the effect of short-term monotherapy with Escitalopram or Quetiapine on serum TNF-α.
Methods: Depressed patients (N=33) and age-matched healthy controls (N=25) with Major Depressive Disorder, first or recurrent episode, with an index episode of at least one month received 12 weeks of monotherapy with Escitalopram or Quetiapine and were compared to the healthy controls. Psychiatric and physiological parameters, TNF-α, HAMD, HAMA, and PSS-14 were measured at baseline, and at weeks 8 and 12.
Results: Depressed patients demonstrated significantly higher average baseline levels of TNF-α (6.25, SD=11.19, p=<0.05) than healthy controls at baseline (2.19, SD=2.54). Higher baseline levels of TNF-α were not associated with poorer treatment response with Escitalopram or Quetiapine. Although TNF-α tended to decrease after 12-week monotherapy with Escitalopram or Quetiapine, the treatment did not lead to statistically significant different TNF-α levels from that of baseline.
Conclusions: Although it is well documented that depression is accompanied by a pro-inflammatory state assessed peripherally, our findings on TNF-α as a possible biomarker for depression are not in agreement with other findings in the literature. Future investigations involving larger numbers of subjects are warranted into TNF-α and long-term antidepressant use, as well as adjuvant uses of anti-TNF-α and anti-inflammatory drugs in the treatment of MDD.
Supported By: Stanley Medical Research Institute (SMRI)
Keywords: Major Depressive Disorder (MDD), Neuroimmunology, TNF, Antidepressant response, Inflammatory Cytokines

S95. Plasma MCP-1 Levels in Bipolar Depression During Cyclooxygenase-2 Inhibitor Combination Treatment

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Background: Neuroinflammation appears to play key roles in the pathophysiology of bipolar depression (BDD). Many patients diagnosed with stress-related mood disorders have altered levels of inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1, AKA CCL2). This is the first study to analyze MCP-1 levels in bipolar disorder patients treated with the cyclooxygenase-2 inhibitor, celecoxib (CBX).
Methods: In this randomized, double-blind, two-arm, placebo-controlled study, 47 patients with BDD received either escitalopram + CBX, or escitalopram + placebo. Plasma MCP-1 levels were measured at 3 times points, and in a healthy control (HC) group, using the Randox® High-Sensitivity Array

assay. Depression severity was quantified using the Hamilton Depression Scale (HAMD-17).
Results: The CBX group had significantly lower HAMD-17 scores vs. placebo at weeks 4 (P=0.026) and 8 (P=0.002). MCP-1 levels were not significantly different in BDD vs. HC subjects at baseline, nor in CBX vs. placebo groups at week 8. Week 8 HAMD-17 scores and MCP-1 levels were significantly negatively correlated in non-responders (P=0.050). Non-responders had significantly lower MCP-1 levels vs. responders at weeks 4 (P=0.049) and 8 (P=0.014). MCP-1 was significantly positively correlated with pro-inflammatory analytes in the PBO group and with anti-inflammatory analytes in the CBX group.
Conclusions: SSRI + CBX combination treatment is more effective than SSRI + placebo in reversing treatment resistance and augmenting antidepressant response. Baseline plasma MCP-1 levels are unlikely to be altered in BDD patients. Elevated MCP-1 may indicate a better response to CBX + SSRI treatment of BDD patients, lending support for a pleomorphic inflammatory role of MCP-1.
Supported By: Stanley Grant
Keywords: Neuroinflammation, Bipolar Disorder, Treatment-Resistant Bipolar Depression, MCP-1, Celecoxib

S96. Peripheral Inflammation and Resting-State Functional Connectivity in Adolescents With Mood Disorders

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Background: Research suggests that mood disorders, including depressive and bipolar disorders, are associated with heightened inflammation and dysregulated resting-state functional connectivity (RSFC). Though mood disorders typically emerge during adolescence, a notable time for brain development, the relationship between inflammatory cytokines and RSFC has not been examined in adolescents. Based on the known impacts of inflammation on brain structure and function, we predicted that elevations in pro-inflammatory markers may impact RSFC cross-sectionally and longitudinally.
Methods: Adolescents with mood disorders underwent resting-state fMRI and a blood-draw at baseline (N=24) and 6-18 months later (N=10). Measures include peripheral inflammatory markers (IL-6, IL-2) and amygdala-frontal RSFC. We tested whether baseline inflammation was related to baseline and longitudinal change in amygdala-frontal RSFC.
Results: At baseline, IL-2 was associated with higher right amygdala and right ACC RSFC (r=.487, p=.019). Longitudinally, higher baseline IL-2 was associated with a reduction in RSFC between right amygdala and right dlPFC (r=-.705, p=.034), right amygdala and right ACC (r=-.691, p=.039) and left ACC (r=-.701, p=.035). Longitudinally, higher baseline IL-6 was associated with a reduction in RSFC between right amygdala and left ACC (r=-.688, p=.028) and right ACC (r=-.669, p=.034).
Conclusions: Baseline inflammation was positively associated with baseline RSFC in one connection but conversely predicted reduced RSFC across time in multiple connections. This preliminary study highlights the complexity of the patterns, suggesting inflammation may be linked differently with concurrent and over-time alterations in amygdala-frontal functioning. The findings emphasize the value of multi-level, longitudinal research in understanding temporal links between inflammation and neural functioning in mood disorders.
Supported By: Ontario Mental Health Foundation
Keywords: Psychoneuroimmunology, Mood Disorders, Resting-State Functional Connectivity, Adolescence, Inflammatory Cytokines

S97. Celecoxib Augmentation of Escitalopram in Treatment-Resistant Bipolar Depression and the Effects on Quinolinic Acid in the Kynurenine Pathway

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Background: Treatment-resistance is high in bipolar disorder and is associated with a pro-inflammatory state and diversion of tryptophan toward the kynurenine pathway. The chronic subthreshold pro-inflammatory status in bipolar patients, especially in those whose treatment-resistance is associated with dysregulation of tryptophan metabolism favoring kynurenine pathway intermediates, may interfere with antidepressant drug effectiveness. Therefore, we hypothesized that a non-steroidal anti-inflammatory agent, celecoxib, that selectively inhibits COX-2, should attenuate or even reverse the pro-inflammatory status and thereby normalize kynurenine pathway intermediates and improve treatment outcome. We focused on quinolinic acid (QA) as the neurotoxic metabolite of the kynurenine pathway and determined whether its blood levels would differ from healthy controls and might predict treatment response.
Methods: This was a randomized, double-blind, two-arm, placebo-controlled study. Subjects who met study criteria were randomized to receive escitalopram + celecoxib, or escitalopram + placebo. Inflammation biomarkers and kynurenine pathway intermediates were determined at baseline and weeks 4 and 8.
Results: Patients receiving celecoxib were 4.13 times likelier to respond and 14.34 times likelier to experience remission. All patients had significantly lower QA at baseline compared to healthy controls (p<.0001). QA did not change significantly

over time (p = .28), but a downtrend was noted. Responders had marginally lower QA (Mean = 50.73) than nonresponders (Mean = 70.98). Factors that might have led to low QA include prior psychoactive agent exposure, related to treatment resistance.
Conclusions: Although QA did not significantly change, symptom reduction and remission occurred more frequently in the celecoxib group, demonstrating the beneficial effect of inflammation modulation.
Supported By: Stanley Medical Research Institute (SMRI)
Keywords: Celecoxib, Escitalopram, Kynurenine Pathway, Quinolinic Acid, Picolinic Acid, Bipolar Disorder, Neuroinflammation

S98. TITLE: Treatment Resistant Bipolar Depression: Effects of Inflammation Modulation on Tryptophan Utilization and Kynurenine Pathway Activation

Stephen Murata[1], Monica Castillo[1], Markus Schwarz[2], Gregor Schutze[2], Natalie Moll[2], Brendan Martin[1], Norbert Mueller[3], and Angelos Halaris[1]

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Background: In bipolar depression, the maintenance of stable clinical remission is complicated by the issue of refractoriness to pharmacologic therapy. To our knowledge, this is the first study demonstrating the efficacy of adjunctive immune modulation via Celecoxib (CBX) for treatment-resistant bipolar depressed (TRBD) patients. Here we report alterations in tryptophan utilization and kynurenine pathway (KP) activation possibly related to the molecular basis of the observed treatment response, which also shed light on the link between immune dysregulation and TRBD generally.
Methods: In this double-blind randomized control study, 47 BDD patients with sufficiently severe HAMD-17 ratings were randomized to receive either escitalopram, ESC (10mg twice/day) + CBX (200mg twice daily), or ESC (10mg twice daily) + placebo (twice daily). Plasma KP metabolite levels were measured in both treatment arms at baseline, week 4, and week 8, and in a healthy control (HC) group of subjects (N=35) once.
Results: Patients receiving ESC + CBX were 4.13 times more likely to respond (p=0.04) with NNT=3, and 14.34 times more likely to remit (p<0.001) with NNT=2, compared with ESC + PBC patients. Treatment remitters exhibited decreased tryptophan by week 8 compared to non-remitters (p=0.02), but no change in Kynurenine/tryptophan ratio by week 8 compared to non-remitters (p=0.56).
Conclusions: The robust clinical response to CBX-augmentation supports the concept that inflammation modulation is effective for TRBD. Interestingly, treatment-response to adjunctive inflammatory modulation was associated with a paradoxical decrease in tryptophan despite unchanged kyn/tryp ratio, which is an indirect biomarker for indoleamine-2,3-dioxygenase (IDO) mediated KP activation.
Supported By: Stanley Medical Research Institute (SMRI)
Keywords: Bipolar Disorder, Kynurenine Pathway, Indoleamine 2,3-dioxygenase, Tryptophan, Treatment Resistance

S99. Herpes Simplex Virus -1 Seropositivity in Treatment Resistant Bipolar Depression

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Background: Exposure to viruses, such as mumps, rubella, poliomyelitis, cytomegalovirus and herpes simplex viruses have been proposed as risk factors for the development of psychiatric disorders and may contribute to cognitive impairment. Reduced cognitive performance was correlated with HSV-1 seropositivity in patients with BD, while cognitive impairment has been associated with a pro-inflammatory state and inflammation as a possible factor in treatment resistance.
Methods: Treatment resistant Bipolar Depressed (BD) patients were treated with Escitalopram (ESC) in combination with Celecoxib (CBX) or placebo. Blood samples were analyzed at baseline and 8-weeks for seropositivity and levels of IgG class antibodies to HSV-1. This was a 10-week, randomized, double-blind, two-arm, placebo-controlled study.
Results: Non-responders to CBX and ESC combination had significantly higher levels of IgG antibodies to HSV-1 (3.26; n =4) at baseline compared to responders (1.38; n=20) (p<0.005). Furthermore, in the CBX arm of the study, out of 24 patients, 16 achieved remission and had HSV-1 IgG antibody levels of 1.10, 8 did not achieve remission and had HSV-1 IgG antibody levels of 2.27 (P<0.10)
Conclusions: Our results showed significantly elevated levels of IgG antibodies to HSV-1 at baseline in non-responders to CBX and ESC in comparison to responders. Anti-inflammatory treatment may reduce IgG levels but a longer observation interval must be tested. These findings suggest that there may be involvement of HSV-1 in the etiopathology of treatment resistant BD. Future research should be designed to elucidate associations between infective agents, such as HSV-1, pro-inflammatory states, and severe psychiatric illnesses.
Supported By: Stanley Medical Research Institute (SMRI)
Keywords: HSV-1, Bipolar Depression, Psychoneuroimmunology, Anti-Inflammatory Drugs, Antidepressant Action

S100. Elevated Matrix Metaloproteinase 9 in Treatment Resistant Bipolar Depression

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Background: Matrix metalloproteinase 9 (MMP9) is a protease that is upregulated in pro-inflammatory states. MMP9

plays a role in the restructuring of the extracellular matrix and adhesion molecules, thus increasing the permeability of the blood brain barrier and potentially having an impact on the milieu of the CNS. A growing body of evidence supports the role of inflammation in the pathophysiology of Bipolar Disorder. Several studies have shown elevated levels of pro-inflammatory cytokines in bipolar patients in comparison to healthy controls.

Methods: In this study, we sought to treat treatment resistant bipolar depressed patients, with escitalopram in combination with celecoxib or placebo. This was a 10-week, randomized, double-blind, two-arm, placebo-controlled study. Plasma samples collected from 25 bipolar patients as well as 20 healthy controls at baseline were sent out for analysis for MMP9 levels.

Results: Baseline MMP9 levels in the BD sample (n=25) were significantly higher than among the healthy controls (n=20), with P = 0.0438. At baseline, MMP9 values for bipolar patients were higher than HC with a mean of 44.19 +/-12.21 and 14.11 +/-5.314, respectively. Standard deviation was 61.07 for BD patients and 23.76 for HC. There was a significant correlation between MMP9 and anxiety and suicidality. Statistical analyses were performed with GraphPad.

Conclusions: Our results showing an elevated level of MMP9 in the plasma of BD patients in comparison to healthy controls is in line with the growing body of evidence suggesting a role of neuroinflammation in the pathogenesis of BD. The results of treatment effects on MMP9 will be presented.

Supported By: Stanley Medical Research Institute (SMRI)

Keywords: Bipolar Disorder, Inflammatory Markers, Metaloproteinase, Anti-Inflammatory Drugs, Antidepressant Action

S101. Inflammatory Response to Electroconvulsive Therapy Predicts Depression Improvement in Women, But Not Men

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Background: Electroconvulsive Therapy (ECT) is effective in treating major depression, but response is variable. Higher levels of inflammation (circulating concentration of interleukin[IL]-6) predict clinical improvement following ECT. This study further evaluates the association between inflammation and ECT response, with examination of baseline markers of inflammation, changes in inflammation across the treatment series, and exploration of sex differences.

Methods: Depressed patients (n=40; 22 females; mean age 42 years) underwent ECT, with levels of C-reactive protein (CRP), IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-a evaluated before ECT ("baseline"), after the second ECT session ("short-term"), and at the completion of the index treatment series ("long-term"). The primary outcome was percent change in Hamilton Depression (HAM-D) score from baseline to end-of-treatment.

Results: In univariate regression analyses, baseline IL-6 (p=0.02) and short-term IL-8 change (p=0.02) were significant predictors of improvement in HAM-D scores. Neither baseline nor change in the other inflammatory markers were related to HAM-D change. Interactions between sex and inflammatory markers suggested that short- and long-term IL-8 change (p=0.03 and p=0.02) predicted HAM-D improvement in females (p=0.003 and p=0.03), but not males. No other inflammatory markers interacted with sex to predict HAM-D.

Conclusions: Levels of IL-6 prior to ECT may be useful in identifying patients most likely to benefit. Additionally, short- and long-term IL-8 change was uniquely related to depression improvement in females, but not males. Sex differences in the relationships between immune markers and response to treatment requires further study; this may inform mechanisms of treatment response and aid in development of personalized medicine strategies.

Supported By: This study was supported by grants from the National Institutes of Health to Dr. Kruse (K23MH116127), Drs. Narr and Espinoza (R01MH092301, K24MH102743, U01MH110008) and to Dr. Irwin (R01-AG034588, R01AG026364, R01CA160245-01, R01CA119159, R01HL095799, R01DA032922). The research described was additionally supported by National Institutes of Health/National Center for Advancing Translational Science UCLA CTSI Grant Number UL1TR001881.

Keywords: Electroconvulsive Therapy (ECT), Inflammation, Sex Differences, Depression, Treatment Response

S102. Interleukin-6, Depressive Symptoms, and Affective Perception in Male and Female Depressed Adolescents

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Background: Depression is characterized by elevated pro-inflammatory cytokines and affective perception difficulties, yet correlations of inflammation with symptoms are inconsistent and studies in relation to affective perception are sparse. Heterogeneity of symptoms, treatment, illness morbidity, obesity, and sex differences may obscure effects, hence measuring these constructs early in the course of illness, in males and females separately, is important.

Methods: Serum interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α were measured in 70 adolescents aged 12-17, including 40 treatment naïve to any current DSM-IV depressive mood disorder (DEP, n=24 female), and 30 healthy controls (HC, n=19 female). Participants were evaluated using the Children's Depression Rating Scale (CDRS), which were factor

analyzed into symptom subscales, and the Facial Emotion Perception Test, a performance-based measure evaluating accuracy of categorizing angry, fearful, sad, and happy facial emotions.
Results: IL-6 correlated with reported depressed mood (β=1.01, p=.04), but not somatic symptom subscale (β=.66, p=.18) or total CDRS score (β=10.59, p=.134), across both DEP and HC. Additionally, DEP demonstrated lower accuracy for identifying angry facial expressions (F(1,66) 4.60, p=.04). Higher IL-6 was inversely related to accuracy for angry faces, preferentially in DEP males (β=-.71, p = .001), but not females (β=.07, p=.67). IL-6 was also inversely related to fearful faces accuracy among DEP males (β=-.51, p=.01) but not females (β=.23, p=.13). IL-1β and TNF-α were unrelated to symptoms or affective processing (all p's>.12).
Conclusions: Cumulatively, these findings implicate IL-6 as a marker of subjective mood complaints and affective dysfunction during adolescence, with potential sex-specific vulnerabilities in the latter.
Supported By: This research was designed under and supported by the National Institute of Mental Health F31 MH108258 (ATP) and the American Psychological Foundation (ATP). Additional laboratory support for the current study was also provided by R01 MH098554 (GNP). ATP is currently supported by T32 MH 112485 and the Dauten Family Center for Bipolar Treatment Innovation.
Keywords: Inflammation, Adolescent Depression, Emotion Perception, Depressive Symptoms

S103. Evidence for Vagal-Immune Dysregulation in Bipolar Disorder

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Background: One well-characterized cytokine-inhibiting mechanism, termed the inflammatory reflex, is dependent upon vagus nerve stimulation that inhibits cytokine production and attenuates inflammation. Low vagal tone was associated with increased IL-6 and TNF levels in mentally healthy adults. We attempted to assess the relationship between heart rate variability (HRV) measures and peripheral inflammatory marker levels of euthymic bipolar patients.
Methods: Forty physically healthy patients with bipolar I disorder in full remission (DSM-IV) aged 20–45 years were recruited. A lead I electrocardiogram recording was taken for 5 minutes at complete rest. Plasma levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), and soluble tumor necrosis factor receptor-1 (sTNF-R1) were measured.
Results: The levels of circulating inflammatory markers (hs-CRP, IL-6, sIL-6R, and sTNF-R1) were all not related to the activity of the autonomic nervous system (i.e. any HRV measure) in the euthymic bipolar sample. Multivariate regression showed that a lower low frequency -HRV (LF-HRV) was associated with higher BMI (β= −.40; P= .009), lower lithium dosage (β= .42; P= .005), and increasing age (β= −.25; P= .09). The regression model for association between high frequency-HRV and other variables revealed that only age (β= −.39; P= .01) remained significant.
Conclusions: It is suggested that the inflammatory reflex action of the vagally dependent anti-inflammatory pathway is not sufficient to modulate the levels of inflammation and HRV in bipolar disorder. However, decreased LF-HRV was associated with increasing age and obesity in these patients as reports of mentally healthy adults.
Supported By: Ministry of Science and Technology, Taiwan
Keywords: Bipolar Disorder, Inflammatory Markers, Autonomic Nervous System, Heart Rate Variability

S104. Impact of CD300f Immunoreceptors in Microglia Phenotype and Behavioural Alterations Relevant to Major Depressive Disorder

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Background: Regulation of microglial phenotype by immune receptors has become a central topic of interest in Psychiatry. In this context, CD300f receptors display dual activating/inhibitory signaling motifs and are highly expressed in microglia. However, their function in neuroimmune communications is still poorly understood.
Methods: Using CD300f-/- mice and a population-based study including 1110 individuals we explored the role of CD300f receptors in the fine regulation of microglial phenotype and their contribution to major depressive disorder (MDD).
Results: No significant changes in expression were found for most of the 179 inflammatory/phagocytic genes analysed in CD300f-/- versus wild-type mice. Despite the absence of neuroinflammation, CD300f-/- mice had several features of altered neuroimmune communications including increased hippocampal microglia number, possible alterations in perivascular macrophages (higher CD163 and Siglec1 expression) and increased expression of few innate mediators (Il1rn and Il6). No alterations were found in key proinflammatory mediators such as CD11b, CCL3/Mip1-alpha, CD86, Ifn-gamma, Tnf-alpha or Il1-beta). In behavioral studies, female CD300f-/- mice had persistent depressive-like and anhedonic phenotypes, lower hippocampal levels of noradrenaline and higher anhedonic behaviour after LPS administration. No behavioral alterations were observed in male mice. Importantly, in the

population-based study (n=625 controls, n=485 MDD), the T allele of CD300f receptors single nucleotide polymorphism (rs2034310 C/T) was associated to protection against MDD in women [OR=0.632 95%CI(0.457-0.874); p=0.006]. No differences in peripheral Il1-beta was observed according to genotype (p=0.559).
Conclusions: Thus, despite the absence of robust inflammation, CD300f receptors seem associated to several features of altered neuroimmune communications which might impact behavioural alterations associated with MDD.
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Keywords: Depression, CD300f receptors, Inflammation, Anhedonia, Microglia

S105. Physical and Sexual Abuse Associated With Platelet and C-Reactive Protein Response to Polysaccharide Typhoid Vaccination

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Background: Adults with a history of childhood maltreatment have been shown to have higher basal levels of inflammatory markers. When faced with an acute psychological stressor, healthy adults with a history of childhood abuse show increased inflammatory responses, but diminished activation of the hypothalamic-pituitary adrenal axis. Little is known about how adults with childhood trauma respond to an acute inflammatory challenge in the form of a vaccine.
Methods: 24 healthy adult men were recruited for this pilot study (mean age = 38, range 20-60). Subjects were given the Childhood Trauma Questionnaire (CTQ). 12 subjects were randomized to receive the polysaccharide typhoid vaccination and 12 received a placebo. Complete blood count (CBC) and high sensitivity C-reactive protein (hsCRP) were assessed prior to vaccine and at four and a half hours after vaccine.
Results: Although there was no association between total childhood abuse (CTQ range = 37-55) and hsCRP, there was a reduced hsCRP response to vaccine in individuals with higher levels of childhood physical abuse (r=-.559, p=.059) and sexual abuse (r= -.558, p=.059). Subjects with more total childhood trauma had a reduced response in platelets (r=-.665, p=.036). Lesser platelet response to vaccine was associated with higher levels of physical abuse (r=-.698, p=.036) and sexual abuse (r=-.728, p=.026).
Conclusions: Subjects with more childhood trauma, particularly sexual and physical abuse, mounted a lesser immune response to the typhoid endotoxin vaccination, evidenced by a reduced increase in platelets and hsCRP. Further research is needed to clarify the relationship between immune system dysfunction and childhood trauma.
Supported By: NIMH K01
Keywords: Neuroinflammation, Childhood Trauma, Inflammatory Markers

S106. Personality Changes in Subcallosal Cingulate Deep Brain Stimulation for Treatment Resistant Depression

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Background: Subcallosal cingulate deep brain stimulation (SCC-DBS) is a promising investigational treatment for treatment resistant depression (TRD). Previous reports suggest changes in social behavior in Parkinson's patients after DBS targeting the subthalamic nucleus. However, the impact of SCC-DBS on personality in TRD patients remains unknown. We examined changes in personality domains in individuals with TRD following SCC-DBS, and personality measures as predictors of response to DBS.
Methods: Twenty-one patients with TRD underwent SCC-DBS. Personality domains were assessed with the NEO-Five-Factor-Inventory at baseline and every 3 months for 15 months post-DBS. Depression was assessed monthly using Hamilton Depression Rating Scale (HDRS).
Results: Neuroticism significantly decreased over time ($p = 0.002$), with post-hoc tests significant from baseline to 9 months ($p = 0.002$) and baseline to 12 months ($p = .002$). Extraversion significantly increased over time ($p = <0.001$) but post-hoc tests were insignificant. Change in HDRS was correlated with decrease in neuroticism at 6 months ($r = -.71$, $p = <0.001$) and at 12 months ($r = -0.73$, $p = <0.001$), as well as with increase in extraversion at 12 months ($r = 0.58$, $p = 0.01$). Responders at 6 and 12 months had higher baseline extraversion scores than non-responders ($p = 0.001$; $p = 0.001$).
Conclusions: Our results indicate positive personality changes following SCC-DBS in terms of reduction in neuroticism and increase in extraversion corresponding to clinical improvement in depression. Pre-DBS extraversion scores predicted DBS responders. The role of personality assessment in the development of SCC-DBS for TRD needs further evaluation.
Supported By: AIHS
Keywords: Personality, Deep Brain Stimulation, Treatment Resistant Depression

S107. Transcranial Direct Current Stimulation for Depression and Risk of Treatment Emergent Mania: An Updated Meta-Analysis

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Background: Emerging evidence suggests that the use of transcranial direct current stimulation (tDCS) for the treatment of depression may be associated with increased risk of treatment-emergent mania or hypomania (TEM). While a previous meta-analysis failed to demonstrate increased risk of TEM during antidepressant treatment with tDCS, subsequent large randomized control trials (RCT) of tDCS have reported additional cases of TEM associated with active tDCS. The current study aims to provide an updated meta-analysis that re-evaluates the association between tDCS and risk of TEM.
Methods: Thirteen RCTs of active vs. sham tDCS for the treatment of unipolar depression were identified through Pubmed. The association between active tDCS and risk of TEM was investigated by constructing a fixed effect meta-analysis model (Mantel-Haenszel method with treatment arm continuity correction) and corresponding sensitivity analyses.
Results: Five RCTs reported 13 cases of TEM, with 12 in the active tDCS groups (12/411=2.9%) and one in the sham groups (1/406=0.24%). Active tDCS was associated with increased risk of TEM versus sham, with an odds ratio of 5.01 (p=0.015) and a pooled risk difference of 0.027 (p=0.026). Sensitivity analyses using alternative meta-analytic approaches yielded similar results confirming the robustness of these findings.
Conclusions: Active tDCS delivered to frontal/prefrontal regions is associated with increased risk of TEM, a safety outcome that merits consideration when designing future studies and treatment protocols of tDCS for depression.
Supported By: R25 MH101076
Keywords: Transcranial Direct Current Stimulation (tDCS), Mania, Neuromodulation, Depression, Meta-analysis

S108. Public Interest Through Web Search Trends of Neuromodulation Treatments in the United States From 2013 to 2018

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Background: Public interest in FDA-approved neuromodulation treatments has not been explored in the literature. Our aim is to compare web search trends, an indicator of public interest, of neuromodulation treatments.
Methods: Web search trends by locations of the three most commonly used neuromodulation treatments: Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS) and Vagus Nerve Stimulation (VNS), in the past five years (between 11/6/13 - 11/6/18) has from Google Trends.
Results: There was a significant difference among groups, with ECT being the most searched in neuromodulation (F=1823.24, P<0.001). ECT was most searched in Rochester MN-Mason City IA-Austin MN metropolitan; TMS mostly searched in Charlottesville VA metropolitan and VNS in Rochester NY metropolitan. There were 2 peaks in ECT web search between 10/2016-12/2016 and 4/2018-6/2018.
Conclusions: ECT still draws considerable attention in the public compared to other neuromodulation treatments. Google Trends shows great potential in obtaining public interest in neuromodulation treatment.
Keywords: Neuromodulation, Public Interest, Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation

S109. Antidepressant Effects of TDCS are Associated With Prefrontal Grey Matter Volumes at Baseline: Evidence From the ELECT-tDCS Trial

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Background: Heterogeneous responses to transcranial direct current stimulation (tDCS) as a novel treatment for major depression underline the need for deeper understanding of its mechanisms. Following the hypothesis from the Escitalopram versus Electrical Direct Current Therapy for Depression Study (ELECT-TDCS), we investigated whether the response to tDCS was associated with volumes of prefrontal and anterior cingulate cortex (PFC and ACC).
Methods: The subsample of ELECT-TDCS consisted of 52 patients (15 males). From their baseline MRI scans, we calculated voxel-based grey matter volumes of left and right PFC and ACC using state-of-the-art parcellation approaches. In the randomized controlled trial, patients were treated with escitalopram 20mg/day, bifrontal tDCS (2mA, 30min, 22 sessions), and placebo, respectively. The antidepressant response was assessed over 10 weeks of treatment.

