Applications of Resting-State Functional Connectivity to Neurodegenerative Disease

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KEYWORDS

• Resting-state fMR imaging • Functional connectivity • Alzheimer disease • Frontotemporal dementia • Neurodegenerative disease • Mild cognitive impairment • Risk factors • Amyloid beta

KEY POINTS

- Resting-state functional MR imaging–based functional connectivity method maps symptoms-associated functional network deterioration in vivo in neurodegenerative diseases.
- Distinct syndrome-specific network functional connectivity changes in clinical and prodromal Alzheimer disease (AD) and frontotemporal dementia (FTD) variants.
- Specific gene expressions moderate functional connectivity in clinical and asymptomatic AD and FTD.
- Amyloid beta accumulation is associated with atypical functional connectivity patterns in preclinical AD.
- Better cohort stratification and advanced computational and statistical techniques are essential for better prognosis and personalized treatment.

INTRODUCTION

Neurodegeneration, characterized by gradual and selective spreading of pathologic changes in a target brain network, leads to specific behavioral and cognitive dysfunctions. Alzheimer disease (AD) and frontotemporal dementia (FTD) are the 2 most common causes of neurodegenerative diseases among patients younger than 65 years,[1,2] whereas AD is more common among patients older than 65 years. AD usually begins with episodic memory loss with prominent medial temporal, posterior cingulate/precuneus, and lateral temporoparietal atrophy.[3,4] In contrast, 3 behavioral or language-related subtypes make up the clinical FTD spectrum: behavioral variant (bvFTD),[5] semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic primary progressive aphasia (nfaPPA).[6] BvFTD features prominent social misconduct and emotional deficits with anterior cingulate, frontoinsular, striatal, and frontopolar degeneration. SvPPA results in loss

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of word and object meaning accompanied by left predominant temporal pole and subgenual cingulate involvement. nfaPPA presents with nonfluent, effortful, and agrammatic speech and is associated with left frontal operculum, dorsal anterior insula, and precentral gyrus atrophy. Moreover, presence of the apolipoprotein E (APOE) ε4 is the strongest genetic risk factor of sporadic AD.[7] FTD syndromes, in contrast, result from a group of distinct underlying molecular pathologic entities referred to collectively as frontotemporal lobar degeneration (FTLD). FTLD is further divided into 3 major molecular classes including tau (FTLD-tau), transactive response DNA-binding protein of 43 kDA (TDP-43, FTLD-TDP), and, least commonly, fused in sarcoma (FUS) protein (FTLD-FUS).[8] Although most patients have sporadic disease, several autosomal dominant culprit genes have been identified, with mutations in the genes encoding microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and *C9orf72* accounting for most known genetic causes.[9]

A network-based neurodegeneration hypothesis was proposed 2 decades ago based on neuropathology studies[10] and transgenic animal models.[11] As effective, disease-specific, and personalized treatments are emerging for neurodegenerative diseases, an objective, noninvasive, biologically based network-sensitive neuroimaging assay is needed to predict risk, diagnose early, stage, and monitor the course and treatment of neurodegenerative diseases. Researchers have demonstrated that, unlike traditional region-based approaches, connectivity-based approaches can map large-scale networks in health and detect the network-level alterations in disease. This review focuses on the recent findings on resting-state functional MR imaging–based (rsfMR imaging) functional connectivity alterations in neurodegenerative diseases,[12–19] especially AD and FTD. as well as preclinical populations.[20] Specifically, we first introduce the rsfMR imaging–based functional connectivity methods and then highlight 3 major aspects: can resting-state functional connectivity analyses (1) reveal syndrome-specific network changes in neurodegenerative diseases, (2) uncover disease mechanism and the underlying neuropathology, and (3) detect early changes and track disease severity. Last we discuss the possible future directions.

MAPPING BRAIN CIRCUITS: RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING

Resting-state fMR imaging can be easily acquired in cognitively impaired populations and has offered valuable insights in the study of AD.[21] Instead of the changes evoked by specific stimuli, rsfMR imaging captures the macroscopic hemodynamic fluctuations at slow frequencies (<0.1 Hz). Regions showing synchronized spontaneous activities are functionally connected, as they also tend to coactivate or deactivate with similar spatial patterns during task,[22] and are often supporting highly relevant cognitive functions.[23,24] Therefore, functional connectivity derived from rsfMR imaging reveals network-based intrinsic functional connectivity.[25] These intrinsic connectivity networks (ICNs) change systematically at different vigilance and wakefulness conditions, developmental stages, and have homologues across species, suggesting their fundamental role in cognition.[21] Importantly, the interaction among networks is also critical to normal and aberrant cognitive performance and mental states,[26] and as such have offered valuable insights about the symptom manifestation and pathologic mechanisms of many neurodegenerative diseases.