Results: As hypothesized a priori, an association between larger grey matter volumes and antidepressant response to tDCS (n=15; compared to sham n=21) was observed in the left dorsal PFC (Cohen's d=0.3, 95% confidence interval [0.01;0.6], p=0.04). No association was observed in the ACC. In an explorative analysis, a left PFC subregion (containing Brodmann areas [BA]9 and BA10; d=0.3 [0.04;0.6], p=0.03), left BA10 (d=0.3 [0.04;0.6], p=0.02), and right BA9 (d=0.3 [0.03;0.6], p=0.03) were associated with tDCS response. No associations were observed for escitalopram or placebo.
Conclusions: The antidepressant response to tDCS was associated with grey matter volumes of specific regions in the dorsal PFC. Prefrontal cortex is a target for tDCS mechanisms and its volume should be investigated as potential neurobiological predictor of tDCS antidepressant effects. ELECT-TDCS: ClinicalTrials.gov NCT01894815
Supported By: São Paulo Research State Foundation (FAPESP) and others
Keywords: Transcranial Direct Current Stimulation (tDCS), Major Depressive Disorder (MDD), Structural Brain Imaging, Noninvasive Brain Stimulation, Antidepressant Response

S110. Is Depression an Illness of Cortical Activation?

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Background: Dysfunctional cortical excitability and inhibition have been postulated as mechanisms associated with the pathophysiology of MDD. TMS combined with electroencephalography (TMS-EEG) affords a window to directly measure evoked activity from the dorsolateral prefrontal cortex (DLPFC), Here, we present TMS-EEG evidence of alterations in the cortex contributing to our understanding of MDD and response to therapeutic brain stimulation.
Methods: 30 participants with MDD and 30 age- and sex-matched healthy participants underwent single pulse TMS-EEG to assess inhibition and excitation from DLPFC. 31 patients underwent TMS-EEG paradigms before and after rTMS. 27 patients underwent TMS-EEG paradigms before and after MST. All patients were diagnosed with TRD.
Results: MDD participants demonstrated abnormalities in inhibitory (N45 [t=24.894, p>.001] and N100 [t=23.496, p=.001]) and excitatory (GMFA-AUC [t=23.114, p=.003], P60 [t=23.260, p=.002]) TMS-EEG markers in the DLPFC. In rTMS subjects, inhibitory TMS-EEG markers decreased with treatment (N45 [t=2.975, p=0.007], N100 [t=2.177, p=0.042]). A strong correlation appeared between ΔN100 Amplitude and ÄHRSD (r = 0.63,p=0.002) in the active rTMS group. Regional waveform analysis demonstrated a change in TMS-evoked potential (TEP) after active rTMS at the site of stimulation (left DLPFC) (t=4.887, p<0.001) and in the right DLPFC (t=4.403, p<0.001). In MST subjects, N100 and LICI predicted remission of suicidal ideation with 90% sensitivity and 89% specificity.
Conclusions: As the TMS-EEG waveform and its components index inhibitory and excitatory activity from the cortex, our results suggest that MDD is associated with abnormal neurophysiological activation of the DLPFC.
Supported By: OMHF
Keywords: TMS-EEG, Major Depressive Disorder (MDD), Biomarkers

S111. A Closed-Loop Adaptive Methodology for Tracking Mood-RPE Sensitivity

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Background: Reward prediction errors (RPEs) are dopamine-encoded signals representing the difference between expected and received rewards. RPEs are fundamental to reward learning, and research conducted by Rutledge et al. (2014) demonstrated the influence of RPEs on momentary mood. Given that aberrant RPE encoding and learning have been associated with mood disorders, we developed a closed-loop mood-machine interface (CL-MMI) task in which RPEs are individually manipulated in real-time to track mood-RPE sensitivity.
Methods: We used a sample of healthy volunteers (HVs) (N=23; ages 11-17). Data of adolescents with Major Depressive Disorder (MDD) is also being currently collected. Participants completed the CL-MMI, a 60-trial gambling task in which RPE values were modified to stabilize mood around a fixed set-point (70% of the mood scale) using a proportional-integral control algorithm.
Results: Average HV ratings were close to the target set point along the task ($\bar{x}$ =645.62, SD= 146.58). However, RPE input values increased across trials, which is validated by significant differences between the average RPEs of the first three and last three trials (t(40.80) = -3.09, p=.004).
Conclusions: The present study introduces a novel task attempting to utilize RPEs to stabilize mood, which could be used to expose individual differences in RPE-mood sensitivity across time and pathology. Though HVs start from high mood ratings, greater RPEs were required to maintain HV mood around the fixed set point, suggesting the possible adaptation of mood to RPE values over time. Additional comparisons between HV and MDD participants are forthcoming.
Supported By: NIMH IRP
Keywords: Mood, Reward Learning, Adolescent Depression

S112. A Spectral Method for Determining Cortical Silent Period Induced by Transcranial Magnetic Stimulation

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Background: Transcranial magnetic stimulation (TMS) of the motor cortex performed during voluntary muscle activity produces motor evoked potentials (MEPs) followed by a period of suppression in electromyographic activity known

as the cortical silent period (CSP). The duration of the CSP can be used to measure cortical inhibition. CSP is typically determined via visual inspection or automated amplitude thresholding methods that can be affected by noisy data. We describe a new technique of quantifying CSPs using a spectral approach.
Methods: MEPs were collected from 30 depression patients pre and post either electroconvulsive seizure therapy or magnetic seizure therapy. TMS was delivered at intensities of 100%, 120%, and 140% of resting motor thresholds. The MEPs were bandpass filtered to reduce noise and then underwent sigmoidal transformation to magnify peaks and flatten out low amplitude oscillations. A time-frequency decomposition was performed on the transformed signals to allow for detection of the inhibited regions of interest. CSPs were analyzed and compared using two-way ANOVA with stimulus intensity and pre vs. post seizure therapy as analysis factors.
Results: CSPs calculated via this spectral method show a statistically significant effect of both pre vs. post therapy ($p = 0.0016$) and of increasing stimulus intensity ($p < 0.0001$). The CSPs show a linear increase across increasing stimulation intensities.
Conclusions: This study demonstrates that this spectral method of CSP quantification is a reliable approach even in MEPs with high levels of noise. Future work may include further comparison of this spectral method with current amplitude threshold-based detection methods.
Supported By: Stanley Research Foundation, Intramural Research Program
Keywords: Cortical Silent Period, Transcranial Magnetic Stimulation (TMS), Methods

S113. Do CSF Biomarkers Correlate to Brain Parenchyma in Psychiatric Disorders?

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Background: A limitation to improving psychiatric diagnoses are the lack of cost-effective biomarkers that correlate with brain parenchyma biology. Cerebral spinal fluid (CSF) is safely accessible and extensively studied, however there has been little direct comparison of biomarkers in human brain parenchyma and CSF within the same individual. In this study we measured brain level and CSF level for IL6, IL1-Beta, brain derived growth factor (BDNF), and glial cell line derived neurotrophic factor (GDNF).
Methods: CSF and brain tissue from Brodmann's area 10 were collected from postmortem donations from the same individual. Normal Control (NC) (N=10), Mood DX with AUD/SUD (MAS) (N=5), Mood DX (MD) (N=7), substance/alcohol use disorder (N=7) and Dementia (N=8). Custom Magnetic Human Premixed Multi Analyte Luminex Kits were used to measure IL-1Beta, Il-6, BDNF, and GDNF (R&D Systems, Minn. MN.). Plates were read on a Luminex 200 platform. Spearman Rho(R) method was used to identify significant correlations $P<0.05$.
Results: We found IL6 -brain to IL-Beta-brain correlation in all groups. Clinically useful significant correlations are NC, BDNF-brain to GDNF-CSF, GDNF-brain to GDNF and IL1-Beta CSF. MAS, BDNF-brain to BDNF and GDNF CSF. MD, IL1-Beta-brain to IL6-CSF and IL6-brain to IL1-Beta CSF.
Conclusions: Only IL6 brain to IL1-beta brain correlation was found to be significant in all groups. Of the CSF measures there was little overlap between groups. Suggesting they would be valid and informative markers of the brain levels.
Supported By: McKee Foundation
Keywords: CSF, Biomarkers, Interleukins, Growth Factors, Psychiatric Disorders

S114. Epitranscriptomic Blood Biomarkers to Manage Depression

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Background: Major depressive disorders are leading causes of disability worldwide, yet many people remain undiagnosed, are misdiagnosed, and/or ineffectively treated. Diagnosis relies on the clinical assessment of symptoms, and no molecular diagnostic test is available. Epigenetic events and among them RNA editing modifications have been associated with neuropsychiatric disorders and form the molecular interface between genome and environment. The aim of this study is the identification of a specific RNA editing signature in blood of depressed patients
Methods: We recruited a cohort of 400 participants. Psychiatric diagnoses were determined according to the DSM-IV. Depression evaluation was assessed with clinical tests (IDS-C; IDS-SR; MADRS, etc.). In parallel, patient's samples were drawn in PAXgene tubes and analyzed on Alcediag's proprietary RNA editing platform using next generation sequencing technology. Biomarkers measured were already described to be altered in depression in the brain like PDE8A. Gene expression analysis was performed by quantitative PCR. We generated a multivariate algorithm comprising various selected different biomarkers to detect depressed patients.
Results: A specific RNA editing signature was identified in the blood of depressed patients. Using multivariate analysis, logistic regression and machine learning approach, we develop a test with high performances: specificity 95% and sensitivity 87%.
Conclusions: The test shows that RNA editing-related blood biomarkers allow to characterize psychiatric conditions like depression and are of great interest due to their capacity to evolve along time. Epigenetic blood biomarkers could provide a more accurate and objective means of diagnosis. This test paves the way for a better management of psychiatric patients.
Supported By: FEDER France
Keywords: Epigenetic Biomarkers, Depression And Suicide, Diagnosis

S115. The Perinatal Gut Microbiome as Possible Biomarker for Psychiatric History

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Background: The gut microbiome may provide insight into a person's health status before and during the perinatal period and risk of depression and anxiety. This study investigates gut microbial composition in relation to psychiatric history and current depressive and anxiety symptoms.
Methods: Thirty pregnant women were administered the SCID to determine current and past psychiatric disorders. Subjects were followed longitudinally for depressive and anxiety symptoms over three time points across pregnancy to five to ten weeks postpartum. Fecal samples were analyzed by 16S sequencing
Results: A linear mixed model found pregnant women with psychiatric history of anxiety prior to pregnancy harbor a less rich intestinal microbial composition. Subjects with a history of anxiety have a Chao1 index, a measure of diversity within an individual's gut microbial community, that is 339 units lower than women without any history of anxiety ($p=0.01$). Similar results are found using the Shannon Index. There is a trend towards lower richness for those with history of depression and those with history of both. Those with history of anxiety were associated with certain taxa (e.g., Lentispherae) and elevated anxiety symptoms associated with certain taxa (e.g., Catenibacterium). Identified taxa have been previously associated with trauma, stress, and poorer diets.
Conclusions: Further research is needed to study diversity of gut microbial composition as a biomarker of psychiatric history as well as to identify presence or absence of certain taxa as indicators of other factors associated with risk for depression or anxiety during the perinatal period.
Supported By: Foundation of Hope, NARSAD Young Investigator, and NIMH K23
Keywords: Microbiome-Gut-Brain Axis, Perinatal Mental Health, Anxiety Disorders

S116. Attenuation of Anti-Suicidal Effects of Ketamine by Opioid Receptor Antagonism

To see this abstract, please see Oral Abstract #O19.

S117. Risk Factors for Treatment Resistant Depression

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Background: Many patients treated for major depression have a hard time achieving remission. Following is an analysis of factors that separate remitters from nonremitters obtained from a self-reported psychosocial history of patients diagnosed with major depression.
Methods: A retrospective chart review was performed on patients seen in a private psychiatric outpatient clinic. Data collected included PHQ-9 scores from every visit, medication and diagnostic history, and results of a psychosocial questionnaire taken prior to their first visit. Patients were included if they made at least ten visits and had a current diagnosis of unipolar depression. They were considered to have treatment resistance if they scored more than 5 points on the PHQ-9 at least 40% of their visits.
Results: 750 patients met criteria for inclusion in this analysis. 20% of patients were considered

treatment resistant. Items on the psychosocial history that showed significant differences between patients who responded and those who were resistant included self-rated physical health (5% of patients who rated themselves in excellent health being treatment resistant, 45% of patients in poor health) and patients who described their childhoods as abusive (40% vs 19%) or unstable (42% vs 19%). Additional significant factors included poor diet, lack of exercise, and early insomnia.
Conclusions: Several factors were identified that separate patients who respond to treatment

compared to those who do not. This longitudinal analysis of real-life patients lends further support to the benefit of modifying lifestyle factors such as diet, exercise and sleep may improve the outcome of depression treatment.
Keywords: Treatment Resistant Depression, Psychosocial History, Screening Tools, Comorbidity

S118. Neurocognition Across Mood States Among Adolescents With Bipolar Disorder

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Background: Neurocognitive dysfunction is evident among youth with bipolar disorder (BD). However, few studies have examined neurocognition across different mood states.
Methods: 151 adolescents aged 13-20 were included: 20 BD-Depressed (BD-D), 28 BD-Hypomanic/mixed (BD-M), 20 BD-Euthymic (BD-E), and 83 healthy controls (HC). Diagnoses were determined using the KSADS-Present and Lifetime Version. Symptomatic status was defined by a score of 3 or more on the Psychiatric Rating Scales for depression and hypomania. Neurocognition was assessed with 7 Cambridge Neuropsychological Tests Automated Battery subtests. A composite score was computed for each subtest. Groups were compared using ANCOVAs covarying for IQ. We hypothesized that HC would have the best and BD-D would have the worst neurocognitive scores compared to other groups.
Results: The groups differed significantly on Affective Go/No-Go (AGN) [$F(3,141)=5.54$, $p=0.001$, $\eta 2=0.11$], Spatial Span (SSP) [$F(3,143)=2.84$, $p=0.04$, $\eta 2=0.06$], Intra-Extra Dimensional Set Shift (IED) [$F(3,143)=3.90$, $p=0.010$, $\eta 2=0.08$], and Rapid Visual Information Processing (RVP) [$F(3,143)=7.614$, $p<.001$, $\eta 2=0.14$]. SSP did not survive Bonferroni's correction.

Post-hoc comparisons revealed a significant difference on RVP: HC performed significantly better than BD-E ($p=0.021$), BD-M ($p=0.012$) and BD-D ($p=0.002$). Similar results were found for IED: HC performed significantly better than BD-M ($p=0.009$). Unexpectedly, for AGN, BD-E participants performed better than HC ($p=0.002$), BD-M (0.019) and BD-D ($p=0.002$).
Conclusions: The association of symptomatic status with neurocognition in adolescents with BD depends on mood polarity and neurocognitive domain. Prospective studies are warranted in order to evaluate the impact of mood symptoms on the course of neurocognition and vice versa.
Supported By: Brain Behavior Research Foundation; Canadian Institutes of Health Research
Keywords: Bipolar Disorders, Youth, Neurocognition

S119. Electrophysiological Differences Between Individuals With Remitted Bipolar Disorder and Major Depression Compared to Healthy Controls

Ana Rita Barreiros[1], Isabella Breuklaar[1], Cassandra Antees[1], Philip Boyce[2], Philip Hazel[2], Leanne Williams[3], Gin S. Malhi[4], Mayuresh Korgaonkar[5], and **Anthony Harris**[2]

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Background: Bipolar disorder frequently presents as a series of depressive episodes prior to the appearance of the first manic or hypomanic swing. This is significant as alternate treatment approaches are indicated for bipolar disorder, however these approaches cannot be instituted in the absence of any useful diagnostic markers to identify people who are likely to develop bipolar disorder. This study examined if electrophysiological measures could differentiate individuals with major depressive disorder, bipolar disorder and healthy controls.
Methods: 25 individuals with Bipolar Disorder 1 (BD) and 25 individuals with Major Depressive Disorder (MDD) were compared with 21 Healthy Controls (HC) as part of a larger study investigating differences between bipolar disorder and major depressive disorder. An auditory oddball paradigm was used to elicit the P300 waveform. P300 peak amplitudes and correspondent latencies at Pz, CPz, P3 and P4 were analyzed.
Results: BD was significantly associated with smaller P300 amplitudes measured in the parietal cortex comparing to controls and to participants with MDD. No significant differences were found between MDD and HC.
Conclusions: The results suggest P300 abnormalities in BD when compared to MDD and HC, possibly reflecting trait-like abnormalities. However, the effects of medication on the differences are difficult to disentangle. These findings support further work in attempting to identify potential electrophysiological markers of BD to support the early identification of the disorder.
Supported By: NHMRC APP1087560
Keywords: Mood Disorders, Event Related Potentials, Bipolar Disorder-I, P300, Trait Marker

S120. Neural Effects of Acute Fluoxetine on Emotional Regulation in Depressed Adolescents

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Background: Antidepressants are often used to treat adolescent depression but the neural mechanisms underlying their action in the young brain are still poorly understood. Depressed adolescents have difficulties in regulating negative emotions, a symptom that has been associated with hypoactivation in the dorsolateral prefrontal cortex (DLPFC), a key region involved in cognitive control. The current study therefore aimed to assess the neural effects of fluoxetine on emotional regulation prior to changes in symptoms.
Methods: Thirty-one adolescents with Major Depressive Disorder were randomized to receive their first dose of fluoxetine or placebo. Participants then completed an emotional regulation fMRI task, in which they were instructed to either view negative images naturally ('maintain'), or to intentionally down-regulate negative affect ('reappraisal'). Whole-brain as well as a small-volume corrected (SVC) analysis for the DLPFC were conducted ($Z>2.3$, $p<0.05$, corrected).
Results: In the whole-brain analysis, participants on fluoxetine revealed increased activation in visual processing areas in both maintain and reappraisal conditions ($p<0.05$). In the SVC analysis, participants on fluoxetine showed increased DLPFC activation in both conditions ($p<0.05$).
Conclusions: These data suggest that fluoxetine increases the visual processing of negative images regardless of the strategies used by participants, which may reflect increased attention towards or less avoidance from such stimuli. Given the role of the DLPFC in emotional control, increased activation in this region suggests that fluoxetine could be increasing cognitive capabilities important for the regulation of emotions. This finding complements our previous work showing that fluoxetine has immediate effects on neural components relevant to the treatment of adolescent depression.
Supported By: Medical Research Council (UK). John Fell Fund (University of Oxford)
Keywords: Adolescent Depression, Fluoxetine, Emotional Regulation

S121. Amygdala Volumes Associated With Impulsivity in Subjects With Bipolar Disorder

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Background: Impulsivity represents one of the pivotal characteristics of bipolar disorder (BD). Structural magnetic resonance imaging techniques have already demonstrated a relationship between high levels of impulsivity and reduced subcortical and limbic structure volumes in subjects with cocaine abuse, depression, and borderline personality disorder. However, such relationship has not established yet in BP. The aim of this study is to investigate the relationship between impulsivity and limbic and subcortical volumes in patients with BD.
Methods: Partial correlation analyses were performed between levels of impulsivity and limbic/subcortical volumes in 67 patients with a diagnosis of BD. Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11), whereas subcortical and limbic volumes were obtained with 3T scans using FreeSurfer. Correlation analyses were corrected for age, education, number of episodes, Hamilton Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) scores. P-values were corrected for multiple comparisons.
Results: BIS-Attentional subscale showed inverse correlations with left ($r=-.57$, $P<.0001$) and right ($r=-.44$, $P<.0001$) amygdala volumes. No other significant correlations were found.
Conclusions: Since amygdala represents a crucial structure involved in the assignment of emotional valence to external stimuli and a driver of attentional resources, reduced amygdala volumes can result in reduced capability of discriminating emotionally valenced stimuli. This can lead to poor allocation of attentional resources towards relevant vs nonrelevant stimuli, which in turn can result to increase reactivity and impulsive actions.
Keywords: Bipolar Disorder, Impulsivity, Amygdala

S122. Poster Withdrawn

S123. Ketamine for Augmentation in Treatment Resistant Bipolar Depression: A Systematic Review and Meta-Analysis

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Background: Ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant effects in treatment-resistant depression (TRD). We conducted a systematic review and meta-analysis of studies evaluating the efficacy of intravenous ketamine augmentation in TRD patients with bipolar disorder.
Methods: Major databases were searched for open-label and randomized controlled trials (RCT). We calculated weighted mean difference (WMDs) for each study and random effect model was used to calculate the pooled WMDs.
Results: A total of 1442 articles were screened, 5 studies were included in the systematic review, and 4 studies (2 open-label, 2 RCTs) enrolling a total of 94 subjects (mean age 46.27±12.68 years, 69.15% females) were included in the meta-analysis. Pooled analysis from 2 RCTs showed significant improvement in depression symptoms measured with MADRS (WMD =−10.86; 95% CI −12.06,-9.67) at 40 minutes, 1 day (WMD =−11.07; 95% CI −12.28,-9.86), and 2 days (WMD =−12.03; 95% CI −13.24,-10.82) after receiving a single infusion of ketamine. There was a significant decline in YMRS scores at day 1 (WMD =-1.87; 95% CI =-2.15,-1.59) and 2 (WMD =-2.15; 95%CI =-2.43,-1.87) after ketamine infusion. Included studies also reported improvement in suicidal ideation and anhedonia after ketamine infusion. Dissociation and transient increase in blood pressure were the most common reported side effects with ketamine.
Conclusions: Limited data shows efficacy and feasibility of intravenous racemic ketamine in treatment-resistant bipolar depression. Further studies with larger sample size are required to strengthen the evidence.
Keywords: Meta-Analysis, Treatment-Resistant Bipolar Depression, Ketamine, Systematic Review

S124. Impact of CYP2C19 and CYP2D6 Genotypes on Clinical Outcomes and Side Effects in Patients Receiving Escitalopram and Aripiprazole for Major Depression: Results From the Can-Bind Cohort

Farhana Islam[1], Victoria Marshe[1], Malgorzata Maciukiewicz[1], Kazunari Yoshida[1], Raymond W. Lam[2], Glenda MacQueen[3], Benicio N. Frey[4], Roumen Milev[5], Sagar Parikh[6], Claudio Soares[7], Rudolf Uher[8], Gustavo Turecki[9], Susan Rotzinger[10], Jane Foster[10], Sidney H. Kennedy[10], and Daniel J. Mueller[1]

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Background: Antidepressants are standard treatment for major depressive disorder (MDD). Genetic variability in cytochrome P450 (CYP) enzymes influences plasma drug and metabolite concentrations. However, the effect of CYP genes on antidepressant response and side effects needs to be elucidated. The present study examines the impact of CYP2C19 and CYP2D6 status on plasma drug levels, treatment response and side effects in the CAN-BIND-1 sample (N=179), treated with escitalopram (ESC) and aripiprazole (ARI) augmentation for up to 16 weeks.
Methods: Regression models assessed the association between CYP2C19 and CYP2D6 metabolizer status and the following phenotypes: 1) plasma concentrations of drug and metabolite; 2) response (the Montgomery−Åsberg Depression Rating Scale; MADRS); and 3) side effects (the Toronto Side Effects Scale and Sex Effects Scale), after adjusting for age, sex, site, ethnicity, and baseline MADRS. Results are corrected for multiple comparisons.

Results: CYP2C19 intermediate and poor metabolizers showed increased ESC levels in the plasma at Week 2 (β=5.4; p=0.002) and decreased metabolite/ESC ratio at Week 10 (β=-0.19, p=0.002) compared to extensive metabolizers. CYP2D6 showed a nominal association with metabolite/ARI ratio at Week 16 (β=-0.11, p=0.006). In the European cohort (N=123), CYP2D6 metabolizer status was nominally associated with response to treatment at Week 16 (β=-1.25, p=0.044) with more extensive metabolizers responding to treatment than intermediate and poor metabolizers.
Conclusions: Our results demonstrate that CYP2C19 and CYP2D6 polymorphisms contribute to treatment outcome. The present findings have implications for clinical practice, as it suggests that having knowledge of a patient's CYP genotype can used to personalize and optimize pharmacotherapy.
Supported By: CIHR
Keywords: Pharmacogenetics, Escitalopram, Aripiprazole, CYP2D6, CYP2C19

S125. Subjective and Behavioral Effects of Microdoses of LSD in Healthy Human Volunteers

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Background: There have been numerous anecdotal reports that very low doses of lysergic acid diethylamide (LSD) reduce depressed mood and improve positive outlook. Yet, the effects of such "microdoses" have not been tested under double-blind, placebo-controlled conditions. As a first step, we examined the subjective and behavioral effects of single low doses of LSD in healthy adults.
Methods: Volunteers (N=20) attended four laboratory sessions during with they received placebo, 6.5μg, 13μg, or 26μg LSD in randomized order. During expected peak drug effect, they completed mood questionnaires and behavioral tasks assessing emotion processing, including i) recognition of emotional facial expressions and ii) responses to simulated social rejection.
Results: LSD dose-dependently increased ratings of "feeling" the drug, "liking" the drug, and "feeling high," in addition to dose-dependently increasing responses to the Altered States of Consciousness questionnaire. The highest dose of LSD increased vigor, elation, and anxiety on the Profile of Mood States. On the emotion recognition task, LSD enhanced participants' ability to recognize both anger and happiness. During the simulated social rejection task, LSD increased participants' desire to play again with the other players, but did not affect their perception of the degree to which they were included or excluded.
Conclusions: These findings with non-symptomatic volunteers suggest that "microdoses" of LSD have dose-dependent effects on mood and emotional behavior. These results set the stage for measuring the clinical efficacy of the drug in the treatment of depressed mood, and help to understand the expanding use of low doses of LSD in the community.
Supported By: NIDA DA02812
Keywords: Microdosing, LSD, Human Behavioral Pharmacology, Emotion Processing, Mood

S126. Pharmacological Treatments for Bipolar Disorders: Pregnancy and Newborn Outcomes

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Background: Pregnant women often stop pharmacotherapy during pregnancy. Recurrence during pregnancy from stopping treatment or as part of the natural course of illness can result in severe episodes, psychosis and increased suicide risk. The aim was to define the maternal-infant outcomes in psychotropic–treated and un-medicated women with BD compared to the outcomes of healthy pregnant women.
Methods: We conducted a prospective study of 174 mother-infant dyads. We enrolled 38 women with BD without psychotropic exposure (BD-NP), 49 with BD with psychotropic treatment (BD-P), and 87 women with neither psychotropic exposure nor major mood disorder (Comp). We assessed maternal characteristics at 20 weeks gestation and evaluated for associations with delivery and birth outcomes. We performed multiple regressions on infant outcomes with adjustment for maternal age, race, employment status, illicit drug use, and pre-pregnancy body mass index (BMI).
Results: Women with BD were more likely to be less educated, unemployed, single, and use tobacco and illicit drugs than women in the Comp group. Approximately 10% of all infants were delivered preterm. No significant differences in outcome occurred for APGAR scores <8, NICU admissions, sex or infant length. Infants of mothers with BD-NP had significantly smaller head circumferences than the other groups, adjustment for confounding variables mitigated this association.
Conclusions: The pregnancy outcomes of women with BD and healthy women were similar. The reduced head circumference of the infants of women with untreated BD may relate to differences between groups in sociodemography, proportion of female births, and possible protective medication effect of the BD treated group.
Supported By: R01-MH60335 and R01-MH07592 (PI: Wisner)
Keywords: Bipolar Disorder, Pregnancy, Treatment Outcomes, Mood Stabilizer Exposure

S127. Heart Rate Variability in Patients With Treatment-Resistant Depression and Healthy Controls After Treatment With Ketamine

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Background: Heart rate variability (HRV) has been shown to be lower in patients with major depressive disorder (MDD) and

is influenced by antidepressants. Unlike standard antidepressants, little is known about the effect of subanesthetic doses of ketamine on HRV, or whether baseline HRV is a biomarker for antidepressant response to ketamine. The present study aimed to explore this relationship.
Methods: Participants (n=26 MDD, n=22 healthy volunteers) were drawn from a double-blind, placebo-controlled crossover trial of ketamine (0.5mg/kg infusion over 40 minutes) versus saline. Photoplethysmograms were collected during 8-minute resting-state MRI scans at study baseline and 2 days post-infusion. Time-domain and frequency-domain measures of HRV were calculated using a modified version of the heartpy python module. Ketamine response was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). A linear mixed model was used to evaluate HRV changes and moderation effects.
Results: Baseline HRV did not differ between MDD and controls ($t(46) = -1.27$, $p = .21$), and no effect of ketamine on HRV was observed at two days post-infusion ($t(33) = 0.27$, $p = .79$). At 1 day post-treatment, baseline HRV did not significantly moderate treatment response ($t(36.1) = 0.40$, $p = .69$). The inclusion of body mass index, sex, and age as covariates did not change the pattern of results.
Conclusions: Neither HRV alterations in MDD nor an association between HRV and antidepressant response to ketamine were found. The stability of HRV in this sample suggests that any potential autonomic effects of ketamine do not persist 2 days post-treatment.
Supported By: NIMH Intramural Research Program
Keywords: Major Depressive Disorder (MDD), Ketamine, Heart Rate Variability

S128. Expectancy and Ketamine's Rapid Antidepressant Effect: A Meta-Analysis

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Background: The role that expectancy plays in response in clinical trials involving ketamine has received little attention. We hypothesized that single dose intravenous ketamine protocols would be associated with increased immediate depressive symptom reduction relative to multiple dose protocols due to a trial design mediated expectation of rapid symptom change.
Methods: In this systematic meta-analysis, we searched MEDLINE for randomized and single-arm studies using intravenous ketamine as the investigational agent, yielding 30 relevant studies (single dose: k= 20, N= 406; multiple dose: k= 10, N= 173). Analyses were performed using Comprehensive Meta-Analysis 3.0. The primary outcome was change in depression severity approximately 24 hours following initial exposure to ketamine.
Results: Contrary to our a priori hypothesis, there was no significant difference in the measured improvement with ketamine from baseline whether subjects expected to receive one (SMD = 1.64, 95% CI: 1.30-1.97, z=9.6, p<0.001) or multiple (SMD = 1.76, 95% CI: 1.04-2.45, z=4.9, p<0.001) ketamine treatments (test for subgroup differences χ^2=0.1, df=1, p=0.76).
Conclusions: Our results suggest that treatment expectations putatively shaped by number of expected ketamine infusions do not affect ketamine's rapid antidepressant properties in the 24-hour period following initial exposure. It is important to note that this study did not directly investigate how dose design impacted treatment expectations. Instead, the design assumed that dose frequency would shape expectations, which would affect short-term response. More direct measures of expectancy are necessary to better understand its role in ketamine response.
Keywords: Ketamine, Expectancy, Trial Design, Non-Specific Effects, Rapid Anti-Depressant Effect

S129. The Hamilton Depression Rating Scale Measures Side Effects and Thereby Underestimates the True Antidepressant Effect of SSRIs and SNRIs

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Background: Previous studies have shown poor efficacy of selective serotonin reuptake inhibitors (SSRIs) with respect to certain items of the 17-item Hamilton Depression Rating Scale (HDRS-17). The objective of this study was to explore if this outcome may be explained by the HDRS-17 capturing common side effects of the studied drugs.
Methods: Data from seven placebo-controlled trials of duloxetine (n = 2,517), some also including an SSRI arm, were pooled in an individual patient-level meta-analysis. Patients were stratified according to whether or not they had reported side effects related to sleep, somatic anxiety, gastrointestinal function, sexual function or weight loss at endpoint. Efficacy was assessed I) on the HDRS-17, II) on the depressed mood item or the core depressive symptoms captured by the unidimensional HDRS-6 subscale, and III) on HDRS-17 items putatively reflecting side effects.
Results: When compared to their absence, the presence of side effects as described above was associated with higher sum scores on the HDRS-17 (beta = 1.27 (0.28), $p < .0001$), but did not affect HDRS-6 (beta = 0.23 (0.17), $p = .17$) or depressed mood (beta = 0.05 (0.05), $p = .26$) ratings.
Conclusions: The sum rating of HDRS-17 as a measure of antidepressant efficacy is contaminated by the fact that this instrument record common side effects of SNRIs and SSRIs as symptoms of depression. The use of the HDRS-17 sum score as outcome measure in research and in clinical practice thus likely results in a significant underestimation of the efficacy and effectiveness of SSRIs and SNRIs.
Keywords: Antidepressant Response, Depression, Psychometrics, Side Effects

S130. Synergistic Action of Aripiprazole and Escitalopram Potentiates Medial Prefrontal Cortical Activity Through Blockade of 5-HT2B Receptors

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Background: Using serotonin (5-HT)-2B receptor KO mice, previous research has demonstrated that 5-HT2BRs contribute to the antidepressant-like response. Several partial serotonin-dopamine agonists (i.e. aripiprazole; previously known as atypical antipsychotics) that exhibit high affinity antagonism at the 5-HT2BR have been successfully used in combination with selective-serotonin reuptake inhibitors (SSRIs) in treatment-resistant depression. However, the exact contribution of the antagonistic action of aripiprazole on 5-HT2BRs in the context of adjunct therapy is not known.
Methods: In-vivo electrophysiological recordings of ventral tegmental area (VTA) dopamine (DA) neurons and medial prefrontal cortical (mPFC) pyramidal neurons were conducted in anaesthetized Sprague-Dawley rats.
Results: Although firing activity of DA neurons was not altered, acute administration of the 5-HT2BR agonist BW723c86 (6 mg/kg, i.v.) decreased their bursting activity (N=7, p=.038), which was abolished by pre-administration of the selective 5-HT2BR antagonist RS127445 (2 mg/kg, s.c). After two days, the escitalopram-induced (10 mg/kg/day via osmotic minipump) decrease in DA firing activity (N=3, p<.001) was rescued by co-administration of the selective 5-HT2BR antagonist LY266097 (0.6 mg/kg/day, i.p.). While escitalopram and aripiprazole (2 mg/kg/day, s.c.) administered alone for 14 days had no effects on mPFC pyramidal neuron firing and bursting activity, their combination significantly increased these parameters (N=5, p<.001). Interestingly, the addition of LY266097 for the last 3 days of a 14-day escitalopram treatment, resulted in an increase of pyramidal neuron activity similar to aripiprazole addition (N=4, p<.001).
Conclusions: Through 5-HT2BR blockade, adjunct therapy with aripiprazole rescues an SSRI-mediated decrease in DA activity in the VTA and synergistically potentiates pyramidal neuron activity in the mPFC.
Supported By: Ontario Brain Institute
Keywords: Atypical Antipsychotics, Selective Serotonin Reuptake Inhibitors, Treatment Resistant Depression, Psychopharmacological Treatment, Electrophysiological Single Unit Recordings

S131. Repeated but not Acute Administration of Ketamine Maintained the Enhanced Activity of Dopamine and Norepinephrine Neurons in Rats

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Background: A single infusion of ketamine has rapid antidepressant effect, although the drawback is a lack of sustained effect. Our previous study showed a rapid enhancement (within 2 hours) in ventral tegmental area (VTA) dopamine (DA) neurons population and locus coeruleus (LC) norepinephrine (NE) firing and bursting activity following a single ketamine administration. The current study investigated whether these changes are present 24 hours after a single administration and if they are maintained with repeated administration.
Methods: Ketamine (10mg/kg, i.p.) was administered to male Sprague Dawley rats once or repeatedly (3 times/week) for 2 weeks. After single and repeated administration of ketamine, electrophysiological recordings were done in the VTA and LC in anesthetized rats, 24 hrs, 3 or 7 days post-administration. Spike frequency, bursting, and for VTA neurons, spontaneously active neurons/trajectory were assessed.
Results: In the VTA, the previously observed increase in number of DA neurons/tract was no longer present 24 hrs after ketamine was injected acutely, but persisted with repeated injections (N=5, p=0.02). Although there was no increase in DA neurons bursting 24 hrs after a single ketamine injection, this was enhanced following repeated administration. This bursting activity persisted after 3 days but dissipated after 7 days (N=5, p=0.03). In LC, there was an increase in spike frequency of NE neurons observed 24 hrs following repeated administration (N=5, p<0.001), but dissipated after 3 days (p<0.001).
Conclusions: These results indicate that repeated but not acute administration of ketamine maintained the increase in population activity of DA neurons and firing activity of NE neurons.
Supported By: CAN-BIND, OBI
Keywords: Ketamine, Dopamine, Norepinepherine, Electrophysiology

S132. Peripheral Signature of Response to Electroconvulsive Seizure in a Murine Model of Anxiety/Depression

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Background: Despite the proven efficacy of antidepressants to treat depressive disorders, around 30% of patients develop treatment-resistant depression (TRD), for which Electroconvulsive Therapy remains the standard treatment. The design of predictive markers of response to treatment, is therefore of major interest. Our aim is to highlight a predictive peripheral signature of the response to electroconvulsive seizure (ECS) in a mouse model of anxiety/depression, based on a proteomic analysis in blood mononuclear cells (PBMC).
Methods: In C57BL/6JRj mouse, an anxio/depressive type phenotype is induced by a 4-week treatment with CORTicosterone (35 μg/ml in drinking water for 4 weeks), to then study the effects of a 4-week treatment with fluoxetine (18mg/kg/d). Non-responder animals to fluoxetine are then subjected to 6 courses of ECS for 2 weeks. At each stage, the emotional behavior is evaluated using a battery of tests allowing the establishment of an Emotionality Score.
Results: Chronic CORT induced an anxio/depressive phenotype in mice, characterized by an increase in Emotionality score (p<0.01 vs. control). Chronic treatment with fluoxetine caused a decrease in this score (p<0.01 vs. CORT). However, around 30% of mice did not respond to fluoxetine (p<0.01 vs. responder mice), for which ECS allowed a reduction in their

score ($p<0.01$ vs. pre-ECS score). Proteins extracted from PBMCs in these mice, pre- and post-ECS, were assayed by mass spectrometry. A panel of 33 proteins were associated with the response to ECS ($p<0.05$).
Conclusions: These preclinical studies suggest a panel of biomarkers associated with ECS response.
Supported By: Fondation de France
Keywords: Electroconvulsive Therapy (ECT), Antidepressant Response, Mouse Model, Treatment Resistant Depression, Biomarkers

S133. AGN-241751, an Orally Bioavailable Positive NMDA Receptor Modulator, Exhibits Rapid and Sustained Antidepressant-Like Effects in Rodents

Pradeep Banerjee[1], John Donello[1], Yong-Xin Li[1], Kirk Bertelsen[1], Yuan-Xing Guo[1], Xiao-Lei Zhang[2], Patric Stanton[2], Roger Kroes[3], Amanda Gross[3], and Joseph Moskal[3]

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Background: Rapastinel, a positive N-methyl-D-aspartate receptor (NMDAR) modulator, produces rapid and sustained antidepressant effects in patients with major depressive disorder (MDD) but is administered intravenously. AGN-241751, an orally bioavailable compound with rapastinel-like properties, may offer an alternative route of drug administration. This study characterized AGN-241751's preclinical pharmacology.
Methods: NMDAR-mediated activity was measured in hNR2A-D subtype-expressing HEK cells ([3H]MK-801 potentiation assays), cultured rat brain cortical neurons (calcium imaging), and rat hippocampal and/or medial prefrontal cortex (mPFC) slices (electrophysiology assays). Pharmacokinetics were evaluated in rats following oral administration. Antidepressant-like effects were assessed in the rat forced swim test (FST).
Results: AGN-241751 (1 fM-0.1 μM) increased [3H]MK-801 binding (35-78%; EC50, 0.1 pM-0.6 nM). AGN-241751 and rapastinel similarly modulated NMDAR activity in cortical neurons, but AGN-241751 was 30X more potent. Low AGN-241751 concentrations (0.3-10 nM) with 10 μM NMDA, but not AGN-241751 alone, potentiated NMDA-induced calcium signal by ~30%. Like rapastinel, NMDAR modulation was independent of the glycine site. Following a single oral dose, AGN 241751 dose dependently enhanced metaplasticity in hippocampal and mPFC slices; effects were sustained for $\geq$1 week postdose. Oral bioavailability was high, with dose proportional increases in plasma, cerebral spinal fluid, and brain exposure (0.003-10 mg/kg). In FST, a single oral AGN-241751 dose (3-100 μg/kg) produced dose-dependent and rapid antidepressant-like effects for up to 2 weeks.
Conclusions: AGN-241751, a novel positive NMDAR modulator, produced rapid and sustained antidepressant-like effects following oral administration. AGN-241751 has progressed through early development safety studies and is currently in phase 2 clinical testing in patients with MDD.
Supported By: Allergan plc.
Keywords: Electrophysiology, Major Depressive Disorder (MDD), NMDA Receptor, Rapastinel, Pharmacokinetics

S134. Glucocorticoid Receptor Signaling and Cognitive Dysfunction in the Rat Chronic Mild Stress Model: Restorative Effects of Prolonged Lurasidone Treatment

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Background: Stress and glucocorticoids play a pivotal role in psychiatric disorders. The aim of the present study was to characterize the involvement of glucocorticoid receptor (GR) signaling in the behavioral alterations of rat exposed to chronic mild stress (CMS) and to investigate the ability of lurasidone treatment in normalizing the behavioral and molecular changes produced by CMS.
Methods: Adult male Wistar rats were subjected to CMS for 7 weeks and received vehicle or lurasidone after the initial 2 weeks. During the 7 weeks stress protocol rats were tested for anhedonia and, at the end of the CMS procedure, animals were exposed to the novel object recognition (NOR) test, before being sacrificed for the dissection of the brain regions for the molecular analyses.
Results: Exposure to CMS produced an anhedonic phenotype and a significant cognitive impairment, which were normalized by chronic lurasidone treatment. Within the dorsal hippocampus, CMS rats show altered subcellular localization of GR protein levels, with an elevation in the membrane compartment. Moreover, exposure to the NOR test increased the nuclear translocation and transcriptional activity of GRs in control animals. Interestingly such mechanisms were impaired in stressed rats, but they were restored by lurasidone treatment.
Conclusions: Our results suggest that exposure to CMS produces complex changes in GR function and signaling, which may contribute to the behavioral abnormalities observed in stressed rats. The ability of chronic lurasidone to normalize such modifications provides further support to its efficacy in restoring key mechanisms relevant for different pathologic domains of mental disorders.
Supported By: This project was supported by funding from Sumitomo Dainippon Pharma Co.
Keywords: Cognitive Deficits, Lurasidone, Glucocorticoid Receptor, Dorsal Hippocampus, Chronic Stress

S135. Stress-Sensitive Antidepressant-Like Effects of Ketamine in the Mouse Forced Swim Test

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Background: Major depression is a stress-linked disease with significant morbidity worldwide. The anesthetic drug ketamine is of growing interest in depression treatment since in responsive individuals a single dose has rapidly acting (i.e., within hours) antidepressant effects that can be sustained for at least a week. This combination of fast action and a

therapeutic effect that lasts far beyond the drug's half-life points to a unique mechanism of action. In this reverse translational study, we investigate how and whether the well-documented effects of ketamine in rodents are sensitive to the stress state of the animal.

Methods: Male C57BL/6J mice (n=8 per stress/drug condition) were given a single injection of vehicle (0.9% saline; i.p.), 10 mg/kg ketamine, or 30 mg/kg ketamine, and were tested in the forced swim test (FST) 24 hours and 7 days later, as well as in the open field test on the eighth day. Unstressed mice had normal group housing, environmental enrichment, and experimenter (5 days) pre-handling, whereas stressed animals were subjected to chronic mild stress, including two-week unpredictable chronic stress (UCS).

Results: Ketamine (24 hours post-injection) increased immobility and decreased swimming behavior (depression-like effects) in unstressed animals and did the opposite in UCS animals (stress x drug interaction: $F(4,59) = 3.42$, $p < 0.05$), where these opposing effects are similar to recent human findings.

Conclusions: Chronic stress interacts with ketamine to modulate its effects in the C57BL/6J mouse FST, which reinforces the relevance of this test, and this strain of mice, to human, stress-induced depression.

Supported By: NIH K08 MH107662, Neuroscience Fellows at the University of Michigan, Frances and Kenneth Eisenberg Scholar Award, University of Michigan Kavli Postdoctoral Enrichment Program

Keywords: Ketamine, NMDA Antagonists, Forced Swim Test

S136. Is Ketamine Metabolism to Norketamine and (2R,6R)-HNK Necessary for its Sustained Antidepressant-Like Activity and Cortical Neurotransmitter Release in Mice?

Thi Mai Loan Nguyen[1], Celine Defaix[1], Indira Mendez-David[1], Thu Ha Pham[1], Jean-Philippe Guilloux[2], Isabelle Etting[3], Jean-Claude Alvarez[3], Josephine C. McGowan[4], Denis J. David[1], Christine A. Denny[4], and **Alain Gardier**[1]

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Background: Ketamine exhibits a rapid and persistent antidepressant (AD) activity, at sub-anesthetic doses in treatment-resistant depressed (TRD) patients and in preclinical studies in rodents. Recent reports suggested that the metabolism of ketamine is essential for antidepressant-like activity. We recently showed that a systemic or intracortical administration of (2R,6R)-hydroxynorketamine, (2R,6R)-HNK displays a sustained AD-like effect and activates glutamate and GABA release by pyramidal neurons and interneurons, respectively in the medial prefrontal cortex (mPFC) (Pham et al., 2018). This metabolite is formed in the liver following a systemic ketamine administration. Here, acting on hepatic cytochrome P450 (CYP) enzymes, we assessed whether metabolism to norketamine - (2R,6R)-HNK is necessary or sufficient to induce behavioral and neurochemical changes.

Methods: A non-selective CYP inhibitor, fluconazole (10 and 20 mg/kg i.p.) was given before ketamine (10 mg/kg, i.p.) in BALB/Cj mice. The forced swim test (FST), mPFC 5-HT, glutamate, GABA extracellular levels, plasma and brain mPFC tissue concentrations of ketamine, norketamine and (2R,6R)-HNK were tested 24 hours later (t24h).

Results: We showed that fluconazole pre-treatment dose-dependently blocked ketamine antidepressant-like activity in the swimming duration (FST) at t24h, but increased plasma concentrations of norketamine and (2R,6R)-HNK.

Conclusions: CYP450 enzymes inhibited by fluconazole (mainly CYP2C19, CYP3A4 and CYP2C9) do not exert a major role in metabolizing ketamine in BALB/Cj mice. The activity of other CYP450 isoforms likely became the dominant microsomal active enzymes (N-demethylation with CYP2B6; hydroxylation with CYP2A6, CYP3A5, CYP2B6. Following a single sub-acute ketamine dose, norketamine and (2R,6R)-HNK are unlikely to support the sustained antidepressant-like activity of the parent drug.

Keywords: Ketamine, Antidepressant, CYP Inhibitor, Glutamate Release, BALB/Cj Mice

S137. Long-Term Effects of Vortioxetine (Lu AA21004) on Adult Hippocampal Neurogenesis Prevents Reinstatement of Anxiety/Depression-Like Phenotype in Mice

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Background: Maintenance of antidepressant treatment in Major Depressive disorder (MDD) patients is often referred to as prophylaxis against the development of additional depressive episodes. Whether this prophylactic effect against symptomatic episodes prevents de novo psychiatric disorders remains to be tested. Using a mouse model of depression, we tested whether a chronic vortioxetine treatment a novel antidepressant could increase stress resilience and prevent anxiety/depression phenotype relapse.

Methods: Using chronic corticosterone (CORT) −induced anxiety/depression-like phenotype in male C57Bl/6J mice, we first tested whether a 4-week vortioxetine or fluoxetine treatment induced antidepressant-like activity in different behavioral paradigms. Then, 3 weeks after vortioxetine or fluoxetine withdrawal, we assessed prevention of anxiety/depression phenotype relapse. One-way ANOVAs was applied as appropriate, followed by Fisher's PLSD post-hoc test.
Results: Following determination of an emotionality score, using complementary behavioral analysis of anxiety/depression across behavioral tests, we showed that, similarly to fluoxetine, chronic vortioxetine −induced antidepressant-like effects, reduced also emotional behavior in CORT-treated animals even after a 3-week withdrawal. Interestingly, in the NSF, a neurogenesis-dependent paradigm, unlike fluoxetine, chronic vortioxetine treatment induced long lasting anxiolytic/antidepressant-like phenotype. Finally, evaluating hippocampal plasticity and adult hippocampal neurogenesis (AHN), we showed that unlike fluoxetine, vortioxetine still corrected chronic CORT −induced decrease in proliferation in the subgranular zone of adult hippocampus and decrease in dentate gyrus volume after a 3-week withdrawal.
Conclusions: Thus, vortioxetine improved synaptic plasticity, including AHN, longer than fluoxetine and could be an excellent candidate for a plausible approach to pharmacologically increasing stress resilience and prevent MDD relapse.
Supported By: Lundbeck INc.
Keywords: Antidepressant, Neurogenesis, Relapse Prevention, Animal Model, Hippocampal Volume

S138. Diagnosis-Independent Loss of T-Cell Costimulatory Molecules, CD27 and CD28, in Individuals With Cytomegalovirus Infection

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Background: Major Depressive Disorder (MDD) is associated with physiological changes that are commonly observed in elderly populations, such as inflammation and impaired immune function. Aging of the immune system (immunosenescence) is characterized by the loss of naïve T-cells and the reciprocal accumulation of memory T-cells together with the loss of co-stimulatory molecules on T-cells, impairing adaptive immunity. This study tested whether MDD influences age-related reduction of T-cell costimulatory molecules in the context of cytomegalovirus (CMV) infection.
Methods: In volunteers with a DSM-IV diagnosis of MDD (n=72, mean age=35.8(10.2), 76.4% female, 61.1% CMV+) and comparison controls (n=100, mean age=34.4(10.6), 69.0% female, 52.0% CMV+), CMV IgG antibody status was determined by immunosorbent assay. Flow cytometry on PBMCs was used to quantify the frequency of CD27-CD28- cells within CD8+ T-cell subsets, i.e. naive (CCR7+CD45RA+), effector memory (CCR7-CD45RA-), central memory (CCR7+CD45RA+) and terminally differentiated effector memory (CCR7-CD45RA+).
Results: ANCOVA models controlling for age and sex showed that CMV seropositivity was associated with a greater frequency of CD27-CD28- cells (p's<0.01) within all four CD8+ T-cell subsets. Neither diagnosis, nor its interaction with CMV serostatus, was significant.
Conclusions: We find an association between CMV infection and age-related T-cell phenotypes but no significant effect of MDD. Reduced CD8+ cytotoxicity and proliferative response has been reported previously in MDD populations but without evaluating the effect of CMV. Since depression is associated with risk factors for CMV, such as low socioeconomic status, and early-life stress, this study highlights CMV's importance as a cofactor in comparative studies of T-cell function.
Supported By: NARSAD
Keywords: Major Depressive Disorder (MDD), T-cell, Immunosenescence, Herpes Virus, Accelerated Aging

S139. 1/f Neural Noise Predicts Outcome to Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression

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Background: Identifying reliable biomarkers to guide patient selection for deep brain stimulation (DBS) in treatment resistant depression (TRD) is critical to improve outcomes. One such marker may be electrophysiological: increased neural noise indicating a shift in excitatory/inhibitory balance and measured by flattening of the 1/frequency (f) slope of the power spectrum. We investigated whether alterations in subgenual cingulate (SCC) neural noise predicted 6-month outcome in SCC-DBS for TRD.
Methods: Intracranial local field potential (LFP) recordings from SCC implanted and externalized DBS electrodes were obtained in 14 TRD participants, in the days after surgery before DBS activation. The 1/f slope was extracted from the broadband power spectrum (3-50Hz), using an automated algorithm (Fitting Oscillations & One-Over F (FOOOF)). Depression severity was evaluated using Hamilton Depression Rating Scale (HDRS) and response was defined as 48-50% change from baseline.
Results: Flatter 1/f slope within the left SCC neural signal significantly predicted response at 6 months post-DBS

(F=18.20, p=0.001) and correlated with improvement in total HDRS (r=-0.743, p=0.006), specific to improvement in mood, sleep and somatic symptoms. A similar but non-significant trend was noted in the right SCC.
Conclusions: Aperiodic neural noise within the SCC might be a promising response biomarker for SCC-DBS in TRD. Increased neural noise in responders could indicate a shift towards excitation in the SCC via a loss of inhibitory function. DBS may reset excitatory/inhibitory balance through inhibition of SCC in responders. The predictive and mechanistic aspects of non-oscillatory neural noise should be explored further in DBS studies for TRD.
Supported By: Alberta Innovates: Health Research
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Local Field Potentials, Subgenual Anterior Cingulate Cortex, Biomarkers

S140. Neurophysiological Data Improves the Prediction of Treatment Outcome in Older Adults With Depression

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Background: Non-response to antidepressant treatment is a common problem in older adults with depression. Treatment decisions stand to benefit from the use of objective, brain-based measures in predictive models. Transcranial magnetic stimulation (TMS) can non-invasively probe numerous physiological characteristics of the human cortex, yet the ability of these characteristics to predict treatment outcome remains unknown.
Methods: TMS measures of cortical excitability, inhibition and plasticity were collected, together with demographic and clinical data, in 76 older adults with depression (27M/49F, 67±7 years of age) prior to 12 weeks of venlafaxine treatment. Features of interest were selected using a genetic algorithm. Support vector machine (SVM), k-nearest neighbors, random forest and logistic regression models were used to predict responders (30) and non-responders (46) to treatment. Model performance was assessed using cross-validation.
Results: SVM consistently outperformed the other classifiers. Predictive features included age, treatment resistance, depressive symptom severity, cortical inhibition, and the magnitude and variance of cortical excitability. Using only demographic and clinical features, SVM predictive accuracy was 61±11% (60% sensitivity, 63% precision). When TMS features were also included in the model, accuracy improved to 76±10% (75% sensitivity, 79% precision). Classification accuracy was significantly greater when TMS and demographic/clinical data were combined, as compared to demographic/clinical data alone.
Conclusions: Indices of cortical excitability, together with standard clinical and demographic information, are predictive of a therapeutic response to venlafaxine in older adults with depression. As psychiatry transitions towards precision medicine, TMS can be a cost effective tool to improve our ability to predict treatment response.
Supported By: CIHR, NIH & Brain and Behaviour Research Foundation New Investigator Award (DMB)
Keywords: TMS, Late-Life Depression, Machine Learning, Prediction of Treatment Outcome, Cortical Excitability

S141. The P300 Event-Related Potential in Bipolar Disorder Compared to Healthy Control: A Systematic Review and Meta-Analysis

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Background: Neurophysiology enables us to measure functional dynamics of the human brain and can be useful towards elucidating the pathophysiology of bipolar disorder (BD). Specifically, P300 may be a biological marker for BD. However, previous findings from P300 studies have been inconsistent due to the heterogeneity of research methods, which make it difficult to understand the neurobiological significance of P300 in this disorder. The aim of this study is to conduct meta-analyses on P300 indices in patients with BD.
Methods: We conducted a literature search using PubMed to identify studies that compared P300 event-related potential between patients with BD and healthy controls (HCs). We analyzed P300 indices such as amplitude and latency of P3a and P3b in auditory or visual paradigms. Further, moderator analyses were conducted to investigate the influence of patient characteristics (i.e. history of psychosis, diagnostic subcategories [BD-I/BD-II], and phase of illness [euthymic, manic, or depression]) on P300 indices.
Results: Out of 124 initial records, we included 30 articles (BD: N = 1331; HC: N = 1818). Patients with BD showed reduced P3a and P3b amplitude in both

paradigms and delayed P3b latency in auditory paradigms compared to HCs. There was no influence of history of psychosis, type of diagnosis, or phase of illness on P300 indices.
Conclusions: This meta-analysis provides evidence for P300 abnormalities in patients with BD in comparison with HCs. Our results suggest that all P300 indices may be trait markers rather than state markers in this illness.
Keywords: Bipolar Disorder, Event-Related Potentials, P300, Trait Marker, Cognitive Deficits

S142. Personality Traits and the Course of Bipolar Disorder Symptoms Among Young Adults: Cross Sectional and Prospective Approaches

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Background: Cross-sectional studies have examined personality traits in individuals with Bipolar Disorder (BD), but few studies have simultaneously examined their impact on long-term outcomes. Thus, we focused on determining whether the personality constructs of low self-esteem and suicide proneness affected suicidal ideation over time among individuals with BD.
Methods: We first compared low self-esteem and suicide proneness assessed via the Schedule for Non-adaptive and Adaptive Personality-2 among participants with BD in the Course and Outcome of Bipolar Youth study (n=49) and a newly recruited group of healthy controls (HC) with no history of psychiatric disorders (n=56). Focusing next on individuals with BD only, we examined whether these personality traits predicted suicidal behavior assessed three times over a 1.5-year follow-up.
Results: We found that BD participants had lower self-esteem (LSE), $F(1, 104) = 28.35$, $p < .001$, $\eta 2 = .22$, and suicide proneness (SP), $F(1, 104) = 37.63$, $p < .001$, $\eta 2 = .27$, compared to HCs at baseline. We also found that LSE, $F(1, 43) = 8.24$, $p = .006$, $\eta 2 = .16$, and SP, $F(1, 43) = 41.04$, $p < .001$, $\eta 2 = .49$, predicted suicidal ideation during follow-up. LSE, $\beta = .05$, Wald = 3.94, $p = .05$, and SP, $\beta = .07$, Wald = 14.19, $p < .001$, also predicted shorter time until occurrence of suicidal ideation during follow-up.
Conclusions: Pending replication, these findings provide exciting initial evidence for the role of specific personality-related vulnerabilities in the course of BD symptoms.
Supported By: R01MH087513
Keywords: Suicidal Ideation, Personality, Bipolar Disorder, Self-Esteem

S143. Poster Withdrawn

S144. Obesity is Associated With Anhedonia Only in the Younger Amish Women

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Background: We recently reported a significant gender-specific association between obesity and cardinal symptoms of depression; (i.e., anhedonia and dysphoria/hopelessness) in the Amish women, but not in men. Having in mind possible hormonal mediation of those differences, we further investigated these associations stratified by age-groups approximating the pre- versus post-menopausal divide.
Methods: Data on current and past symptoms of depression, i.e., anhedonia and dysphoria/hopelessness (by PHQ 2) and obesity status were obtained in 2,627 Old Order Amish women enrolled in the Amish Wellness Study, with a mean age (SD) of 42.7 (17.1) years. Stratification for age was performed using a median split ($\geq$54 years old and $<$54 years old), and logistic regressions were used to test the obesity-mood associations.
Results: Only in the younger group, obesity was significantly associated with current anhedonia (but not with dysphoria/hopelessness) (p=0.038).
Conclusions: The results implicate female hormones, or sociopsychological factors associated with younger age in women as potentially leading to associations between obesity and cardinal symptoms of depression. Alternatively, it is also possible that other confounding variables might introduce a greater heterogeneity in older women. Limitations include cross-sectional design not adjusting for relatedness between participants, and not accounting for multiple comparisons. The results require replication with longitudinal ratings of depression and BMI measurements. Confirming hormone-mediating effects of this association may lead to interventional paradigms that could contribute towards better prevention and therapeutic control of both obesity and depression.
Supported By: This work was supported by the Mid-Atlantic Nutrition Obesity Research Center Preliminary Developmental NORC grant (Postolache, PI), a sub-award of the parent grant P30 DK072488 (Mitchell, PI).
Keywords: Anhedonia, Obesity, Sex Hormones, Gender Differences

S145. Association Between Impulsivity and Suicide Behaviors in Female Veterans

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Background: Women constitute the fastest-growing contingent of the military veteran population and report to the VA with a variety of physical and psychiatric symptoms. Suicidal behaviors in female veterans are an area of national concern, yet limited research has focused on how impulsivity is related to suicidal behaviors by sex.
Methods: Participants consisted of 48 female and 181 male veterans ages 18-55. Each completed the Columbia Suicide Severity Rating Scales, Barratt Impulsiveness Scale (BIS), Hamilton Anxiety Scale, and Hamilton Rating Scale for Depression.
Results: Male veterans showed significant correlations between lifetime history of suicidal behaviors (including ideation and attempts) and BIS Planning, Motor, Attention, and Total. Conversely, females only showed associations between history of suicidal behaviors and BIS Motor and Total. Female and male veterans did not show significant differences in symptoms of depression, anxiety, total impulsivity, or history of suicidal behaviors.
Conclusions: Results suggest that impulsivity is related to suicidal behaviors differently by sex.

For male veterans, difficulty planning, maintaining attention, and doing things without thinking were related to suicidal behaviors. However, for female veterans saying things without thinking, difficulty sitting still, and acting on the spur of the moment also were related to suicidal behavior. Prior research has shown biological underpinnings related to sex differences in impulsivity, including differences in brain morphometry and resting state functional connectivity in the frontal cortex. Hormone levels including cortisol and testosterone also have been related to impulsivity and suicidal behaviors. Further research should focus on biological factors related to impulsivity and suicide by sex in veterans.

Supported By: Rocky Mountain MIRECC, Salt Lake City VA
Keywords: Sex Differences, Suicide Behavior, US Veterans

S146. The Antidepressant Effects of Ketamine on Lateral Habenula Activity Require Endogenous Opioid Signaling

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Background: Depression leads to significant impairment in daily function. The prolonged time course necessary for current pharmacological treatment may extended suffering and increase risk of suicide. Acute administration of ketamine rapidly alleviates depressive symptoms and reduces suicidality. Ketamine is a non-competitive antagonist of the NMDA receptor but also displays activity on a wide variety of neuronal receptors. Recent studies suggest that the effects of ketamine may be mediated by a variety of systems including AMPA, and opiate receptors.

We used an inbred line of congenital learned helplessness (cLH) rats, a validated model of Major Depressive Disorder (MDD), to examine the synaptic effects of ketamine administration. This model displays hyperactivity in the lateral habenula (LHb), an epithalamic nucleus that inhibits activity of the Ventral Tegmental Area (VTA). Hyperactivity in the habenula leads to decreased dopamine release from the VTA, and manifestation of anhedonia and avolition. In this model, acute ketamine administration results in a reduction in LHb activity, and improved performance in metrics of depressive-like symptoms.
Methods: We used a variety of systems neuroscience techniques, including ex vivo calcium imaging, to examine alterations in habenular signaling resulting from ketamine administration
Results: Our results demonstrate that ketamine administration is effective in reducing depression-like symptoms, and LHb activity, in cLH rats. These beneficial effects on behavior and neural activity are blocked by prior administration of the opioid antagonist Naltrexone.
Conclusions: The antidepressant effects of ketamine administration in cLH rats are likely mediated by an acute reduction in LHb activity that requires intact, endogenous opioid signaling.

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R25-MH101072-05; NIMH; N. Swerdlow, Psychiatric Research Residency Training Track
Keywords: Ketamine, Treatment Resistant Depression, Lateral Habenula, Opioid System, Learned Helplessness, Systems Neuroscience

S147. Evidence for the Involvement of the Serotonergic System in the Therapeutic Mechanism of Deep Brain Stimulation of the Subcallosal Cingulate (SCC-DBS) for Treating Depression

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Background: Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) is a promising investigational treatment for depression, but little is known about the therapeutic mechanism. Preclinical studies suggested a role for serotonin in the antidepressant effects of SCC-DBS. Here we aimed to determine whether an electrophysiological indicator of central serotonergic activity, the loudness dependence of the auditory evoked potential (LDAEP), predicts outcome and whether it changes after chronic SCC-DBS.
Methods: The LDAEP was measured with EEG at baseline in 12 patients who underwent SCC-DBS, and again at 6 and 12 months after surgery in 7 of these patients.

Results: For treatment prediction, we found significant negative correlations between the steepness of the LDAEP slopes and change in Hamilton Depression Rating Scale (HDRS) at 6 and 12 months (N=12; r=-0.674, p=0.023; r=-0.716, p=0.013, respectively); those with a more shallow LDAEP slope at baseline showed a better response. As a treatment marker, there was a significant correlation between change in LDAEP from baseline to 12 months and change in symptom severity (N=7; r=-0.933, p=0.007); the LDAEP slope became steeper with greater symptom reduction. All patients except two were on antidepressants.
Conclusions: Our results show that greater central serotonergic activity at baseline predicted better response, and a greater improvement in symptoms following 12 months of chronic SCC-DBS was associated with a decrease in central serotonergic activity. The effects of medication cannot be excluded. These findings suggest that the brain's information processing system needs to be more protected for SCC-DBS to provide benefit.
Supported By: AIHS CRIO grant
Keywords: Deep Brain Stimulation, Treatment Resistant Depression, Electroencephalography (EEG), Event Related Potentials

S148. Lifestyle Intervention Improve the Weight and Exercise Patterns of Geriatric Depressed Patients

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Background: We explore the effect that a medical residential lifestyle intervention has on its patients.
Methods: The 18-day intervention took place in Weimar, CA. Patients were evaluated by board certified physicians, some came with the diagnosis of depression, some were diagnosed with depression at the program. The program included vegetarian diet, exercise, rest, and emotional, relational support. A baseline measurement of weight miles walked and other information was captured, at the end the same evaluation was repeated.
Results: In a year, n=96 were geriatric, had depression at baseline and were retrospectively used for this study.

Average age was 66.7 SD 8.6. At the beginning their weight in pounds listed as mean, stdev, mode, median were (164.3, 38.5, 158, 157.7). Using the baseline values of Body Mass Index, 23% were overweight and 23% were obese.

At the end of the program, the mean, stdev, mode and median weight were (159.6, 36.2, 146, 155).

Regarding exercise patterns at baseline the mean, stdev, mode, median, minimum, maximum miles that they were walking per day were (.5, .9, 0, 0, 0, 4), their end walking values listed in the same order were (3, 1.9, 4, 3, 0.25, 9).
Conclusions: This short-term lifestyle intervention program of change in diet, exercise and other health components was able help patients improve their wait and increase their physical activity. The long-term effects of this lifestyle intervention need to be studied.
Keywords: Weight Loss, Depression, Geriatric

S149. Gene Expression in Dorsolateral Prefrontal Cortex: A Master Regulator Analysis of Major Psychiatric Disorders

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Background: Traditional genetic studies have failed to find individual genes of large effect size in major psychiatric disorders. Using network-based approaches, we aimed to (1) identify transcription factors acting as potential master regulators (MRs) in Bipolar Disorder (BD), Schizophrenia (SZ) and Major Depressive Disorder (MDD); (2) Investigate the activation/repression patterns of these MRs, as well as the enriched biological processes in each disorder, to characterize diseases' transcriptional phenotypes.
Methods: High-throughput gene expression data was used to construct the normal regulatory transcriptional network in the human prefrontal cortex, which was used to query the MRs of major psychiatric disorders using 12 independent case-control gene expression datasets (475 cases; 414 controls). Two-tail gene set enrichment analysis was performed to investigate the activation pattern of MRs in each disorder and then to perform cluster analysis and functional enrichment analysis.
Results: Thirty-one, thirty-four and fifteen MRs were identified in BD, SZ and MDD, respectively. Using the activation pattern of the MRs, these disorders were grouped in three clusters: one associated solely with MDD, another with a prevailing BD diagnosis and a third one more heterogeneous including BD and SZ. BD and SZ shared relevant biological processes related to cation transport, synapse, and immune function, while MDD was associated with biological processes related to glial development and fatty acid metabolism.
Conclusions: Our findings suggest notable molecular differences among these disorders indicating similarities between BD and SZ, and sorting MDD. Network-based approaches are innovative tools to unravel the pathophysiology underlying mental illnesses and reveal therapeutic targets.
Supported By: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Keywords: Transcriptomics, Systems Biology, Bipolar Disorder, Schizophrenia, Major Depressive Disorder (MDD)

S150. Nightly Melatonin Administration Attenuates Olanzapine-Induced Disturbance of the Circadian System

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Background: Second generation antipsychotics (SGA) induce adverse metabolic effects (SGA-AME) that increase morbidity and cardiovascular risk, but the mechanisms involved are unknown. Recent human and animal studies suggest the circadian system is implicated in SGA-AME, and nightly melatonin administration (NMA) shows promise in their prevention. We evaluated the effect of repeated olanzapine administration and NMA on cardiovascular and temperature circadian regulation.
Methods: A radio-telemetric device was implanted to record cardiovascular parameters (blood pressure and heart rate), locomotor activity and core body temperature (CBT) in awake adult male Wistar rats. Animals were under 12hr L/D cycles and randomly assigned to oral saline, olanzapine (5mg/kg/day), olanzapine+melatonin (2.5mg), or melatonin. Olanzapine was administered at Zeitgeber (Zt)11 (night) and Zt23 (morning). NMA was at Zt11 only. Repeated measures ANOVA, mixed model and comparative analysis were used to examine data. Exploratory Wavelet transform denoising was used to further evaluate CBT changes.
Results: Data from Saline (n=6), 2) Olanzapine (n=5), Olanzapine+ Melatonin (n=6), and Melatonin (n=5) groups were analyzed. Olanzapine induced a disturbance in cardiovascular and CBT circadian regulation that was prevented by NMA. Olanzapine induced a greater decrease in CBT at Zt11 compared to Zt23 administration ($p=0.002$). Wavelet transform denoising showed olanzapine induced a more pervasive imbalance in CBT than the one observed under traditional factorial analysis, which is also prevented by NMA.
Conclusions: Our results further implicate the circadian system in SGA-AME, and as a potential target for their prevention with NMA. Time of drug administration might have clinical implications for SGA-AME and requires additional study.
Supported By: The Pilot Translational Research Program (#T30175) Grant issued by the Department of Psychiatry and Behavioral Neurosciences, University of Cincinnati College of Medicine funded this study.
Keywords: Second Generation Antipsychotics, Melatonin, Circadian System, Autonomic, Temperature

S151. Investigating the Genetic Architecture of Psychiatric Disorders and Their Medical Comorbidity

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Background: Previous work has demonstrated pervasive comorbidity between medical and psychiatric disorders in both adults and youth. In this study, we examine these patterns of comorbidity across development and evaluate the extent to which they may result from common underlying genetic etiologic factors.
Methods: The sample includes 5175 European-ancestry youth (ages 8 to 21 years; 51.7% female) from the University of Pennsylvania Neurodevelopmental Cohort Study sampled from pediatric clinics at the Children's Hospital of Philadelphia. Medical conditions were derived from interview data and medical record information. Psychiatric disorders were assessed with a structured diagnostic interview. Polygenic Risk Scores (PRS) were calculated with the PRSice2 software package using publicly available GWAS summary statistics. Sex and age-adjusted logistic regression models were used to evaluate the associations between medical and psychiatric disorders, and for PRS predicting medical and psychiatric disorders.
Results: Specific associations emerged between ear, nose, and throat disorders with psychosis symptoms; central nervous system disorders with ADHD, behavior disorders, and general psychopathology; whereas developmental disorders were associated with a broad range of psychiatric disorders. The overall medical disorder severity rating was associated with anxiety, ADHD, behavior disorders, mood disorders, and overall psychopathology. There was no evidence for associations between psychiatric PRS and comorbid medical disorders.
Conclusions: These findings a demonstrate strong overlap between medical and psychiatric conditions in youth, but common psychiatric genetic risk factors do not appear to underlie this comorbidity early in development. Other mechanisms (including environmental factors) that may influence these associations are examined.
Supported By: NIH NCATS UL1TR001878
Keywords: Polygenic Risk Score, Comorbidity, Developmental Psychopathology, Medical Co-Morbidities

S152. Genetic Risk for Hospitalization in Serious Mental Illness

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Background: Mood disorders such as major depressive and bipolar disorders, along with posttraumatic stress disorder (PTSD), schizophrenia (SZ) and other psychotic disorders constitute serious mental illnesses (SMI), leading to inpatient psychiatric care for adults. These disorders are heterogeneous with variable phenotypes, which make them challenging to diagnose prior to the onset of severe symptoms, and difficult to treat effectively. Risk factors increasing the rate of hospitalization in SMI are largely unknown, but likely involve a combination of genetic, environmental, and socio-behavioral factors.

We performed a genome-wide association study (GWAS) in an African-American cohort with high trauma exposure (Grady Trauma Project, GTP), to identify possible genes associated with hospitalization due to SMI (H-SMI).

Methods: Patients hospitalized for psychiatric disorders (H-SMI; n=690) were compared with demographically-matched controls (n=4469). Quality control and imputation of genome-wide data (Omni-Quad1M) were performed following the PGC-PTSD guidelines. Imputation of the HLA locus was performed using HIBAG software package. Logistic regression, adjusting for ancestry and gender, was used for the analyses.
Results: GWAS revealed a genome-wide significant association at 6p22.1 locus in the ubiquitin D (UBD/FAT10) gene (rs362514,p=9.43x10-9) and around the HLA locus. We also observed a nominally significant correlation in 2 HLA alleles among the 87 tested alleles in 7 HLA genes: HLA-A*23:01 (OR=1.4,p=2.9x10-3) and HLA-C*06:02 (OR=1.4, p=0.9x10-3).
Conclusions: We observed a strong association between H-SMI and a locus that has been consistently and strongly associated with SZ in multiple studies (6p21.32-p22.1), possibly indicating an involvement of the immune system and the immune response in the development of severe trans-diagnostic SMI.
Supported By: R01 MH071537 "Genetic and Trauma-Related Risk Factors for PTSD"
Keywords: MDD, PTSD, Serious Mental Illnesses, GWAS, HLA

S153. Life-Time Lead Exposure and its Association With Cognitive Function and Resting-State Connectivity in Cocaine Addiction

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Background: Life-time lead exposure detrimentally impacts cognitive function in the general population. Cognitive function is associated with drug use and predicts initiation and escalation of drug use, length of use and treatment outcomes. The link between life-time lead exposure, cognitive function, its neural correlates and drug use has not been investigated in cocaine-addicted individuals.
Methods: We acquired in vivo tibia lead levels (using x-ray fluorescence), a measure of cognitive function (WAIS Matrix Reasoning) and drug use variables from 20 individuals with Cocaine Use Disorder (iCUD) and 17 healthy controls (HC), matched for gender and race. Age was included as a covariate in all analyses. In a subsample (N=15 iCUD; N=11 HC) that underwent a resting-state functional magnetic resonance imaging scan, we applied Graph theory methods to extract whole-brain resting-state connectivity (Global Efficiency; 638-region parcellation).
Results: Across participants, higher tibia lead levels were associated with lower cognitive function (P=0.009). Within iCUD, lower cognitive function showed a trend for an association with life-time cocaine use (years of use; P=0.05). Whole-brain analysis of resting-state connectivity revealed that across participants higher tibia lead levels were linked to decreased global efficiency, with the largest effects being focused in the ventral basal ganglia (pallidum, putamen; P=0.04, FWE-corrected). In HC, higher efficiency of the ventral basal ganglia was linked to better cognitive function, while there was no such relationship in iCUD.
Conclusions: Higher tibia lead levels were linked to impaired basal ganglia and cognitive function, which in turn was associated with higher drug use, providing a potential mechanism underlying drug use.
Supported By: 1R01DA041528; P30 ES023515
Keywords: Addiction, Lead, Cognitive Function, Resting State fMRI, Environmental Risk Factors

S154. Elimination of Olfactory Reference Syndrome With L-Methylfolate Calcium/Methylcobalamin/N-Acetylcysteine (Cerefolin NAC)

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Background: Resolution of Olfactory Reference Syndrome (ORS), the delusion that one is exuding a foul aroma, with L-methylfolate calcium/methylcobalamin/N-acetylcysteine (Cerefolin NAC) has not heretofore been described.
Methods: Case Report: Eight months prior to presentation, a 73-year-old right-handed woman developed an upper respiratory infection with an acute loss of smell. Since then, the patient also described her skin smells putrid all the time and constantly placed her hand to her nose to check the odor of her own skin. She was concerned that her aroma was perceived by others in a negative light. Despite reassurances to the contrary, she remained convinced that she exudes a malodourous effluvium from her epidermis. This persisted until Cerefolin NAC was begun as part of treatment for her chemosensory condition. Within two weeks of initiation, she perceived that her skin was no longer emanating a foul aroma. This elimination of her perception of exuding a putrid body odor was sustained while on treatment with Cerefolin NAC.
Results: Abnormalities in neurological examination: General: Decreased blink frequency. Hypomimetic. Gait: Heel walk with decreased bilateral arm swing. Sensory Examination: Vibration: Absent lower extremities. Reflexes: 3 throughout. Chemosensory Testing: Olfaction: Pocket Smell Test 2/4 (Hyposmia). Brief Smell Identification Test: 4 (Anosmia).
Conclusions: The ORS may have represented pathological discharge of the olfactory system. The Cerefolin NAC may have acted to stabilize such olfactory discharge and thus minimize the perception of an aroma. Use of Cerefolin NAC should be considered in initial management of ORS.
Keywords: Olfactory Reference Syndrome, L-methylfolate, N-acetylcysteine

S155. Associations Between Cytokines and Cortical Thickness in Patients With Late-Life Depression

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Background: Immune factors are now recognized as involved in the pathophysiology of depression. We aimed to evaluate the relationship between plasma cytokine levels and cortical thickness in patients with late-life depression (LLD).
Methods: Blood samples and structural magnetic resonance imaging scans (Siemens 3T Prisma) were acquired in 29 older adults (>60 years old) with major depression (62% female; mean age, 70.7 (7.3) years; mean MADRS, 15.9 (3.2)). Associations between plasma cytokine levels (log-transformed) and cortical thickness were evaluated using partial least squares. Cytokines with detectable levels in at least 27 patients (exotaxin, IFN-a2, GRO, MDC, IL-12(p70), sCD40L, IL-8, IP-10, MCP-1, MIP-1b, TNF-a, and VEGF) were analyzed.
Results: The first latent variable was significant (accounting for 32% of the cross-block covariance, p=.036) and reflected negative correlations between exotaxin, IL-8, IP-10, MIP-1b, and TNF-a levels and cortical thickness in numerous brain regions, including cingulate, insular, temporal, orbitofrontal, and prefrontal cortices.
Conclusions: Patients with LLD who have high serum exotoxin, IL-8, IP-10, MIP-1b, and TNF-a have reduced cortical thickness in brain regions previously implicated in depression compared to that in patients with lower serum levels. The affected brain regions have functions in self-referential processes, emotional regulation, social cognition, and attentional switching. Thus, the observed reductions in cortical thickness may contribute to the emotional, cognitive, and behavioral disturbances in LLD. Recently, chemokines have been implicated in many neurobiological processes and are considered to play a role in linking peripheral and central inflammation. The present results further support the importance of chemokines and proinflammatory cytokines in depressive pathophysiology.
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Keywords: Late Life Depression, Cytokines and Chemokines, Structural MRI, Cortical Thinning

S156. Progression of Subcortical Changes After First-Episode of Psychosis: A 3-Year Longitudinal Structural Magnetic Resonance Imaging Study

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Background: Structural brain volume changes have been demonstrated at the onset of first-episode of psychosis (FEP). However, data pertaining to the potential volumetric progressions remain inconsistent. We examined if there are progressive changes in ventricular and subcortical volumes over a 3-year period in individuals with FEP compared to healthy controls (HC) and if any such changes are associated with clinical and functional outcome.
Methods: High resolution 1.5T T1-weighted MR images were obtained from 28 FEP's and 28 HC's at baseline and 3-year follow-up and were processed with the longitudinal pipeline in FreeSurfer (v.5.3.0). Repeated-measures ANCOVA and partial correlation were used to compare progressive changes between groups and to determine associations with clinical and functional characteristics. Age, gender and ICV were included as covariates.
Results: A significant group by time interaction was noted for reduced volume of the caudate [F(1,51)=5.86,p=0.02], putamen [F(1,51)=6.06,p=0.02] and thalamus [F(1,51)=6.99,p=0.01] in FEP, with a trend towards significance for increased lateral ventricular volume [F(1,51)=3.37,p=0.07]. In FEP individuals, cumulative antipsychotic medication as assessed by chlorpromazine equivalents was associated with increased putamen volume (r=0.50,p=0.01). Increased lateral ventricular volume was associated with more negative symptoms (r=-0.41,p=0.04) and poorer global assessment of functioning (r=0.41,p=0.04).
Conclusions: Our results indicate significant progression of neuroanatomical deficits in striatal, thalamic and lateral ventricular regions after a first episode of psychosis. Increased ventricular volume overtime is a neuroanatomical marker of poorer clinical outcome.
Supported By: Health Research Board (HRA_POR/2011/100) and NUI Galway Postgraduate Scholarship Fund
Keywords: First-Episode Psychosis (FEP), sMRI, Subcortical Structures, Schizophrenia

S157. Neural and Clinical Correlates of Optimal Risk-Taking in Early Psychosis

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Background: In adolescence, normative imbalance between reward and executive systems can facilitate optimal risk-taking (OR). Adolescents early in the course of psychosis (EP) may show variability in OR propensity. This variability can be impacted by motivational deficits (e.g. avolition) which may limit engagement with reward-seeking behavior regardless of degree of risk. OR can be further impacted by atypical reward-processing, supported by regions like the nucleus accumbens (NAcc).
Methods: 53 EP participants completed a behavioral risk-propensity task, the Balloon Analogue Risk Task (BART), and an fMRI reward-sensitivity task. BART trials were low- or high-risk; to perform optimally, performance must be altered based on trial type. OR was defined as increased engagement during low-risk/maximum likelihood of reward contexts. Percent

signal change values were extracted from an a priori NAcc of interest (ROI). Hierarchical regressions were conducted to test if ROI data significantly improved prediction of OR over and above ratings of avolition.
Results: Avolition significantly predicted OR, such that avolition was associated with decreased OR. Right NAcc percent signal change significantly improved model fit for prediction OR over and above avolition (N=53, F(4,49)= 3.874, p=.009); NAcc recruitment was associated with increased OR.
Conclusions: Results suggest that both NAcc recruitment and avolition in EP individuals account for unique variance in risk behavior, such that lower avolition and increased NAcc recruitment are critical to engaging in OR. When risk is high, NAcc recruitment may not be as critical to OR, given that reward may be less salient when probability of negative outcome is high.
Supported By: NIMH R01 MH101506
Keywords: Early Psychosis, Risk-Taking, Reward

S158. Cortical Localization of N2pc Impairments Following First Psychotic Episode

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Background: Impairments in selective attention during first-break psychosis remain understudied. Our previous data showed scalp EEG-based N2pc impairments following first psychotic break (FESz) compared to healthy controls (HC). The present investigation used combined MEG and EEG data to identify source patterns of cortical activation underlying the N2pc impairment.
Methods: MEG/EEG were simultaneously recorded from 22 FESz and 22 HC during pop-out and visual search target detection. The inverse solution for cortical activity contributing to the N2pc signal (275−325ms post stimulus) was derived. Brodmann's areas 7, 39, and 37 were selected a priori as regions of interest (ROIs) based on previous literature. Activity was compared between groups.
Results: Groups differed in hemispheric activation across the tasks (p=.03). HC differentially activated the left hemisphere for some ROI (p<.01) with larger left-hemisphere activity at BA7 (p=.03) and BA39 (p<.01), but not BA37 (p=.12), across task condition. Within FESz, greater activity was also observed in the left-hemisphere across ROI during pop-out (p=.02). However, an analysis of visual search revealed an interaction between ROI and hemisphere among FESz (p<.01) driven by greater right-hemisphere BA7 activity (p=.03).
Conclusions: The data suggest greater contribution of the left-hemisphere to the N2pc in HC across tasks as well as within FESz in the less taxing pop-out condition. However, FESz engaged more right-hemisphere cortical structures, specifically within BA7, during the serial self-terminating search condition. This pattern suggests FESz, in response to a minimum attentional challenge, had to recruit additional posterior parietal networks previously implicated in inefficient search strategies.
Supported By: P50MH103204
Keywords: Selective Attention, First Episode Psychosis, Magnetoencephalography

S159. NMDA Receptor Antagonism Effects on Delayed Spatial Working Memory and Distraction in Comparison With Schizophrenia

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Background: Robust working memory (WM) requires shielding internal representations from interference by external distraction. While there is a rich behavioral literature showing sensory gating problems in schizophrenia (SCZ), less work has been done to understand how compromised filtering may lead to impaired WM. The administration of an NMDA glutamate receptor antagonist, ketamine, can be used to study the role of specific neural mechanisms which may play a part in SCZ, as it transiently induces comparable cognitive deficits and symptoms. No fMRI studies of WM in SCZ patients have directly compared results with those obtained from a pharmacological manipulation via ketamine.
Methods: An fMRI delayed spatial-WM task with imbedded distraction was collected on healthy controls (N=40) and SCZ patients (N=39). The scanning design followed a 2x2 factorial framework, with one between-group factor (Group: controls, patients) and one within-group factor (Infusion: placebo, ketamine). Patients were not administered ketamine.
Results: WM was significantly impaired in SCZ and in HCS during ketamine vs. placebo. Distraction degraded WM precision in patients, however, there was a trend towards subtle improvement in HCS while on ketamine. Neuroimaging results indicate that impaired performance in SCZ patients, particularly in the distraction condition may be linked to reduced DMN suppression.
Conclusions: SCZ patients and HCS on ketamine exhibited impaired sWM, implicating glutamate in spatial WM tuning. However, distracters mildly improved precision on ketamine while deficits were observed in SCZ. This suggests the underlying neuropathology of putative 'filtering' deficits in SCZ may encompass additional mechanisms (e.g. dopamine, GABA).
Supported By: NIH Early Independence Award (DP5)
Keywords: Schizophrenia, Ketamine, NMDA Antagonists, BOLD fMRI, Spatial Working Memory

S160. Disrupted Salience and Cingulo-Opercular Network Connectivity Underlies Impaired Rapid Task-Learning in Schizophrenia

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Background: The salience network (SAN) and cingulo-opercular network (CON) support goal-directed behavior through orienting attention to goal-relevant stimuli and stably maintaining task-context. Both networks are integral in successful cognitive performance, particularly when the task relies on rapid instructed task learning (RITL), the ability to rapidly transform task information into goal-directed behavior without relying on trial-and-error. RITL has recently been found to be impaired in schizophrenia, a disorder characterized by aberrant SAN and CON connectivity during rest.
Methods: Task-based network connectivity during early and late RITL learning trials was compared between patients with schizophrenia (N=29) and healthy controls (N=31), using 8 a priori network pairs. Multivariate pattern analysis (MVPA) was used to determine which network connectivity patterns predicted diagnostic group, correcting for multiple comparisons. Connectivity patterns significantly predicting group were tested for correlations with behavioral performance (improvement in reaction time during learning).
Results: Of all network pairs, only CON-SAN connectivity during learning classified patients and controls with significant accuracy (80%). A significant interaction during late-learning ($p=.03$) revealed a significantly stronger ($Z=2.19$, $p=.029$) association between overall task performance and CON-SAN connectivity in schizophrenia ($r=.44$, $p=.016$) than controls ($r=-.12$, $p=.524$), not seen during early-learning trials.
Conclusions: CON-SAN connectivity is specifically altered during instructed task learning in schizophrenia. These data further demonstrate that group differences in connectivity during late-learning, as opposed to early-learning, drives task performance in schizophrenia. These findings suggest a later, less "rapid" learning process in schizophrenia, possibly due to impaired interactions between identification of salient stimuli and maintenance of task goals.
Keywords: Salience Network, Rapid Instructed Task Learning, Cingulo-Opercular Network, MVPA, Neurocognition

S161. Dimensions of Social Cognition in the Schizophrenia Spectrum and Personality Disorders

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Background: Both schizophrenia (SCZ) and schizotypal personality disorder (SPD) are characterized by impaired social functioning. However, few studies have compared SCZ and SPD subjects on mentalizing (the ability to understand mental states of others), a social cognitive domain key for social functioning. We aim to characterize similarities and differences between schizophrenia and SPD subjects by comparing them to individuals with another personality disorder (borderline personality disorder, BPD) and healthy controls (HC) on a mentalizing task.
Methods: 105 subjects − HC (n=34), SPD (n=36), BPD (n=20), SCZ (n=15) − completed the Movie for the Assessment of Social Cognition (MASC), a naturalistic video task assessing mentalizing accuracy and errors ("no-mentalizing," "hypermentalizing," and "hypomentalizing"). Mentalizing measures were compared across groups using ANCOVA, with age and gender as covariates.
Results: There were significant group differences on overall accuracy ($F(3,104)=10.667$, $p<0.001$) and hypomentalizing errors ($F(3,104)=9.196$, $p<0.001$), but not on hypermentalizing ($F(3,104)=2.629$, $p=0.054$) or no-mentalizing errors ($F(3,104)=2.666$, $p=0.052$). Pairwise comparisons revealed significant differences on mentalizing accuracy between HC and BPD as compared to SPD and SCZ groups (post-hoc SPDvHC, SPDvBPD, SCZvBPD $p<0.001$, SCZvHC $p<0.01$). There were significant differences on hypomentalizing errors between SCZ and all other groups, including SPD (post-hoc $p<0.001$). While the overall models were not significant for hypermentalizing or no-mentalizing, a priori pairwise comparisons revealed significant differences between SCZ and all other groups and significant differences for SCZ versus BPD and HC, respectively ($p<0.05$).
Conclusions: SPD and SCZ patients display similar deficits in mentalizing ability and hypomentalizing errors.
Keywords: Social Cognition, Schizotypal Personality Disorder, Schizophrenia Spectrum, Borderline Personality Disorder, Personality Disorder

S162. Widespread Amygdala Nuclei Reductions Across the Psychosis Spectrum and in Their First-Degree Relatives: A BSNIP Study

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Background: The amygdala underlies emotional regulation and is mediated by nuclei differing in functionality and topographic projections. Post-mortem and in vivo neuroimaging studies are inconclusive, and no group has investigated amygdala nuclei differences in psychosis using an automated MRI probabilistic atlas. We examined amygdala nuclei in

psychosis, their first-degree relatives and controls, and their associations with cognition and symptomatology.
Methods: Psychosis participants included schizophrenia (n=193), schizoaffective (n=116), and bipolar (n=156), relatives (n=391), and controls (n=283). Freesurfer 6.0 extracted basal (Ba), accessory basal (AB), lateral (La), and central (Ce) nuclei volumes from T1 MPRAGEs and symptoms and cognition were collected. Contrasts were run using a linear mixed-effects model with age, sex, race, and total intracranial volume as fixed effects and site as a random effect. Partial correlations were run and p values were FDR corrected.
Results: Probands showed significant reductions in all regions and relatives showed smaller left Ba, AB, and Ce compared to controls. All diagnostic groups showed significant reductions in bilateral Ba and AB compared to controls. SZP showed significant reductions in bilateral La and Ce, SADP showed smaller left La, and BPP showed reduced La compared to controls. Increased AB, Ba, and La were significantly associated with better cognition and functioning, and lower positive and manic symptoms for probands. Lithium usage was associated with higher nuclei volumes and no effects were shown with chlorpromazine equivalence, illness duration or hospitalizations.
Conclusions: This is the first structural-MRI study of amygdala nuclei showing psychosis-related bilateral nuclei atrophy may underlie cognitive dysfunction, positive, and manic symptoms.
Supported By: NIMH RO1 MH078113, MH077945, MH077852, MH077851, MH077862, MH072767, and MH083888
Keywords: Amygdala, Psychosis Spectrum, Mania

S163. Mapping Functional Thalamic Subnuclei Alterations Across the Psychosis Spectrum

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Background: Psychosis spectrum disorders (PSDs) exhibit multidimensional symptoms such as hallucinations, delusions, disorganized thought, affective dysregulation and cognitive deficits. Brain-wide thalamic circuit disruptions feature prominently in psychosis pathophysiology. Yet, no study tested if distinct thalamic subnuclei disruptions map onto the severity of PSD symptoms across the broad range of diagnoses.
Methods: We examined resting-state fMRI from N=436 PSD patients and matched controls (N=219) collected by the Bipolar & Schizophrenia Consortium for Parsing Intermediate Phenotypes. This cohort captures categorical diagnoses of schizophrenia, bipolar disorder with psychosis and schizoaffective disorder and dimensional PSD features across broad PSD symptoms. All imaging data were processed using Human Connectome Project (HCP) Pipelines. The BOLD timeseries were functionally parcellated in the CIFTI format via our novel whole-brain network parcellation. We computed brain-wide seed-based thalamic maps for each individual across distinct sub-nuclei, each mapping onto a functional network. We computed a non-parametric GLM via PALM to quantify the relationship between grayordinate-wise thalamic FC and symptoms as well as categorical diagnoses.
Results: We observed disrupted thalamic FC across all PSD diagnostic categories, building on and extending previous findings that have implicated thalamic network disruptions in the underlying pathophysiology of psychosis. Thalamic FC alterations were especially prominent in the associative and sensory thalamic nuclei, and tracked symptom severity.
Conclusions: The study implicates associative thalamic FC alterations across PSD, but also highlights the importance of linking punctate thalamo-striato-cortical network alterations to specific patterns of symptom alterations, which can help inform translational models and therapeutics for individualized neuro-behavioral alterations.
Supported By: 5R01MH112189-02; 5R01MH108590-03
Keywords: Psychosis Spectrum, Functional Neuroimaging, Clinical

S164. A Functional Neuroimaging Meta-Analysis of Self-Related Processing in Schizophrenia

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Background: Schizophrenia is characterized by self-disturbances, including impaired self-evaluation abilities and source monitoring. The core brain regions of the default-mode network (e.g. medial prefrontal cortex, precuneus) are known to play a key role in self-related processing. In theory, self-disturbances in schizophrenia may arise from impaired default-mode network activity. We performed a functional neuroimaging meta-analysis to verify this hypothesis.
Methods: A literature search was performed with PubMed and Google Scholar to identify functional neuroimaging studies examining the neural correlates of self-processing in schizophrenia, using self-other or source monitoring paradigms. Fifteen studies were retrieved, involving 307 patients and 235 controls. Using peak coordinates to recreate an effect-size map of contrast results, a standard random-effects variance weighted meta-analysis for each voxel was performed with the Seed-based d Mapping software.
Results: During self-processing, decreased activations were observed in schizophrenia patients relative to controls in the bilateral thalamus (x=10;y=-26;z=12; 321 voxels) and the right superior frontal gyrus (x=14;y=12;z=50; 34 voxels), as well as the right precuneus (x=26;y=-72;z=34), but only in a small cluster (22 voxels). Increased activations were observed in patients relative to controls in the right posterior insula (x=46;y=-34;z=18; 146 voxels) and the right putamen (x=20;y=16;z=-6; 101 voxels).
Conclusions: The current results do not support the hypothesized impaired activity of default-mode brain regions in schizophrenia during self-processing. Rather, decreased activations were observed in the thalamus, which is involved in information integration. These thalamic alterations may compromise the self-coherence in schizophrenia. The meta-analysis also highlighted aberrant limbic reactivity during self-processing in schizophrenia.

Keywords: Schizophrenia, Neuroimaging, Thalamus

S165. Limbic Hyperactivity in Response to Neutral Stimuli in Psychosis: A Functional Neuroimaging Meta-Analysis of the Suspicious Mind

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Background: It has long been assumed that paranoid ideation may stem from an aberrant limbic response to threatening stimuli. Unfortunately, results from functional neuro-imaging studies have failed to confirm this assumption. One of the reasons for the lack of effect is that psychosis participants may display aberrant brain responses to neutral material rather than to threatening stimuli (e.g. fearful and angry faces). A functional neuro-imaging meta-analysis was performed to test this hypothesis.
Methods: A literature search was performed with PubMed and Google Scholar to identify functional neuroimaging studies examining brain responses to neutral material in psychosis. Thirty-one studies were retrieved: 20 studies involving schizophrenia patients, and 11 studies involving psychosis risk individuals. Using t-maps of peak coordinates to calculate effect sizes, a random-effects model meta-analysis was performed with the Seed-based d Mapping software
Results: In schizophrenia, increased activations were observed in the bilateral amygdala / parahippocampus (x=28;y=0;z=-18; 324 voxels) and left putamen (x=-24;y=-4; z=-4; 545 voxels) in response to neutral stimuli, relative to controls. In psychosis risk individuals, increased activations were only observed in the left putamen (striatum; x=-26; y=18; z=10; 113 voxels), relative to controls.
Conclusions: Given the well-known role of the amygdala in threat detection, the results of this meta-analysis strongly suggest that schizophrenia patients confer aberrant emotional significance to non-threatening stimuli. In theory, this abnormal brain reactivity may fuel suspicious thoughts. Our results also tentatively suggest that aberrant striatal response to neutral stimuli may represent an early marker of psychosis vulnerability. Longitudinal functional neuroimaging studies in psychosis risk individuals are warranted.
Keywords: Schizophrenia, Neuroimaging, Amygdala

S166. Brain Energy Metabolism and Myelin and Axon Integrity in Patients With First Episode Psychosis and Unaffected Siblings

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Background: We have previously reported abnormalities of both brain energy metabolism and white matter (WM) in psychotic disorders. As maintaining WM integrity and myelination are energy-intensive functions, dysfunctional bioenergetics in psychosis may be related to WM abnormalities. The present study examined the relationships between markers of brain bioenergetics and WM, including axon geometry and myelin content, in patients with first episode psychosis, unaffected siblings and healthy individuals.
Methods: We used a combination of MRI/MRS approaches in 35 patients with first episode psychosis, 11 unaffected siblings and 16 healthy controls. To examine WM, we used magnetization transfer ratio (MTR) to quantify myelin content and diffusion tensor spectroscopy (DTS) to quantify axon geometry with the apparent diffusion coefficient of N-acetylaspartate (NAA ADC) within axons. We used 31P MRS approaches to examine energy metabolism and measured the forward reaction rate constant (kf) of creatine kinase (CK) and brain parenchymal pH. MRI/MRS data were collected at 4 Tesla.
Results: Brain pH was significantly correlated to NAA ADC in patients with first episode psychosis (r= 0.44, p=0.009) and unaffected siblings (r= 0.62, p=0.04), but not in healthy controls. pH was not significantly associated with MTR across groups. In addition, there were no significant correlations found between CK kf and axon and myelin measures.
Conclusions: Rather than independent bioenergetic and WM anomalies in psychotic disorders, these results suggest that brain pH and axon geometry may be mechanistically related in early psychosis and high risk for psychosis, in contrast to healthy controls.
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Keywords: First Episode Psychosis (FEP), Energy Metabolism, White Matter, High Risk for Psychosis

S167. Increased N-Acetylaspartate and Myo-Inositol Levels in Clozapine-Responders and Clozapine-Resistant Patients With Schizophrenia

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Background: Patients with schizophrenia can be categorized into three treatment-response-groups; treatment-responsive

(TxR), respond to a first-line antipsychotic; clozapine-responsive (ClzR), only respond adequately to clozapine; and clozapine-resistant (ClzRes), do not adequately respond to any antipsychotic, including clozapine.

We hypothesize heterogeneous pathophysiology between treatment-response-groups reflected by neurometabolite differences. Proton magnetic resonance spectroscopy (1H-MRS) allows in vivo measurement of neurometabolite levels including; N-acetylaspartate (NAA), precursor to the neurotransmitter N-Acetyl-aspartyl-glutamate (NAAG); and myo-Inositol (mI), a measure of astrocyte function.

Methods: In a 3T 1H-MRS (PRESS, TE=35ms) study of 74 participants with schizophrenia classified according to antipsychotic treatment responsiveness (TxR=21, ClzR=27, ClzRes=26) and healthy controls (HC=26), NAA and mI levels were measured in the dorsal anterior cingulate cortex (dACC), dorsal striatum (caudate), and dorsolateral prefrontal cortex (DLPFC). Groupwise mean differences were tested using analysis of variance (ANOVA).

Results: Increased NAA ($F=4.331$, $p=0.007$) and mI ($F=9.518$, $p<0.001$) was observed in ClzR ($p=0.016$, $p=0.014$ respectively) and ClzRes ($p<0.001$, $p<0.001$ respectively) in the dACC when compared to HC. No other significant group differences were observed in the dACC nor the dorsal striatum, or DLPFC.

Conclusions: Higher NAA and mI in clozapine-treated, treatment-resistant-groups compared to controls suggests an association with treatment-resistance or clozapine treatment. Previously, these neurometabolites have been associated with neuronal viability and astroglial activation. Altered NAA synthesis and astrocyte function may have downstream effects on neuronal transmission, GABA and glutamate. Further exploration may reveal whether clozapine treatment leads to localized elevations in the dACC or whether NAA and mI are biomarkers associated with treatment resistant schizophrenia.

Supported By: Canadian Institute of Health Research (CIHR)

Keywords: Multimodal Neuroimaging, Schizophrenia, Treatment Resistant Schizophrenia, Neurometabolite, Clozapine

S168. Social Cognition and Resting State Networks in Schizophrenia and Bipolar Disorder

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Background: Individuals with schizophrenia (SZ) and bipolar disorder (BD) show alterations in functional neural connectivity during rest. However, resting state network (RSN) disruptions have not been systematically compared between the two disorders. Further, the impact of RSN disruptions on social cognition, a key determinant of functional outcome, has not been studied.

Methods: 48 individuals with SC, 46 with BD, and 48 healthy controls (HC) completed resting state fMRI. An atlas-based approach was used to examine functional connectivity within 10 RSNs. RSN connectivity was assessed via non-parametric permutation testing, and associations with performance on identifying emotion in biological motion, mentalizing (TASIT), and emotion management (MCCB-Social Cognition) were examined.

Results: Group differences were observed in the medial (MVN) and lateral (LVN) visual networks and the sensorimotor network. SZ demonstrated reduced connectivity relative to HC in all three networks ($p<.05$). BD demonstrated reduced connectivity relative to HC in the MVN ($p<.05$) and activity within the MVN was significantly positively correlated with emotion management ($r=.44$, $p<.01$). In HC, activity within the LVN correlated with mentalizing ($r=.39$, $p<.01$). No significant correlations were found for either visual network in SZ.

Conclusions: Results highlight the role of altered early visual processing in social cognitive deficits in both SZ and BD. However, individuals with BD appear to compensate for disrupted visual network connectivity on social cognitive tasks, whereas those with SZ do not. The current study adds clarity on the neurophysiology underlying social cognitive deficits that result in impaired functioning in serious mental illness.

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Keywords: Schizophrenia, Bipolar Disorder, Resting State Functional Connectivity, Social Cognition

S169. Effect of Attention on N100 in First Episode Psychosis

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Background: Reductions of the auditory N100 have been reported in first episode psychosis (FE). It is unclear whether this abnormality results from sensory deficits or impaired enhancement of N100 by attention.

Methods: N100 was recorded from 21 FE and 22 matched healthy controls (HC) on two tasks. On a single-tone task, participants ignored tones in one block, and pressed a button to every 7th tone in another. On a two-tone oddball task, participants ignore tones in one block, and responded to infrequent target tones in the other.

Results: N100 was smaller in FE ($p<.05$). Attention modulated N100 ($p<.001$), but this differed between groups ($p=.018$). The oddball task showed greater modulation than the single-tone task ($p=.002$), but this differed between groups ($p=.035$). HC modulated by attention ($p<.001$), more so on the oddball task ($p=.001$). FE modulated N100 by attention ($p=.003$), albeit less than HC, but did not increase modulation on the oddball task. Groups differed on the N100 enhancement on the oddball task with a sizeable effect (Cohen's $d=.98$). However, analysis of N100 in the attend oddball alone revealed a comparable effect size (Cohen's $d=1.06$).

Conclusions: N100 is smaller in FE, likely a failure in sensory modulation by attention. This suggests distributed system

dysfunction early in disease rather than late sensory/perceptual abnormalities. Comparison of the N100 on the attended oddball task between FE and HC also showed a large effect size, suggesting it may be a useful biomarker in early psychosis without need to assess attention modulation of N100.
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Keywords: N100, Schizophrenia, Attention

S170. Are Cannabis-Using and Non-Using Patients Different Groups? Evidence for Altered Volume Striatal Glutamate Relationships in Cannabis-Using Patients in Early Psychosis

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Background: The associative striatum, an established substrate in psychosis, receives widespread glutamatergic projections. The cannabinoid 1 receptor (CB1R) is an ubiquitous G-Protein Coupled Receptor in the brain with high levels of expression in cortical and medio-temporal regions. We sought to see if glutamatergic indices are altered between early psychosis patients who use cannabis and who do not.
Methods: 86 participants were scanned: Early Psychosis with cannabis use (EPC=26); Early Psychosis without (EPNC=23); Healthy Controls with cannabis use (HCC=16); Healthy Controls without (HCNC=21). Whole brain T1 weighted scans were acquired and a MR Spectroscopy voxel (2cm3) placed at the head of caudate. We obtained volumetric segmentation (Freesurfer 6.0); caudate Glx levels (LCM6.3) and corrected for partial-volume. We examined grey matter, white matter and ventricular volumes. We further examined relationships in regions with known high CB1r expression (cortex, hippocampus, amygdala) and low expression (brainstem).
Results: Patients were clinically well matched (PANSS, GAF, chlorpromazine equivalents). There was no significant difference in caudate Glx or volume. Total grey matter volume was associated with caudate Glx in cannabis-users but not non-users (EPC: r2=0.313, p=0.003; EPNC: r2=0.007, p=0.699; HCC r2=0.230, p=0.058, HCNC r2=0.025, p=0.494). The interaction for EPC vs EPNC was significant (Fisher r-to-z p=0.0367). In EPC a relationship between caudate Glx and volume was shown in regions with high but not low CB1R expression after multiple comparison correction.
Conclusions: These results are the first to demonstrate widespread association of grey matter volume and striatal glutamate in cannabis-using patients. This suggests altered circuitry between cannabis-using and non-using patients.
Supported By: Medical Research Council (United Kingdom)
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Keywords: Cannabis, Early Psychosis, Schizophrenia, MR Spectroscopy, Brain Magnetic Resonance Imaging (MRI)

S171. Striatal Glutathione in First-Episode Psychosis Patients

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Background: Deficits of glutathione, the most abundant and primary antioxidant in living tissue, and the resulting redox imbalance are implicated in schizophrenia.
Methods: The aim of this pilot clinical study was to compare levels of striatal glutathione measured in vivo with proton magnetic resonance spectroscopy (1H MRS) at 3T in 10 drug-naïve, first-episode psychosis (FEP) patients with those in 9 matched healthy control subjects.
Results: Analyses of the resulting data revealed a significant glutathione deficit in FEP patients compared to the healthy control group (U=25.00, p=0.02), as well as a positive correlation between glutathione levels and the Positive Symptoms subscale of the PANSS scale in the FEP group (ρ=0.96; p<0.001).
Conclusions: These preliminary findings are consistent with a striatal glutathione deficit in early-stage psychosis and warrant further exploration and confirmation in larger studies.
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Keywords: Glutathione, Proton Magnetic Resonance Spectroscopy, First-Episode Psychosis

S172. Elevated Distractibility of Schizophrenia in Visual Working Memory

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Background: Visual working memory (VWM) deficits have been broadly found in schizophrenia (SZ) patients, while the underlying mechanisms still remain unclear. One possible mechanism is that SZ have larger distractibility at the encoding stage of VWM such that they cannot appropriately distribute processing resources to task-relevant information while effectively filtering out task-irrelevant information.
Methods: Sixty SZ and sixth-one healthy control (HC) subjects participated in a modified color delay-estimation task. In this task, subjects were asked to first remember colors of targets and ignore distractors. After a short delay, they recalled the color of one prompted target. The set size levels of both targets and distractors were independently manipulated. We used the variable precision (VP) model to characterize the process of resource allocation in both

groups. The VP model can estimate not only the overall amount of resources but also the variability of allocating resources to individual items.
Results: We found that the two groups exhibited no differences in the amount of raw recall errors at each set size level of targets or distractors. However, the results from the VP model revealed that adding distractor significantly enlarges the variability of resource allocation in SZ but not in HC. Moreover, there was no significant group difference in the overall amount of memory resources and the variability at the choice stage.
Conclusions: Our results demonstrate that SZ have larger distractibility at the encoding stage of VWM. Particularly, the presence of distractor elevates the resource allocation variability but not the memory resource per se.
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Keywords: Schizophrenia, Visuospatial Working Memory, Distractibility, Bayesian Observer Model

S173. Altered Structural Covariance Networks of Cortical Gray Matter and Surface Area in First-Episode Antipsychotic-Naïve Psychotic Disorder

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Background: Structural covariance networks (SCNs) can show morphological similarity of atlas-defined regions-of-interest (ROIs) that may reflect combined neurodevelopmental and pathophysiological changes associated with psychosis. We examined whether the SCNs of first-episode antipsychotic-naïve psychosis (FEAP) subjects show differences in modularity and network features compared to healthy controls.
Methods: Gray matter volume and surface area of 54 Freesurfer atlas-based ROIs were extracted from T1-weighted MRI images of 81 patients and 76 controls. For each morphological feature, the SCNs were built using graph theory methods, which were compared between groups for modularity, and degree of connectedness. Connectivity was assessed by Differential Network Analysis (DNA) to determine the ROIs that show significant case-control differences and characterize sub-network(s) that differentiate the two graphs.
Results: FEAP patients showed significantly reduced modularity and denser whole-brain SCNs among the modules with medium to large effect sizes (Cohen's $d \geq 0.5$). The DNA revealed significantly higher nodal degrees and mean absolute distance of gray matter volume and surface area nodes of the middle frontal, inferior temporal, lingual and fusiform gyri, and pars triangularis among patients compared to controls.
Conclusions: Our main findings are decreased brain modularity resulting in fewer meta-nodes suggesting decreased morphological differentiation of the cortex in patients compared to controls. Strongly connected networks among the fewer modules suggest less enriched community structure of networks in patients that may be inefficient in processing visual learning and memory, working memory, sustained attention and executive function. Greater modularity with distributed connectedness among modules in controls may provide greater flexibility in cognitive processing.
Supported By: RO1MH112584
Keywords: Structural Covariance, Graph Theory, First Episode Psychosis (FEP), Network Analysis, Mathematical Framework

S174. Longitudinal Invariance of Structural Covariance Networks in First-Episode Antipsychotic-Naïve Psychotic Disorders

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Background: Morphometric alterations in psychosis are distributed across the brain and form interconnected networks. We examined structural covariance networks (SCNs) of gray matter volumes and surface areas among 36 first-episode antipsychotic-naïve subjects with psychotic disorders over 1-year treatment compared to 41 healthy controls hypothesizing that the SCNs of patients would be more similar to that of healthy controls at the end of 1-year.
Methods: SCNs of gray matter volume and surface area of 54 Freesurfer atlas-based regions-of-interest (ROIs) from T1-weighted MRI images of FEAP and controls were identified using graph theory methods and compared between groups for modularity and other network metrics. Differential Network Analysis (DNA) was used to determine the nodes that showed significant case-control connectivity differences at each timepoint.
Results: We found significant between-groups differences in the SCNs of gray matter volume and surface area at each time point (baseline, 4 weeks, and 52 weeks) but not within-groups. FEAP SCNs at each time point showed lower modularity and more highly connected nodes across the modules demonstrated by significantly higher mean nodal strength ($p<0.001$, Cohen's $d > 0.5$). DNA consistently identified the middle frontal, fusiform, and left lingual gyrus as differentiating the FEAP and healthy control networks at each time point.
Conclusions: Our findings suggest that SCNs of gray matter volumes and surface area do not change over 1-year of treatment. Such invariance of SCN to antipsychotic treatment suggest that these are trait markers of psychosis and may

underlie poor long-term outcome associated with current treatments.
Supported By: RO1 MH112584
Keywords: First Episode Psychosis, Network Analysis, Graph Theory, Longitudinal Brain Imaging, Structural Covariance

S175. Large-Scale Model of Human Cortex Captures LSD-Induced Functional Alterations via HTR2A-Mediated Neural Gain Modulation

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Background: Computational models of large-scale human brain circuits provide an integrative framework to study relationships between molecular alterations and systems-level effects on brain function. We recently showed that the neural and subjective effects of the psychoactive drug LSD are primarily mediated by the serotonin-2A receptor (5-HT2AR). Yet the dynamic circuit mechanisms linking 5-HT2AR manipulation to large-scale functional disruption remain unclear.
Methods: We combined structural and pharmacological neuroimaging with gene expression mapping, from the Allen Human Brain Atlas, to simulate effects of LSD in a large-scale model of human cortex. Neural gain modulation—a consequence of 5-HT2AR agonism—in the model was parametrized by the regional expression levels of HTR2A, the gene which codes for the 5-HT2AR. We fit model parameters to capture fMRI-derived functional connectivity alterations observed following acute LSD administration.
Results: The large-scale model captured the empirical topography of LSD-induced functional alterations in global brain connectivity, including hyper- and hypo-connectivity of sensory and association areas, respectively. The model mechanistically links this pattern of functional disruption to region-specific neuromodulatory changes in local excitation-inhibition balance. Empirical GBC patterns were not as well captured by alternative models: gain modulation at other synaptic receptor sites, or gain modulation parametrized by spatial autocorrelation-preserving surrogate maps.
Conclusions: Our findings link LSD-induced functional alterations to emergent circuit dynamics shaped by the spatial topography and neurophysiological properties of the 5-HT2AR. Our model establishes an extensible framework for linking molecular hypotheses to human neuroimaging markers via biophysical modeling, which may guide the development of novel therapeutics for neuropsychiatric disorders.
Supported By: Swiss National Science Foundation (SNSF, P2ZHP1_161626, KHP), the Swiss Neuromatrix Foundation (2015 - 0103, FXV), the Usona Institute (2015 - 2056, FXV), the NIH (R01MH112746, JDM; DP5OD012109, AA; R01MH108590, AA), the NIAA (P50AA012870-16, AA & JHK), the NARSAD Independent Investigator Grant (AA), the Yale CTSA grant (UL1TR000142 Pilot Award, AA)
Keywords: LSD, Computational Modeling, Resting State Functional Connectivity MRI (fcMRI), Transcriptomics, Computational Psychiatry

S176. Relationships Between Inflammatory Markers and Kynurenine Metabolites in Patients With Schizophrenia but Not Healthy Controls

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Background: Previous work has demonstrated that inflammation induces the kynurenine pathway of tryptophan metabolism by increasing the activity of indoleamine-2,3-dioxygensase. Previous studies in schizophrenia have shown alterations in these markers/metabolites, though have only considered a small number of each.
Methods: Inflammatory marker and kynurenine metabolites concentrations were measured in 43 patients with schizophrenia and 29 controls. Due to concerns for collinearity, principle components analysis with varimax rotation was used to create inflammatory marker factor loadings: Factor1 (interleukin (IL)-6 soluble receptor and tumor necrosis factor (TNF) receptor-2), Factor2 (TNF and IL-10), and Factor3 (IL-1beta, IL-6, IL-1receptor antagonist). The following kynurenine metabolites were measured: tryptophan (TRYP), kynurenine (KYN), kynurenic acid (KYNA), anthranilic acid (AA), and 3-hydroxyanthranalic acid (3OHAA). KYN:TRYP and 3OHAA:AA ratios were also calculated. Linear regression models were used to test the relationship between factors and kynurenine metabolites, including age, sex, race, smoking, and Toxoplasma gondii serointensity.
Results: In controls, only Factor3 and TRYP (beta=-0.436,p=0.026) were associated. In patients with schizophrenia, significant relationships were found between the following factors and kynurenines: KYN and Factor1 (beta=0.508,p=0.001), AA and Factor1 (beta=0.309,p=0.02) as well as Factor2 (beta=0.367,p=0.006), KYNA and Factor1 (beta=0.392,p=0.009), KYN:TRYP and Factor1 (beta=0.627,p<0.001), and 3OHAA:AA and Factor 3 (beta=-0.319,p=0.026).
Conclusions: We found evidence for relationships between inflammatory markers and kynurenines in patients with schizophrenia, but not controls. These data suggest that the immune system may play a role in tryptophan degradation into kynurenine metabolites, which have been shown to be related to symptoms of schizophrenia, including cognitive deficits. As such, inflammation and kynurenines represent potential treatment targets in patients with schizophrenia.
Supported By: Veterans Affairs Merit Review grant (1 I01 CX000974-01A1, E.D.)
Keywords: Schizophrenia, Inflammation, Inflammatory Cytokines, Kynurenine

S177. Self-Disturbance Scale and its Application in Schizophrenia

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Background: The self-disturbances (SDs) concept is considered to be part of the Schneider's first rank symptoms, i.e., thought-withdrawal, thought-insertion, thought-broadcasting, somatic-passivity experiences, mental/motor automatisms, disrupted unitary self-experience (Mishara et al., 2014). SDs were originally described by W. Mayer-Gross (1920), who observed them in psychotic patients.
Methods: We classified Mayer-Gross' findings on SDs into the following categories: experience is new/compelling (aberrant salience), reduced access/importance of autobiographical past, cognitions/emotions occur independently from self's volition, foreign agents have power over self and developed an SDs scale based on these categories and cognitive domains (perception, motor, speech, thinking etc.). Scale is applied as a measure of the frequency of the experiences. In our current study on phenomenology and neurobiology of psychotic symptoms, we administered the scale to a study group of patients with schizophrenia (N=84) and healthy volunteers (N=170)
Results: We found substantial differences in the frequency of self-disturbances in patients with schizophrenia compared to healthy controls (total score differences, Z=-5.83, $p < 0.001$). In both Cognitive and Mayer-Gross domains, the between-group differences were obtained in all scale items, except for the perception of smells and body experience. The differences remained significant after Bonferroni correction (p adjusted to $p < 0.005$).
Conclusions: The scale aims to identify self-disturbances in different stages of schizophrenia and to stratify them based on the cognitive domains. Additional quantitative analysis is planned to discern more details to phenotype SDs.
Supported By: MH CR AZV 17-32957A and MEYS NPU4-NUDZ: LO1611.
Keywords: Schizophrenia, Self-Disturbances, Psychometric Scale, Phenomenology

S178. All-Optical Electrophysiology in a Human iPS Cell-Based Model of Schizophrenia

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Background: Recent advances in stem cell biology can be harnessed for the generation of human disease-in-a-dish models of neuropsychiatric disorders. Induced pluripotent stem (iPS) cells derived from patient material can be differentiated into neuronal populations enriched for various subtypes. Cellular assays with high information content are needed to characterize the phenotypic response of disease-relevant neurons and to detect pharmacological effects on the observed phenotypes.
Methods: Here we focused on a human cellular model of schizophrenia and investigated the response of neuronal excitability to the atypical antipsychotic, aripiprazole. We used the all-optical electrophysiology platform Optopatch: action potentials were stimulated with the blue light-activated channel rhodopsin variant CheRiff and voltage was recorded with the red fluorescent Archaerhodopsin variant QuasAr. We characterized the pharmacological effects of aripiprazole treatment on human iPS cell-derived excitatory neurons. Neurons were produced via transcriptional programming by overexpressing the pro-neuronal transcription factor NGN2 and matured by co-culture with mouse astrocytes. Optopatch recordings enabled electrophysiological characterization of thousands of neurons with single-cell resolution.
Results: We detected a significant reduction in the spike frequency during CheRiff stimulation upon chronic but not acute treatment with aripiprazole. Investigation is underway of the intrinsic excitability and synaptic phenotypes of neurons derived from a cohort of schizophrenia patients and healthy controls.
Conclusions: The Optopatch platform rapidly and robustly characterizes the phenotypic response of iPS cell-derived neurons and provides an information-rich readout of pharmacological changes to neuronal electrophysiology. This approach can profile neurons derived from schizophrenia patients and may open a path towards precision medicine.
Supported By: Otsuka Pharmaceutical and Commercial Development, Inc
Keywords: Induced Pluripotent Stem Cells (iPSCs), Electrophysiology, Schizophrenia, Precision Psychiatry, Optogenetics

S179. Transdiagnostic Prediction of Memory and Executive Function From Whole-Brain Functional Connectivity

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Background: Functional connectivity patterns elicited in task-based fMRI experiments can predict behavioral performance in healthy subjects (Greene 2018). Here we demonstrate the system-level neural correlates of individual behavioral performance on memory and executive function tasks across a transdiagnostic cohort.
Methods: Six whole-brain task-based fMRI experiments from 236 subjects (122 healthy, 36 schizophrenia, 39 bipolar disorder, and 39 ADHD) were used in this analysis (Poldrack 2016). fMRI data was preprocessed, parcellated, and averaged within each of 268 nodes using standard protocols (Finn 2015; Shen 2013 & 2017). Inter-node Pearson r-values were Fisher transformed to produce a 268x268 matrix of functional connection (edge) strengths for each task, for each participant. Edges were correlated the first PCA score of sub-components

of the Weschler Memory Scale and the Weschler Adult Intelligence Score (WAIS), thresholded ($p<0.05$), binarized, and used in the subsequent ridge regression analysis wherein functional connectivity was used to predict these phenotypic PCA scores.
Results: The brain's functional anatomy predicts working memory ($r=0.49, p<0.01$) and executive function ($r=0.41, p<0.01$) performance. Schizophrenia and ADHD patient groups showed a trend towards being under-predicted relative to healthy controls and bipolar disorder. This prediction was based on a small subset of 35,778 possible edges: 1.6% in the WMS prediction; 0.5% in the WAIS prediction.
Conclusions: Functional anatomy can predict behavioral performance in a transdiagnostic sample. The same functional anatomy subserves similar behaviors across diagnostic groups. Diagnostic groups have dysfunctions in specific systems-level neural processes. Future work will assess how symptom severity correlates with prediction accuracy and these underlying brain systems.
Supported By: DSB: T32 MH019961, R25 MH071584;
Keywords: Functional Brain Connectivity, Prediction, Connectome Fingerprinting, Parcellation, Cognitive Dysfunction

S180. Defining Clinical Sentiment in Psychosis Patient Health Records

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Background: Recently natural language processing (NLP) tools have been developed to identify important risk factors in electronic health records (EHRs). Sentiment analysis, a field of NLP defined as an individual's attitude towards a topic, has been widely used in non-medical industries for improving decision making. In this study, we undertook a first-of-its-kind annotation project to extend sentiment analysis to psychiatry, defining it as a clinician's prognosis of a patient at a fixed time point. The sentiment analysis models trained using the results from this project will be incorporated in a feature engineering pipeline for a machine learning model that predicts inpatient readmission risk.
Methods: Two corpora of clinical narratives from institutional EHRs (one containing 1,650 paragraphs and the other 3,500) were annotated by two clinicians. The clinicians labeled each example for the patient's likely clinical outcome, either positive, negative, or neutral, within the context of seven specific readmission risk factors. Disagreements between the annotators were adjudicated by a third clinician to create a 'gold standard'.
Results: Inter-annotator agreement was substantial on the first corpus (Scott's Pi=0.691, Cohen's Kappa=0.693) and higher on the second (Pi=0.768, Kappa=0.768). This is primarily because the first corpus contains many paragraphs involving multiple readmission risk factor domains and annotators were instructed to provide clinical sentiment labels for each. The second corpus is entirely single-domain examples.
Conclusions: We developed an annotation scheme to define clinical sentiment in EHRs and used it to create training and testing corpora for NLP models that will be used to improve a readmission risk prediction model.
Supported By: NIMH (grant no. 5R01MH109687 to Mei-Hua Hall)
Keywords: Natural Language Processing (NLP), Electronic Health Record (EHR), Machine Learning, Psychotic Disorders, Outcome Prediction

S181. Kaleidoscope: A New Bioinformatics Pipeline Application for in Silico Hypothesis Testing of Gene Expression Changes in Severe Mental Illness

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Background: There are a large number of bioinformatics tools and databases that are relevant to psychiatric disorders and studies that are relatively untapped. We addressed this opportunity by developing a platform that provides easy access to these tools and datasets with a user-friendly interface that can be explored by researchers to test hypothesis in silico.
Methods: An interactive web application (called Kaleidoscope) was developed to serve as a platform for exploratory and confirmatory in silico data analyses for relevant neuroscience fields. This web application was developed using the R Shiny coding platform. The application takes advantage of online application programming interfaces (APIs) and publicly available datasets. The bioinformatics tools connected to our software include Brain RNAseq, Brain Cloud, STRING, iLINCS and Allen Brain Atlas.
Results: Fold-change values for mRNAs and proteins from microarray, RNAseq, and mass spectrometry datasets are harmonized for side by side comparison with visual interpretation using scalable heat maps. Our initial launch includes access to more than 15 schizophrenia versus control databases covering diverse brain regions, cell types, and tissue sources. We have successfully deployed this software for confirmation studies for two manuscripts.
Conclusions: The platform can be utilized in many forms and offers great scalability with the option of uploading user defined datasets for comparison alongside the pre-defined datasets. While still in development, our program is available for download on github (https://kalganem.shinyapps.io/SCZ_Databases_F/). Demonstrations will be performed at SOBP 2019. This tool will also facilitate introduction of bioinformatics approaches to biological psychiatrists, promoting educated use of bioinformatics pipelines in our field.
Keywords: Bioinformatics, Schizophrenia, In Silico, Gene Expression Profiling, Postmortem

S182. Effect of Adverse Life Events on Global Methylation and Perceived Stress in Schizophrenia

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Background: Epigenetic mechanisms such as DNA methylation can explain the molecular interaction between genetics and environmental factors. Compelling evidence suggests that such epigenetic alterations are involved in the pathophysiology of stress. In addition, accumulating results shows that stressful life events could modify gene methylation patterns. Hence, we analyze the link between global DNA methylation level, stressful life events and perceived stress in schizophrenia.
Methods: We analyzed 45 patients with schizophrenia, recruited at the Center for Addiction and Mental Health. The psychiatric diagnosis was confirmed using the structured clinical interview for DSM-V. Adverse life events were measured using Childhood Trauma Questionnaire (CTQ), Holmes-Rahe's Social Readjustment Rating Scale (HR-SRRS) and Stressful Life Events Screening Questionnaire (SLESQ). The Perceived Stress Scale (PSS) was used to measure current stress level. For each individual, genomic DNA was extracted from whole blood and the absolute measurements of 5methylCytosine (5Mc) content were determined as ng of 5mC per μg of DNA, using a competitive enzyme immunoassay.
Results: Our preliminary study did not find significant correlations between DNA global methylation and PSS (P=0.594). Furthermore, there was no correlation between global methylation and CTQ (P=0.923), SRRS (P=0.766) or SLESQ (P=0.821).
Conclusions: Although there were no significant correlations between global methylation and the stress variables. We believe that a larger sample size could explain the link between adverse events, global methylation and perceived stress in schizophrenia
Supported By: CIHR
Keywords: Epigenetic, DNA Methylation, Perceived Stress, Schizophrenia

S183. Childhood Trauma and Lifetime Experience of Delusions

Haley Church[1] and Sarah Keedy[1]

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Background: Childhood trauma is a risk factor for psychopathology. Emerging evidence suggests an association of emotional neglect and paranoia, but further investigation is needed (Wickham et al, 2016). The present study aims to explore childhood trauma associations of delusion subtypes.
Methods: In a sample of both healthy and psychotic participants of the ongoing BSNIP2 study (N=976), a binomial logistic regression was performed using subscales of the Childhood Trauma Questionnaire (CTQ) to assess the likelihood of any lifetime delusions using the Lifetime Dimensions of Psychosis Scale (LDPS). Separate logistic regressions were conducted on just the patient population (N = 633) to observe the effects of childhood trauma on type of delusion (i.e. paranoid, grandiose, somatic, religious, and nihilistic).
Results: The logistic regression model looking at delusions across healthy and psychotic participants was statistically significant, $\chi 2(4) = 225.645$, $p < .005$, explained 28.4% (Nagelkerke R2) of the variance in delusions and correctly classified 73.5% of cases. All 4 subscales included in the model were statistically significant: physical abuse, sexual abuse, emotional neglect, and physical neglect, with physical neglect being the strongest predictor. Among regressions on childhood trauma and type of delusion, emotional abuse was found to be a significant predictor of both grandiose and somatic delusions ($p < 0.030$), but this relationship was not mirrored in other delusion subtypes.
Conclusions: CTQ subscales predicted whether participants would express delusions over the course of their lifetime. Among psychotic participants, only emotional abuse predicted grandiose and somatic delusions, suggesting unique associations with specific childhood trauma experiences and delusion types.
Supported By: NIMH
Keywords: Delusions, Specificity, Psychosis-Proneness, Childhood Trauma, Symptom Dimensions

S184. Classification of Schizophrenia Using Machine Learning With Multimodal Markers

To see this abstract, please see Oral Abstract #O5.

S185. Treatment Response Trajectories in Treatment-Resistant Schizophrenia: A Chart Review Study

Parita Shah[1], Yusuke Iwata[1], Eric Brown[1], Fernando Caravaggio[1], Julia Kim[1], Marcos Sanches[1], Hiroyoshi Takeuchi[2], Shinichiro Nakajima[2], Margaret Hahn[1], Gary Remington[1], Philip Gerretsen[1], and Ariel Graff-Guerrero[1]

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Background: Although clozapine is the only antipsychotic indicated for treatment-resistant schizophrenia, 40-70% of clozapine patients have persistent psychosis (ultra-treatment-resistant schizophrenia, URS). Treatment response trajectories in patients on clozapine remain unclear; thus, we aimed to characterize treatment-resistant patients based on clozapine response and explore the clinicodemographic predictors of patients who were resistant to clozapine since its initiation.
Methods: Clinicodemographic characteristics of 241 patients on clozapine (mean±SD age=48.9±13.6 years) were collected through a retrospective chart review. The mean±SD follow-up from illness onset was 23.4±13.4 years. Clozapine response was assessed 1.6±2.4 years and 10.2±7.5 years after initiation. Independent t-tests were conducted to examine clinicodemographic differences between patients who responded to clozapine at both time points (Early-Clozapine Responders, Early CLZ-R) and those who did not respond (Early-Clozapine Non-Responders, Early CLZ-NR), and binomial regression was used to determine clinicodemographic predictors of non-response.
Results: Among clozapine responders (n=117), 87% were Early CLZ-R and 13% became responders after not responding initially. In the URS group (n=124), 84% were Early CLZ-NR and 16% became non-responders after responding initially.

Compared to Early CLZ-R, Early CLZ-NR had greater illness duration (t(187=2.05, p=0.042), hospitalizations (t(156)=3.37, p=0.001), clozapine dose (t(202)=4.39, p<0.0005), clozapine delay (t(124)=2.07, p=0.041), and number of unique past typical antipsychotic trials (t(197)=2.43, p=0.016). Greater clozapine delay (OR=0.94, Wald X2=4.64, p=0.031) and number of hospitalizations (OR=0.95, Wald X2=5.64, p=0.018) were associated with Early CLZ-NR.
Conclusions: Most URS patients were clozapine non-responders from the start of treatment. Reducing the delay in starting clozapine and number of relapses may help promote clozapine response.
Supported By: Canadian Institutes of Health Research (CIHR)
Keywords: Clozapine, Treatment Resistant Schizophrenia, Treatment Response, Predictors of Response, Schizophrenia

S186. Effects of Ketamine on Oculomotor and Neuroimaging Biomarkers of Schizophrenia

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Background: The uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is studied widely as an experimental medicine model of schizophrenia. Support for the validity of this model comes from studies that report ketamine-induced alterations in cognition and brain function that resemble the deficits observed in schizophrenia. In this talk, I will present recent data from studies of ketamine effects on two well-established biomarkers of schizophrenia, i.e. smooth pursuit eye movements (SPEM) and antisaccades.
Methods: Healthy male volunteers (N=26) underwent intravenous administration of racemic ketamine (target plasma levels of 100ng/ml) in a counter-balanced, placebo-controlled, double-blind, within-subjects design whilst performing SPEM and AS tasks. Eye movements were recorded using video-based oculography during blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) at 3T.
Results: Ketamine administration was found to cause reliable SPEM impairments (p<.01). Antisaccade performance, in contrast, was found to be uninfluenced by ketamine (p>.05). At the neural level, ketamine caused a pronounced reduction in BOLD signal during SPEM in task-related visual and oculomotor areas compared to placebo. In contrast, BOLD response during the AS task was characterised by compensatory BOLD signal increases in somatosensory cortex.
Conclusions: The deficits in SPEM following ketamine administration resemble the pattern of dysfunction in schizophrenia. The finding of unimpaired antisaccades is surprising, however, given that antisaccade performance is reliably and robustly impaired in schizophrenia. The fMRI findings during SPEM resemble the reductions in task-related areas found in schizophrenia patients. Overall, these findings provide partial support for the use of ketamine as a pharmacological model of schizophrenia.
Supported By: Deutsche Forschungsgemeinschaft (Et 31/3-1)
Keywords: Ketamine, Eye Movements, Biomarkers, Schizophrenia, BOLD fMRI

S187. Subchronic PCP Treatment in Mice Recapitulates Synaptic Proteomic Changes in Schizophrenia Cortex via Effects on CAMK2 and Microtubules and Rescue by Atypical Antipsychotic, Lurasidone

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Background: Sub-chronic(sc) treatment with phencyclidine (PCP), a noncompetitive antagonist of NMDA receptors, induces persistent deficits in rodent cognition which can be reversed by atypical antipsychotic drugs (AAPDs), e.g. lurasidone. We examined scPCP-induced synaptic proteins dysregulation followed by 7 days treatment with lurasidone, using a quantitative synaptic proteomics.
Methods: Synaptoneurosomes were prepared from homogenated brain tissue collected from prefrontal cortex (PFC) of 3-month-old scPCP, lurasidone, and scPCP + lurasidone groups, mixed with 15N internal standard from vehicle group. We performed LC-MS/MS analyses to obtain relative 14N/15N peptide ratio. Significantly altered protein levels were identified by ANOVA. We compared these data with that of published postsynaptic density (PSD) proteomic study from schizophrenia cortex (Focking M et al., 2015 Molecular Psychiatry)
Results: 18/20 and 12/15 scPCP down or up-regulated proteins were normalized by lurasidone. PCP-downregulated proteins include CAMK2 subunits (CAMK2A/2B/2D), microtubules (TUBB2A/2B/5), and synaptic vesicle exocytosis (CPLX1/2), of which many were normalized by lurasidone. Top protein families related to CAMK2 and microtubules are significantly down-regulated in postmortem PFC of schizophrenia. Long-term potentiation and calcium signaling, in schizophrenic PSD were overrepresented in PCP synaptoneurosome proteome. Increased locomotor activity, decreased social interaction, and impaired cognition in CAMK2A+/- mice were rescued by lurasidone
Conclusions: We provide new evidence that the scPCP rodent model recapitulates proteomic changes in schizophrenia, indicating that CAMK2 pathway is important for the pathophysiology of schizophrenia and the mechanism of action of AAPDs.
Supported By: Brain Research and Weisman Foundations
Keywords: Targeted Proteomics, CaMKII, Atypical Antipsychotics, Schizophrenia, Cognitive Deficits

S188. The Phosphodiesterase-9 Inhibitor BI 409306 Attenuates Social Interaction and Dopaminergic Deficits in Adult Offspring of poly(I:C)-Based Maternal Immune Activation Neurodevelopmental Mouse Model

Roberto Arban[1], Juliet Richetto[2], Joseph Scarborough[2], Cornelia Dorner-Ciossek[1], Holger Rosenbrock[1], and Urs Meyer[2]

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Background: Maternal immune activation (MIA) is used as a neurodevelopmental model mimicking part of the behavioral and molecular deficits observed in schizophrenia. In the present study, the effects of the selective PDE9 inhibitor, BI 409306, in adult offspring from the poly(I:C)-based MIA mouse model were evaluated.
Methods: Pregnant C57BL6/N mice were treated with poly(I:C) (5mg/kg, i.v.) or saline on gestation day 12. Male offspring (n=9/group) were administered orally once daily with BI 409306 (0.2, 0.5, 1mg/kg) or vehicle starting at post-natal day (PND) 70 and subjected to a battery of behavioral tests. Working memory performance, social behavior, sensorimotor processing and response to amphetamine were assessed in sequence from PND70 to PND120.
Results: Maternal poly(I:C) injection induced a significant decrease in social interaction ($p<0.01$, one-way ANOVA followed by Fisher's LSD) in the adult offspring. A trend was observed for potentiation of the amphetamine-induced hyperlocomotion and for decrease in pre-pulse inhibition (PPI); working memory performance was not affected. Chronic treatment with BI 409306 at the dose of 1mg/kg significantly attenuated the social interaction deficits ($p<0.05$) and showed a trend for a reduction of amphetamine-induced hyperlocomotion in the adult offspring. BI 409306 did not show any effects in the PPI test nor on working memory performance.
Conclusions: In this study we showed that chronic treatment with the PDE9 inhibitor BI 409306 led to an attenuation of behavioral deficits induced by MIA in the mouse. The current findings support the test of BI 409306 for prevention of relapse in patients with schizophrenia (NCT03351244).
Keywords: PDE9 Inhibitor, Schizophrenia, Maternal Immune Activation, Pharmacology

S189. Disordered Patterns of Communication Within Local Cortical Circuits in a Mouse Model of Schizophrenia

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Background: A distinguishing feature of schizophrenia is the pervasive disorganization of thought. To the extent that thought processes emerge from the integration of information across complex networks, one might expect a disorganization of neuronal networks themselves in schizophrenia. In order to study cellular-level organization in cortical circuits, we evaluated synchronous activity and the transfer of information between neurons in mice carrying a deletion of the schizophrenia risk gene Dgcr8.
Methods: We performed multi-electrode neural recordings in awake mice to measure timing relationships between the activity of neighboring neurons in the medial prefrontal cortex (mPFC). The timing relationships between spiking activity in simultaneously recorded pairs of cells were evaluated through cross-correlation and transfer entropy analyses (4,732 pairs from control mice, 5,574 from Dgcr8+/-). Transfer entropy quantifies the transmission of predictive information between network nodes and is used to characterize effective connectivity between neurons.
Results: Increased bursting activity in the mPFC was found in the Dgcr8+/- mouse that may imply an increase in the frequency of sharp waves generated in the hippocampus ($p = 0.007$). Furthermore, both zero-lag synchrony and transfer entropy were significantly reduced in the Dgcr8+/- mouse ($p < 0.05$ in both analyses), suggesting a loss of both network coherence and effective communication.
Conclusions: While imaging and histological studies have described disordered connectivity in humans with schizophrenia, functional communication at a cellular level is less well characterized. In a genetic mouse model of schizophrenia, we present evidence of both inter-regional and local disruptions in neuronal communication.
Supported By: F30 MH108205-03
Keywords: Schizophrenia, Neural Networks, Animal Models, Frontal Cortex

S190. Does Cannabis Use Interact With Neurophysiological Vulnerability in the Early Expression of Psychosis and Conversion Status in Clinical High-Risk (CHR) Individuals?

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Background: Endocannabinoid function is implicated in schizophrenia pathogenesis. Cannabis disrupts brain plasticity through down-regulation of N-methyl-D-aspartate (NMDA) receptors and attenuated glutamatergic neurotransmission. We examined the interaction of cannabis use and mismatch negativity (MMN), a biomarker associated with NMDA-mediated neurotransmission, to determine the combined influence on expression and progression of illness in those at clinical high-risk (CHR) for psychosis.
Methods: K-means cluster analysis was used to classify four subgroups based on cannabis use history and MMN

in CHR participants (N=533) of the North American Prodrome Longitudinal Study. MANOVAs compared clusters on Scale of Psychosis-Risk Symptoms (SOPS), MATRICS cognitive battery, and Global Function Scale. Clinical status (psychotic conversion, n=70/non-conversion, n=285) was evaluated in a subsample who completed 2-year follow-up.

Results: Clusters were defined as: 1) low cannabis/impaired MMN (n=254); 2) low cannabis/intact MMN (n=162); 3) high cannabis/intact MMN (n=60); and 4) high cannabis/impaired MMN (n=57). Clusters differed in several cognitive domains (3,4>1,2), suspiciousness and persecutory ideas (2,3>1=4), global function (1,3,4>2), and in 2-year clinical outcome (chi-square=15.15, p=.002), with the highest percent of converters in cluster 4 (51.6%; p<.05).

Conclusions: Although conversion rate was highest in those defined by impaired MMN and high cannabis use, this combination did not reflect the most severe cognitive impairment, elevated symptom severity, or poorest global function. This observation might suggest increased influence of environmental factors, such as cannabis use, over those traditionally associated with psychosis risk. As cannabis may disrupt NMDA-mediated neurotransmission, it is also possible that associated risk is elevated through interaction with neurophysiologic vulnerability.

Supported By: This work was supported by the National Institute of Mental Health (grant U01MH081984 to J.A.; grants U01 MH081928; P50 MH080272; Commonwealth of Massachusetts SCDMH82101008006 to L.J.S.; grants R01 MH60720, U01 MH082022 and K24MH76191 to K.S.C.; grant U01 MH081902 to T.D.C.; P50 MH066286 (Prodromal Core) to C.E.B.; grant U01 MH082004 to D.O.P.; grant U01 MH081988 to E.F.W.; grant U01MH082022 to S.W.W.; and U01 MH081857-05 grant to B.A.C). No funding agency had any role in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Keywords: Clinical High-Risk States for Psychosis, Cannabis, Neurophysiology, Mismatch Negativity, Neurocognition

S191. Molecular Characterization of Stress Reactivity Regions in the Brain

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Background: The mechanisms underlying interindividual differences in how the brain responds to stress are poorly understood. Therefore, we aimed to identify molecular correlations of neural stress reactivity in individuals genetically at-risk for development of psychotic disorders.

Methods: We linked mRNA expression data from the Allen Human Brain Atlas (n = 6 donors) to fMRI-based data (control n = 39, at-risk individuals n = 39) to assess gene expression in brain regions differentially activated by an emotion processing task follow exposure to acute social stress in at-risk individuals (healthy siblings of schizophrenia patients) compared to healthy controls.

Results: We identified 261 differentially expressed genes in stress-vulnerability related regions compared to the rest of the brain which are, therefore, likely involved in mounting an adaptive stress response. These genes were associated to stress-related psychiatric disorders (e.g. schizophrenia and anxiety) and stress- and glucocorticoid responsiveness. Several markers for specific neuronal populations (e.g. VIP, CCK and NPY), as well as neurotransmitter receptors (e.g. HTR1A, CHRNA3) were also among the differentially expressed genes.

Conclusions: This is the first study to link stress-related fMRI data to gene expression in the brain. We identified a set of genes that likely underlie altered stress reactivity in individuals at-risk for psychiatric disorders. These genes point to involvement of specific subtypes of neurons, and include signaling factors and proteins that interact with GR signaling and hypothalamic-pituitary-adrenal axis activation. Together, linking gene expression to functional neuroimaging can provide insights in putative cell populations, mechanisms, and potentially drugable targets for stress reactivity.

Supported By: None

Keywords: Brain Imaging, fMRI, Stress Reactivity, Human Postmortem Brain, Schizophrenia, Emotion Perception

S192. Characterizing Variation in Connectivity and Behavior in the Psychosis Spectrum: Towards Identifying Individualized Treatments

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Background: A key challenge in neuropsychiatry is matching patients to effective treatments. Attempts to robustly characterize the neural substrates of categorical diagnostic groupings and pre-existing symptom measures have yielded limited success, suggesting an inadequate mapping to neurobiologically meaningful variation. Here we describe a framework under which behavioral variation in psychosis spectrum disorders can be mapped to features of specific neural systems.

Methods: We leverage fMRI-derived neural and behavioral data from 202 healthy controls and 436 patients along the psychosis spectrum. We identify dimensions of behavioral variation in patients and show using multivariate techniques that variation along these behavioral dimensions relates to variation in the global brain connectivity of specific neural systems. Finally, we demonstrate that these brain-behavioral relationships can be readily mapped to neural/cellular properties such as gene expression.

Results: The identified behavioral dimensions are oblique to traditional symptom scales and do not reflect conventional diagnostic boundaries. Further, we observe robust neuro-behavioral relationships using our behavioral dimensions that

are not present using traditional schema. We show that this mapping can inform the identification of pharmacological targets aimed at treating specific symptom profiles and assist in selecting behavioral measures that precisely pinpoint neural variation at the individual level.
Conclusions: Using this framework, we can identify molecular targets that are associated with specific dimensions of behavioral variation and develop pharmaceutical agents that may address deficits along these axes. We propose the Neuro-Behavioral Relationships In Dimensional Geometric Embedding (N-BRIDGE) framework as a key step towards unified mapping between the geometry of behavioral and neural variation in psychiatry.
Supported By: RO1; DP5
Keywords: Psychosis Spectrum, Individualized Treatment, Functional Neuroimaging, Cognition Behavior, Gene Expression

S193. Aggressive Behaviors and Risk Factors in a Large Schizophrenia Sample (n=625)

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Background: People with schizophrenia are more likely than others to behave aggressively. However, there are few large, broadly-phenotyped samples available for comprehensive testing of associations of documented physical aggression history with the sorts of clinical, demographic, and behavioral risk factors reported in the literature. Additionally, to our knowledge, aggression has not been tested for association with polygenic scores (PGS) for different traits and disorders.
Methods: Comprehensive demographic, clinical, behavioral, cognitive, and personality phenotyping was completed for participants in an NIMH study of schizophrenia. Study files included historical medical records for most participants. We abstracted and coded information about aggressive behaviors, and a wide range of risk factors, from a detailed review of NIMH study participation files of 625 people with schizophrenia or schizoaffective disorder. Ordered logistic regression analyses tested the associations of risk factors with documented physical assault history and sought to tease apart the unique contributions of different predictors.
Results: Documented physical aggression (generally mild or moderate in severity) and related behaviors and traits were quite common: physical violence (32.7%), hostile personality (43.8%), past destructive behavior (32.7%), and verbal assault/threat (42.7%). Analyses highlighted certain risk factors (e.g., male sex, p=6.5E-04, r2=.026; prodromal age, p=.007, r2=.016; destructive behavior, p=5.0E-06, r2=.042; and hostile/confrontational disposition, p=2.9E-09, r2=.075). Of a number of PGS tested, only trait anxiety showed a modest association with physical aggression (p=.017, r2=.014).
Conclusions: Documented physical aggression was very common in a large, clinically stable, schizophrenia sample. Analyses highlighted particular risk factors, including destructive behavior and hostile/confrontational disposition.
Supported By: NIMH
Keywords: Aggression, Schizophrenia, Polygenic Risk Score, Sex Differences, Anxiety

S194. Does Cognitive Control of Emotion Drive Sex Differences in the Clinical Presentation of Schizophrenia?

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Background: In females with schizophrenia (SZ) psychotic symptom severity relates to mood symptom severity, indicating a link between psychosis and emotion processing not observed in SZ males. Sex differences in cognitive control of emotion (CCoE), mediated by the frontal-limbic network, may drive this but have not been examined. This study investigates sex differences in the frontal-limbic network during CCoE and its relationship to SZ symptoms.
Methods: Twenty-one healthy (11 female) and 17 SZ (10 female) individuals completed psychosocial assessments and an fMRI Social Evaluation Task examining reactivity to and regulation of negative social evaluation (NSE). Independent sample T-tests ($p<0.05$ two-tailed) tested sex differences in reactivity to and regulation of NSE (i.e., CCoE) within diagnostic group, and diagnostic differences within sex. Region-of-interest (ROI) analyses examined neural activation during CCoE in the frontal-limbic network.
Results: Compared to healthy males, healthy females demonstrate greater reactivity to (d=1.45) and greater regulation of (d=1.18) NSE (ps<0.05). Compared to healthy females, SZ females demonstrate a non-significant pattern of reduced reactivity to (d=-0.32; $p>0.05$) but significantly reduced regulation of NSE (d=-1.64; p=0.001). There were no significant differences between SZ males and SZ females, or healthy males and SZ males. ROI analyses demonstrate healthy females show greater reduction of amygdala activity during CCoE compared to healthy males and SZ participants.
Conclusions: Females may be more reactive to NSE, and SZ females may have impaired regulation of NSE. Future analyses will examine relationships between frontal-limbic activity and symptoms. This work directly examines how sex differences in CCoE contributes to SZ symptomatology.
Supported By: This research was supported by a Building Interdisciplinary Research Careers in Women's Health award (K12 HD051958) awarded to Laura M. Tully, funded by the National Institute of Child Health and Human Development (NICHD), Office of Research on Women's Health, Office of Dietary Supplements, and the National Institute of Aging.
Keywords: Schizophrenia, Sex differences, Early Psychosis, Emotion Regulation, Cognitive Control

S195. Improvement in Prolactin and Sexual Side Effects in Patients With Schizophrenia Who Switched From Paliperidone Palmitate or Risperidone Long-Acting Injectable to Aripiprazole Lauroxil

Deanna Kelly[1], Amy Claxton[2], Ilda Bidollari[2], Yangchun Du[2], and Matthew Young[2]

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Background: Hyperprolactinemia is commonly encountered with risperidone or paliperidone and may lead to sexual dysfunction, amenorrhea, and galactorrhea. We examined changes in prolactin and reported sexual functioning in patients switching from paliperidone palmitate (PP) or risperidone long-acting injectable (RLAI) to aripiprazole lauroxil (AL).
Methods: Post hoc analysis of a Phase 4, open-label, 6-month prospective study in patients with schizophrenia transitioning to AL from PP or RLAI due to persistent symptoms or tolerability concerns. Serum prolactin was measured twice before starting AL, and then 1, 2, 3, and 6 months after AL began. Sexual side effects were elicited using the UKU sexual function subscale before starting AL and at the last AL visit.
Results: Almost all (49 of 51; 96%) of the PP (n=50) and RLAI (n=1) patients had hyperprolactinemia at the screening visit. Over 6 months, prolactin levels declined in all patients, normalizing in 94%; normalization occurred within 2 months, on average. Sexual dysfunction in at least one domain was reported by 82% at screening, decreasing to 58% at 6 months. "Diminished sexual desire" was reported by 48% at screening, decreasing to 18% after 6 months of AL. One patient with hyperprolactinemia at screening discontinued due to gynecomastia.
Conclusions: In patients with schizophrenia taking PP or RLAI, 94% of patients sampled (n=33) who switched to AL achieved normalization of serum prolactin at 6 months; on average, prolactin levels normalized within 2 months of AL initiation. Overall, sexual side effects improved following the switch, most notably in the sexual desire domain.
Supported By: This study was funded by Alkermes, Inc.
Keywords: Aripiprazole Lauroxil, Paliperidone Palmitate, Hyperprolactinemia, Sexual Dysfunction, Long-Acting Injectable Antipsychotics

S196. Cerebellar Endocannabinoid Down-Regulation Accompanies Early Life Stress Induced Facilitation of Eyeblink Conditioning

Alexandra Moussa-Tooks[1], John Green[2], Ken Mackie[1], Alex Gimeno[1], Eric Larson[1], Heather Bradshaw[1], Emma Leishman[1], Brian O'Donnell[1], and William Hetrick[1]

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Background: Early life stress (ELS) impacts neurodevelopment during critical periods, conferring risk for various psychopathologies, such as psychosis, substance use, and/or anxiety. One potential mechanism is through the endocannabinoid system, integrated in the stress response circuit.
Methods: Long-Evans rats were reared with or without limited bedding material during postnatal day (PND) 2-9 to evaluate (1) long-term endocannabinoid changes and (2) behavioral impairment following ELS. Lipid analysis was performed on cerebellar interpositus and crus I, regions dense with cannabinoid receptors and involved in EBC (PND70). Acquisition, extinction, and reacquisition of eyeblink conditioning (EBC), a cerebellar- and endocannabinoid-mediated task, were assessed in males (PND55-70).
Results: ELS males exhibited significantly decreased 2-arachidonoyl glycerol (2-AG) and arachidonic acid levels in the interpositus only compared to normally-reared males. Females experiencing stress exhibited significantly increased prostaglandin E2 levels in the interpositus and decreased 2-AG in crus I compared to normally-reared females. Preliminary data shows ELS males trended towards facilitated acquisition and had significantly facilitated re-acquisition of EBC.
Conclusions: Findings suggest that ELS causes long-term down-regulation of endocannabinoid levels in males, specifically in the interpositus, perhaps contributing to EBC facilitation. Decreased negative feedback of stress cues may maintain sensitivity to EBC stimuli, increasing EBC learning. This pattern of facilitation and endocannabinoid dysregulation mirrors human anxiety disorder pathology, suggesting the translational power of this paradigm. Sex differences in endocannabinoids may explain basal enhanced EBC performance reported in female rats, warranting further investigation. Understanding stress-related endocannabinoid dysregulation may provide insights into risks for, and the development of, psychopathology and uncover novel therapeutic targets.
Supported By: Indiana CTSI Pre-Doctoral Fellowship; NIMH T32 Pre-Doctoral Fellowship
Keywords: Early Life Stress, Cerebellum, Endocannabinoids, Sex Differences, Research Domain Criteria (RDoC)

S197. An International Machine Learning Study of Modeling the Psychopathology in Schizophrenia: From Symptomatology to Neuroimaging Endophenotypes

Ji Chen[1], Kaustubh Patil[1], Susanne Weis[1], Kang Sim[2], Thomas Nickl-Jockschat[3], Juan Zhou[4], André Aleman[5], Iris Sommer[6], Edith Liemburg[6], Ute Habel[7], Birgit Derntl[8], Xiaojin Liu[1], Lydia Kogler[8], Christina Regenbogen[7], Vaibhav Diwadkar[9], Jeffrey Stanley[9], Valentin Riedl[10], Renaud Jardri[11], Oliver Gruber[12], Aristeidis Sotiras[13], Christos Davatzikos[13], and **Simon Eickhoff**[1]

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Background: Disentangling psychopathological heterogeneity in schizophrenia is challenging and results remain inconclusive. We employed advanced machine-learning to identify a stable and generalizable factorization of the "Positive and Negative Syndrome Scale (PANSS)" and used it to identify psychopathological subtypes as well as their neurobiological differentiations.
Methods: PANSS data from the Pharmacotherapy Monitoring and Outcome Survey cohort (1545 patients, 586 followed up after 1.35 (SD, 0.70) years) were used for learning the factor-structure by an orthonormal projective non-negative factorization. An international sample pooled from nine medical centers across Europe, USA, and Asia (490 patients) was used for validation. Patients were clustered into psychopathological subtypes based on the identified factor-structure and the neurobiological differentiability between the subtypes was assessed by classification analysis on functional MRI connectivity patterns.
Results: A four-factor structure representing negative, positive, affective and cognitive/disorganized symptoms was identified as the most stable and generalizable representation of psychopathology. It showed higher internal consistency than the original PANSS subscales and previously proposed factor-models. Based on this representation, the positive-negative dichotomy was confirmed as the (only) robust psychopathological subtypes and these subtypes were longitudinal stable in around 80% of the repeatedly assessed patients. Finally, individual subtype could be predicted with good accuracy from functional connectivity profiles of the ventro-medial frontal cortex, temporoparietal junction, and precuneus.
Conclusions: Machine-learning applied to multi-site data with cross-validation yielded a factorization generalizable across ethnic groups and medical systems. Together with sub-typing and the demonstrated ability to predict subtype membership from neuroimaging data, this work further disentangles the heterogeneity in schizophrenia.
Supported By: European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 720270 (HBP SGA1) and 785907 (HBP SGA2).
Keywords: Schizophrenia, Brain connectivity, Psychopathology, Machine Learning, Cross-Cultural

S198. Effects of Transcranial Photobiomodulation With Near-Infrared Light on Sexual Dysfunction

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Background: Transcranial photobiomodulation (t-PBM) consists of the delivery of near-infrared (NIR) or red light to the scalp designed to penetrate to subjacent cortical areas of the brain. NIR t-PBM has recently emerged as a potential therapy for brain disorders. This study assessed the efficacy of repeated sessions of NIR t-PBM on sexual dysfunction.
Methods: We performed a secondary analysis of a double-blind clinical trial on t-PBM for major depressive disorder (MDD). Twenty individuals received NIR t-PBM (n=9) or sham therapy (n=11) twice a week for 8 weeks. Sexual desire, arousal, and orgasm were assessed using the Systematic Assessment for Treatment-Emergent Effects-Specific Inquiry (SAFTEE-SI).
Results: The mean improvement in sexual function (decrease in SAFTEE sex total score) in subjects receiving t-PBM in NIR-mode was significantly greater than in subjects receiving sham-mode in the whole sample (NIR [n = 9] -2.55 ± 1.88 vs. sham [n=11] -0.45 ± 1.21; z = 2.548, P = 0.011]) and in the completers (NIR [n = 5] -3.4 ± 1.95 vs. sham [n = 7] -0.14 ± 1.21; z = 2.576, P = 0.010]).
Conclusions: This exploratory study with a small sample size indicates that repeated sessions of NIR t-PBM may be associated with therapeutic effects on sexual dysfunction. The latter appeared unrelated to the antidepressant effect of t-PBM in our cohort.
Supported By: Brain and Behavioral Research Foundation (NARSAD - Dr. Cassano); Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, NIH Award UL1 TR001102), and financial contributions from Harvard University and its affiliated academic healthcare centers
Keywords: Transcranial photobiomodulation, Sexual Dysfunction, Near-infrared light (NIR), Neuromodulation, Depression

S199. Neural and Affective Effects of Reproductive Steroid Manipulation in Reproductive-Related Mood Disorders

Crystal Schiller[1], Gabriel Dichter[1], Joshua Bizzell[1], Sarah Johnson[1], Erin Richardson[1], Peter Schmidt[2], Aysenil Belger[1], and David Rubinow[1]

[1]University of North Carolina at Chapel Hill, [2]National Institute of Mental Health

Background: Neuroendocrine factors are purported to play a role in the etiology of reproductive-related mood disorders. Here we present data from two pharmaco-fMRI studies investigating the effects of experimentally controlled reproductive steroid exposure on reward circuit activation.
Methods: In Study 1, the hormone states of pregnancy and parturition were simulated in women with a history of PPD (n=15) and controls (n=15) by inducing hypogonadism, adding back supraphysiologic doses of estradiol (E2) and progesterone for 8 weeks ("addback"), and then withdrawing both steroids ("withdrawal"). In Study 2, depressed perimenopausal women (MDD; n=20) and controls (without depression) (n=23) were treated with transdermal E2 for 3 weeks. In both studies, fMRI sessions, conducted at baseline and post-treatment, included the monetary incentive delay task (MID).
Results: In Study 1, 11 of the 15 women with a history of PPD were "hormone sensitive" (i.e., showed 30% increased mood symptoms during the hormone challenge). Hormone sensitive women showed decreased activation of the bilateral putamen

($p<.01$) during hormone withdrawal (compared with baseline), whereas controls showed no change in brain activation. In Study 2, MDD women showed decreased mood symptoms ($p's<.005$) following E2 treatment, whereas controls showed no change. fMRI analyses are underway.
Conclusions: Our data support a role of E2 and progesterone in reproductive-related mood disorders. Steroid changes were associated with perturbation of neural reward circuitry and consequent depressive symptoms in hormone sensitive women, and E2 reduced mood symptoms in those with perimenopausal depression. The neural reward circuitry may underlie both the susceptibility to and mediation of hormone-related affective dysfunction.
Supported By: NARSAD, K23 MH105569, R21 MH101409, Foundation of Hope
Keywords: Estradiol, Pharmaco-fMRI, Postpartum Depression, Perimenopause, Estrogen/Progesterone

S200. Time-Dependent Changes in Affect-Related Behavior and VTA DA Activity Throughout the Rodent Postpartum Period

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Background: The onset of motherhood is accompanied by alterations in emotional and affective behaviors (O'Hara, 2014). However, there is little data regarding the neural adaptations occurring shortly after birth associated with these changes. Although the dopamine (DA) system is involved in affect, maternal motivation and postpartum depression (Moses-Kolko et al. 2014; Nephew et al. 2015), little is known about postpartum DA function. To this end, we evaluated affect-related behavior and ventral tegmental area (VTA) DA neuron activity in virgin and postpartum female rats.
Methods: Virgin and postpartum (PP) female rats were tested in an affect-related behavioral tes battery (e.g. elevated plus maze, social approach, novelty suppressed feeding, and forced swim) across different timepoints (i.e. early/late postpartum; n=9-16 per group). In vivo single-unit recordings of VTA DA neurons were conducted and 3 activity parameters were measured: i) number of spontaneously active DA cells (i.e. population activity), ii) basal firing rate and iii) firing pattern (i.e. percentage of spikes firing in bursts). Comparisons of +3 groups were analyzed using one-way ANOVA; pairwise comparisons were analyzed using t-tests.
Results: Early postpartum rats exhibited reduced social motivation (1d-PP, 3d-PP; $p<0.05$), increased immobility (1d-PP, $p < 0.5$) and a reduction in the number of active VTA DA cells (1d-PP, 3d-PP; $p<0.01$) compared with virgins. These changes were not observed in late (22-24d-PP) postpartum rats.
Conclusions: Our findings suggest parity-driven changes in affect and VTA DA neuron activity vary throughout the postpartum period and are more pronounced in early postpartum females, which exhibit blunted DA activity.
Supported By: F32-MH110128; RO1-MH101180
Keywords: Postpartum, Social Behavior, Dopamine, Electrophysiology, Ventral Tegmental Area

S201. Sex Differences in the Reward System: Neural, Autonomic, and Behavioral Responses in Healthy Humans

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Background: Sexual dimorphism of reward-related circuitry and behaviors have been described in rodents, but sex differences across multiple outcome types (behavioral, autonomic, and neural) in humans are not well studied. Here we report responses from healthy young adults as they perform a monetary incentive delay (MID) task.
Methods: We enrolled 222 subjects to perform a MID task in which stimuli varied by salience (high versus low) and valence (win versus loss), while electrodermal responses were measured as an index of autonomic arousal. Some participants also underwent functional magnetic resonance imaging (fMRI) while performing the same task. Subjects were analyzed according to behavioral (n=222), autonomic (n=201), and neural (n=44) outcomes. Salience and valence contrasts were calculated, and sex differences were characterized with Hedges' effect size (g), t-tests, and general linear models.
Results: Male subjects reported greater subjective arousal to salient stimuli ($g = 0.51$, $p = 0.0005$) and their performance was more sensitive to condition salience ($g = 0.39$, $p = 0.007$). Autonomic responses to salience were greater among male participants ($g = 0.47$, $p = 0.001$). Furthermore, fMRI analyses showed that nucleus accumbens responses to salience were greater in men ($g = 0.93$, $p = 0.006$).
Conclusions: Relative to men, women in our sample demonstrated less sensitivity to salience of monetary incentives across behavioral, autonomic, and neural outcomes. These findings represent evidence in agreement across multiple domains of sex differences in monetary reward-related circuitry and behaviors in humans. These differences may be relevant to sexually dimorphic disorders of reward circuitry.
Supported By: NIMH (K23 MH092648); NCRR (UL1 RR024986); NCATS (2UL1 TR000433)
Keywords: Skin Conductance Responses, Autonomic Nervous System, BOLD fMRI, Sex Differences, Electrodermal Response

S202. T2-Relaxation Time in Prefrontal Regions and Cerebellar Lingula Size Prospectively Predict Degree of Substance Use in Maltreated Individuals

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Background: Childhood maltreatment accounts for 64% of the population attributable risk for addiction to illicit drugs. We

previously reported that degree of drug use in maltreated individuals correlated with T2-relaxation time (T2-RT- an indirect measure of relative cerebral blood volume) in prefrontal regions and size of the lingula of the cerebellar vermis. A key question is whether there is a causal relation and if these measures could predict subsequent degree of use in a prospective longitudinal study.

Methods: We recruited subjects at 18-19 years of age (N=148, 48M/100F, 77% maltreated) neuroimaged them at this time point, and collected Timeline Followback data on degree of alcohol, cannabis and other drug use at entry and then annually thereafter as they entered the 20-21-year period of accelerated use. Brain regions examined were limited to those identified prior to study initiation.

Results: Lingula size was associated with increased frequency and quantity of alcohol use and strongly moderated (amplified) the developmental increase in alcohol use that occurred after age 19 (p=.001, linear mixed model). Similarly, T2-RT in the dorsolateral prefrontal cortex predicted the frequency and moderated the development increase in use of drugs other than cannabis, whereas T2-RT in the ventral portion of the orbital frontal cortex predicted the frequency and severity of cannabis use.

Conclusions: These studies provide further support for the role of the cerebellar vermis, dorsolateral prefrontal and orbitofrontal cortex in drug and alcohol abuse and also suggest an unanticipated degree of specificity between brain region affected and drug class used.

Supported By: RO1 awards MH-091391 and DA-017846 to MHT

Keywords: Childhood Maltreatment, Substance Use, T2 Relaxometry

S203. Fatty Acid Amide Hydrolase Polymorphism C385A Associated With Dopamine D2/3 Receptor Levels: A PET Study With [11C]-(+)-PHNO

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Background: A common missense variant (Pro129Thr) in the gene encoding fatty acid amide hydrolase (FAAH; rs324420 C385A), the degradative enzyme for the major endocannabinoid anandamide, results in reduced levels of FAAH protein. This polymorphism is associated with elevated risk for addiction and obesity. It has been suggested that enhanced anandamide signaling may be associated with alterations in dopaminergic neurotransmission which have been noted in addictions. Here we tested whether this functional variant of FAAH (C385A) is associated with differences in brain D2/3 receptor availability.

Methods: Brain binding of the dopamine D3 preferring radioligand [11C]-(+)-PHNO was measured with positron emission tomography (PET) in 79 healthy control subjects genotyped for FAAH (C385A).

Results: We found that the FAAH genetic variant C385A is associated with measurable regional differences in [11C]-(+)-PHNO binding. Those with the FAAH variant (AA / AC; n = 36 of 79), associated with reduced FAAH activity, had significantly greater [11C]-(+)-PHNO binding in the D3-rich limbic striatum (LST), globus pallidus (GP) and ventral pallidum (VP) (9%-14%; $p < 0.05$) but not in the dorsal striatum, where binding of [11C]-(+)-PHNO is due to D2 receptors.

Conclusions: We report for the first time that a common genetic polymorphism of FAAH leading to reduced enzymatic activity is associated with greater [11C]-(+) PHNO binding, predominantly in dopamine D3-rich brain regions. These results suggest a dopaminergic mechanism involving greater D3 dopamine receptors in the risk for addiction and obesity among those with the FAAH C385A variant. Replicating these findings in FAAH knock-in mice may help confirm these results.

Supported By: NIH, NIDA

Keywords: [11C]-(+)-PHNO, FAAH polymorphism (rs324420, C385A, P129T), Endocannabinoid System, Dopamine, PET Imaging

S204. Distinct Neural Networks Predict Opioid Versus Cocaine Abstinence in Polysubstance Users

To see this abstract, please see Oral Abstract #O16.

S205. "Super Bingers": Traits and Consumption Patterns Associated With High-Intensity Drinking

Vijay Ramchandani[1], James Morris[1], Julia Swan[1], Joshua Gowin[2], Bethany Stangl[1], Melanie Schwandt[1], Falk Lohoff[1], and Nancy Diazgranados[1]

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Background: High intensity drinking, i.e., drinking alcohol at multiple levels of the binge threshold (5+ drinks for males (M), 4+ drinks for females (F)) has been identified as a significant risk factor for developing alcohol problems. This study aims to evaluate personality traits in high-intensity drinkers and consumption patterns in a human laboratory intravenous alcohol self-administration (IV-ASA) study.

Methods: We analyzed data from a non-treatment seeking sample (M: 706, F: 474), classified into 4 groups: Level 0 (no binges), Level 1 (F: 4-7, M: 5-9 drinks) Level 2 (F: 8-11, M: 10-14 drinks) and Level 3 (F: 12+, M: 15+ drinks), based on the highest drinking session in the 90-day Timeline Followback assessment. We examined several trait measures (UPPS-P Impulsivity Scale, Barratt's Impulsiveness Scale, Buss Perry Aggression Questionnaire) to identify mean differences between groups. A subset of participants (n=200) completed a

free-access IV-ASA session to assess alcohol consumption in a controlled setting.
Results: Alcohol consumption patterns showed significant differences between groups, with number of drinking days and average drinks/drinking day all increasing with binge-intensity level. There were also significant differences for impulsivity and aggression measures ($0 = 1 < 2 = 3$). During IV-ASA, greater consumption (number of alcohol rewards, peak level) was proportional to the binge-intensity level ($0 < 1 < 2 = 3$).
Conclusions: High-intensity drinkers showed greater alcohol consumption overall and during the IV-ASA session. The elevated aggression, impulsivity, and overall heavy drinking patterns of super-bingers suggest a behavioral profile associated with greater risk for developing alcohol use disorder.
Supported By: NIAAA Division of Intramural Clinical and Biological Research (Z1A AA000466)
Keywords: Binge Drinking, Impulsivity, Aggression, Alcohol Self-Administration

S206. Effect of Alcohol on Ad Lib Eating: The Role of Food-Related Reward and Inhibitory Control

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Background: Heavy alcohol use is associated with obesity. This may be due to calories in the alcohol beverage itself or to effects of alcohol on food consumption. For example, alcohol may increase food consumption by increasing the value of food rewards, or by decreasing inhibition, which limits food intake.
Methods: We examined the effects of alcohol on tasks measuring the value of food, inhibitory control, and consumption of snack foods. Healthy social drinkers participated in three sessions where they received alcohol (0.8 g/kg), a placebo beverage and Gatorade, in a counter balanced order. After consuming the beverage subjects completed a food purchasing task, a Cued Go/No-go task and a taste test measure of snack food consumption.
Results: Alcohol did not increase either the value of food or snack food intake, but it did increase the total number of calories consumed [$F(1.84, 36.78) = 36.24$, $p < .001$], and impaired inhibitory control [$F(1.86, 33.45) = 3.81$, $p = .03$]. To calculate relationships between the effect of alcohol on inhibition and calories consumed from food, inhibition performance and food intake during placebo sessions were subtracted from alcohol sessions and then correlated. There was a marginal correlation between effects of alcohol on dis-inhibition and effects on food intake [$r(19) = .340$, $p = .077$].
Conclusions: This suggests the dis-inhibitory effect of alcohol contributes to increased food consumption. In conclusion we found little evidence that alcohol increased food intake or food value, but the effects of alcohol on inhibition may influence subsequent food consumption.
Supported By: NIDA DA02812
Keywords: Alcohol, Inhibition, Food-Related Reward

S207. Cortical-Brainstem Projections Gate Compulsive Alcohol Drinking

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Background: Alcohol-induced plasticity in medial prefrontal cortex (mPFC) has been implicated in the development of compulsive drinking, a cardinal symptom of alcohol use disorders. However, we have little understanding of how neurons in mPFC are encoding alcohol-related stimuli in real-time, and what downstream circuits are involved.
Methods: Head-mounted mini-microscopes and the genetically-encoded calcium indicator GCaMP6m were used to record calcium activity in mPFC neurons with single-cell resolution during free behavior in male C57BL/6J mice. We developed a novel Pavlovian conditioning task where a cue predicted availability of either alcohol (15% v/v), or alcohol adulterated with the bitter tastant quinine (0.25-1.0mM), to test for compulsion, before and after two weeks of access to alcohol in binge drinking model.
Results: Binge drinking produced wide individual differences, whereby approximately 50% of animals continued to consume high levels of alcohol despite quinine adulteration after binge exposure, but not before. We identified a population of mPFC neurons that project to the dorsal periaqueductal gray (dPAG), which are robustly modulated during drinking (352 neurons, 57 exited, 77 inhibited). Surprisingly, the excitation/inhibition balance during animals' first experience with alcohol predicted compulsive drinking more than three weeks later ($n=14$, $r=-0.58$, $p=0.04$). Optogenetic activation (eYFP, $n=6$; channelrhodopsin-2, $n=9$, $p<0.01$) or inhibition (eYFP, $n=6$; halorhodopsin, $n=10$; $p<0.0001$) of mPFC-dPAG neurons decreased or increased alcohol consumption, demonstrating bi-directional control of compulsive drinking behaviors.
Conclusions: mPFC-dPAG neurons attribute positive or negative valence to unconditioned stimuli. Binge drinking reduces the sensitivity of this cortical-brainstem pathway to punishment, thereby driving compulsive drinking in a subset of animals.
Supported By: NARSAD Young Investigator Award; K99/R00 DA045103
Keywords: Calcium Imaging, Machine Learning, Optogenetics, Individual Differences, Binge Drinking

S208. The BrainPAC Project: Developing and Validating a Purpose-Built, RDoC-Informed Assessment Tool for Addictions

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Background: Neurocognition is rarely assessed and targeted in addiction treatment, despite a wealth of evidence supporting its role in driving addictive behaviors. Further, there are currently no scalable tools measuring reward-, fear- and control-related, neural processes central to addictions. The BrainPAC Project sought to develop a purpose-built technology to assess the key NIMH-RDoC constructs driving addictions, as identified by a Delphi panel of 44 international experts.
Methods: Psychometrically robust neurocognitive paradigms and self-report scales were selected for the constructs of response selection/inhibition, reward valuation, action selection, reward learning, expectancy/reward prediction error, habit and compulsivity. An app was developed together with Torus Games, which involved the gamification of neurocognitive tasks and the development of an app environment for the measures. The app was validated online and in an inpatient addiction clinic.
Results: Gamified tasks were highly correlated with the original paradigms ($n = 100$, r's = 0.73-0.83, p's < 0.05), with no differences in key metrics (p's > 0.05). The gamified tasks were rated as more mentally stimulating, less boring/repetitive, and easier to concentrate on (p's < 0.05). The gamified tasks were associated with real-world behaviors, such as gambling status [$n = 501$, $F(1,84) = 4.4$, $p < 0.05$] and past alcohol use (timeline follow-back; $r = 0.27$, $p < 0.05$).
Conclusions: A neuroscience-informed, purpose-built and self-administered, gamified battery can be a reliable and valid approach for the online assessment of addictive behaviors. Moreover, this innovative tool is sensitive to real-world behaviors, and has significant implications for risk detection and the monitoring/personalisation of addiction treatment.
Supported By: Government Industry Grant - ICG000342 and ICG000737; NHMRC Grant - 1162031
Keywords: Research Domain Criteria (RDoC), Addiction, Transdiagnostic, Neurocognition, Translational Neuroscience

S209. Machine Learning Identifies Common and Specific Markers of Addiction to Five Different Classes of Drugs

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Background: The goal of this study was to identify behavioral markers that classify opiate dependence (OD), stimulant dependence (SD), alcohol dependence (AD), cannabis dependence (CD), and nicotine dependence (ND) using machine-learning approaches.
Methods: The sample included 595 participants (42 AD, 92 CD, 187 ND, 168 SD, and 159 OD). LASSO penalized regression models and 10-fold cross validation were used to predict OD, SD, AD, CD, and ND, based on 54 demographic, psychiatric, personality, and neurocognitive variables. Psychiatric measures included conduct disorder, ADHD, antisocial personality disorder, psychopathy, depression, and anxiety. Personality measures included trait impulsivity, sensation seeking, aggression, and anxiety sensitivity. Neurocognitive measures included decision-making, delay discounting, risk taking, and response inhibition.
Results: Machine-learning models achieved high out-of-sample classification accuracy (OD AUC=0.91; SD AUC=0.89; AD AUC=0.84; CD AUC=0.82; ND AUC=0.74). Psychopathy was the only predictor common to all drug classes. Sensation seeking was a common predictor for all drugs except nicotine. Depression was common to dependence on AD and ND. Urgency uniquely predicted HD & AD, trait anxiety – HD & CD, and anxiety sensitivity – AD & CD. Increased delay discounting predicted AD, ND, and SD, whereas decreased delay discounting predicted HD & CD. Disadvantageous decision-making was specific to AD.
Conclusions: Our findings reveal both common and substance-specific predictors of dependence on five different classes of drugs. Overall, personality variables had higher predictive utility than neurocognitive variables. Psychopathy was the only common predictor of dependence on all drug classes, suggesting that it may be an important diagnostic marker for addiction, regardless of drug class.
Supported By: This research was supported by the National Institute on Drug Abuse and the Fogarty International Center under award number R01DA021421 to Jasmin Vassileva.
Keywords: Addiction, Risk Factors, Machine Learning

S210. Comparison on Sex Differences With Resting-State Functional Magnetic Resonance Imaging Shows Opposite Patterns of Functional Brain Connectivity

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Background: Cocaine users have increased brain functional connectivity (FC) within mesocorticolimbic areas, as shown by resting-state functional magnetic resonance imaging (rsfMRI). However, cocaine use manifestations have sex differences, particularly for smoked cocaine. Thus, we aimed to test sex differences in the FC of cocaine smokers.
Methods: Cocaine users (20 males, CKM; and 20 females, CKF) and healthy controls (20 males, HCM; and 20 females, HCF) undertook a rsfMRI exam. Results were analyzed with Regional Homogeneity (ReHo) and based on the areas that showed sex differences, seed-based FC was investigated.
Results: CKF showed lower ReHo than other groups in bilateral postcentral gyri; and lower regional ReHo only than CKM in right claustrum, superior frontal and parahippocampal gyri. CKM showed higher ReHo than other groups in right middle temporal gyrus, left superior frontal gyrus and claustrum. Related to CKF, CKM showed results of higher FC

between frontal, central and paralimbic areas. Differences between male groups were restricted to higher FC for CKM across temporal areas; for female groups there were lower FC for CKF within cortical areas. Correlational analyses indicated that claustrum-precuneus FC associates with years of cocaine use for CKF (r= -0.553, p= 0.011), but not for CKM (r= 0.258, p= 0.273). Differently, years of cocaine use associated with parahippocampal-middle frontal gyrus FC for CKM (r= 0.555, p = 0.011), but not for CKF (r= -0.222, p= 0.348).

Conclusions: Findings support sex differences in intrinsic brain functioning of cocaine users, suggesting sex-specific cocaine effects, which needs consideration when targeting evidence-based interventions in the future.

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Keywords: Sex Differences, Cocaine, Resting State Functional Connectivity MRI (fcMRI), Addiction, Gender

S211. Sex Differences in Neural Cue-Reactivity are Moderated by Early Life and Currently Perceived Stress in a Population of Heavy Drinkers

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Background: While relapse in women with alcohol use disorder (AUD) is suggested to be more strongly related to childhood trauma and currently perceived stress than in men with AUD, the underlying neural mechanisms are unclear. The aim of this study is to investigate if the relation between sex and neural cue-reactivity is moderated by childhood trauma and/or state anxiety.

Methods: Neural cue-reactivity was measured using fMRI while 27 females and 28 males performed an alcohol cue reactivity paradigm. Standard preprocessing and first level analyses were performed in SPM8. Cue-reactivity data were extracted from the ventral (VS) and dorsal (DS) striatum and included in hierarchical regression analyses to predict striatal cue-reactivity from sex, childhood trauma and state anxiety, the 2-way and the 3-way interactions.

Results: Cue reactivity in the DS (but not VS) was most strongly predicted by the 3-way interaction between sex, childhood trauma and state anxiety (ΔR2=0.15, p=0.005, sr2=0.14). Within group regression analyses revealed that there was a negative correlation between state anxiety and cue-reactivity in males with a low history of childhood trauma, but a positive correlation between state anxiety and cue-reactivity in males with a high history of childhood trauma (ΔR2=0.28, p=0.006, sr2 =0.27). Striatal cue-reactivity in females was unrelated to childhood trauma and/or state anxiety.

Conclusions: These findings do not explain why relapse in women is more strongly driven by early life and perceived stress. To fully understand the clinical value of this study, the findings should be replicated AUD patients and related to AUD treatment outcome.

Supported By: Amsterdam Brain Mind Project

Keywords: Alcohol Use Disorder, Sex Differences, Childhood Trauma, Perceived Stress, Striatum

S212. The Role of Somatostatin Positive Interneurons in the Prelimbic Cortex in Alcohol Consumption

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Background: Alcohol Use Disorders (AUDs) and major depressive disorder (MDD) are highly comorbid disorders, both of which are major health and social concerns. Somatostatin (SST) expressing GABAergic interneurons in the forebrain have long been implicated in MDD, though their role in AUDs is currently under investigated. Previous work has shown that artificially increasing the function of SST neurons globally in the brain has antidepressant drug treatment-like consequences. Due to the comorbidity between AUDs and MDDs, we further investigated how SST neurons in the prelimbic cortex are altered following DID-binge like ethanol exposure.

Methods: Binge-like ethanol consumption & DREADDs: Following one week of DID, mice underwent surgery (below). They then underwent 3 subsequent cycles of DID. On the second week they received saline injections 45 minutes before the binge session, and on the third week they received 3 mg/kg CNO. DREADD surgeries: SST-ires-Cre mice were injected with AAV2-hSyn-DIO-hM3D(Gq)-mCherry or AAV2-hSyn-DIO-mCherry control, 400nl to the PLC. Mice were given 1 week to recover before DID.

Electrophysiology: Experiments on spontaneous inhibitory post-synaptic transmission were conducted as previously published. Mice were sacrificed at 10am on the “binge day” during the 4th cycle.

Results: SST neurons in the PLC may play a role in binge-like ethanol consumption. We assessed both the ability of increasing and decreasing SST neuron excitability on binge drinking, as well as SST neuronal features.

Conclusions: SST neurons are a promising target for the treatment of AUDs, and further research will seek to understand the underlying circuity involved and relevant therapeutic targets on these neurons.

Supported By: NARSAD Young Investigator Award, Penn State Social Science Research Institute

Keywords: Drinking In The Dark, Somatostatin Neuron, Electrophysiology

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