Functional connectivity is often measured by temporal correlations between spatially distributed brain regions based on rsfMR imaging data. **Fig. 1** summarizes 4 primary methods for deriving functional connectivity from rsfMR imaging data. Seed-based analysis extracts ICNs by correlating the blood-oxygenation-level-dependent (BOLD) signals of a seed region to other target regions or with the rest of the brain (see **Fig. 1**A).[23] The representativeness and utility of the connectivity and network is therefore seed-dependent, as showcased by Seeley and colleagues,[27] who used 5 characteristic seeds of 5 distinctive neurodegenerative syndromes and showed the correspondence between unique syndrome and specific ICNs (**Fig. 2**).

Other approaches consider multiple brain regions simultaneously. In independent component analysis (ICA), spontaneous BOLD signals from all brain voxels are decomposed into spatially nonoverlapping and temporally coherent networks[28] (see **Fig. 1**B). Wu and colleagues[29] used ICA to extract ICNs associated with high-level cognition and reported that at-risk individuals, namely APOE ε4 carriers, had lower within-network functional connectivity that might precede cognitive decline. In analysis using parcellation-based connectivity matrices, the brain is segregated into predefined regions of interest (ROIs).[30] The functional connectivity between all pairs of regions are computed and arranged in matrix format (see **Fig. 1**C). Univariate or multivariate statistical analysis is then performed on the matrices to identify discernable differences between groups or conditions.[31]

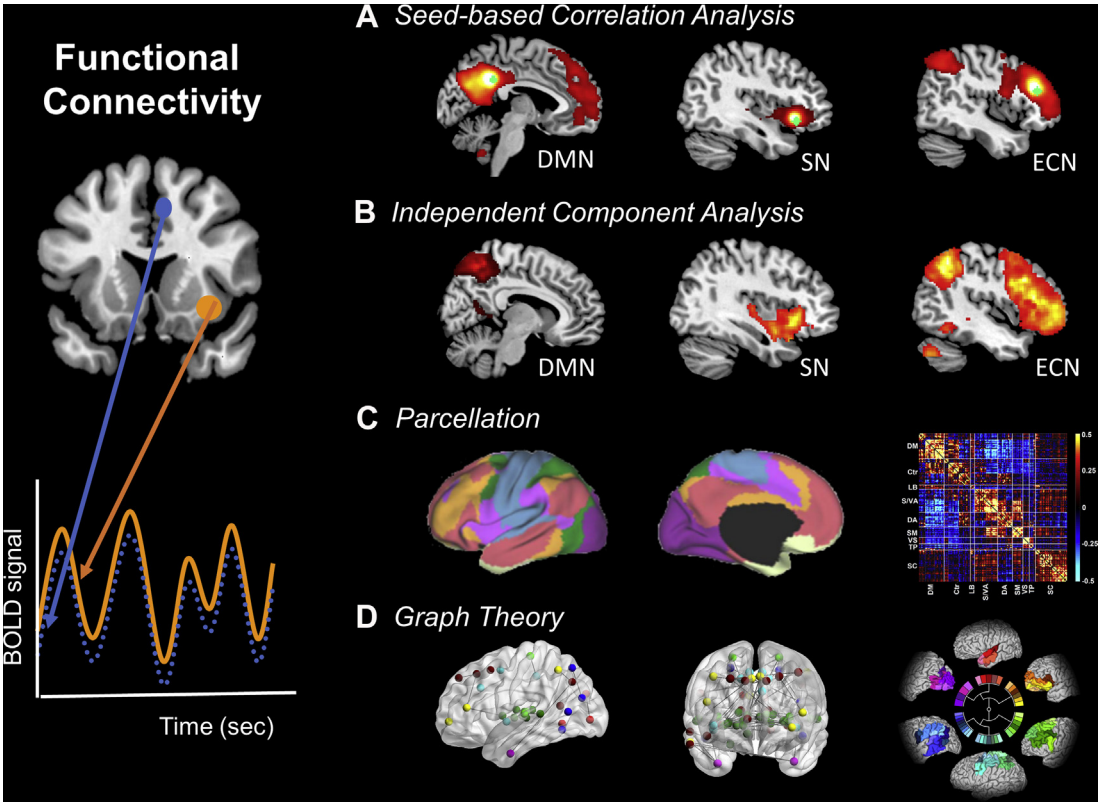

Fig. 1. Summary of common techniques to derive functional connectivity from rsfMR imaging data. Intrinsic functional connectivity describes the synchronized spontaneous low-frequency BOLD fluctuations (<0.1 Hz) between brain regions during task-free or resting-state condition (*left panel*). There are several analytical methods to derive functional connectivity from rsfMR imaging data. (*A*) In seed-based correlation analysis, large-scale functional connectivity networks are extracted with respect to a seed region (*green dots*). Three networks of primary interest in studies of neurodegenerative diseases are illustrated. (*B*) In ICA, multiple brain networks are identified by maximizing the spatial independence of the hemodynamic signals. A network comprises brain regions sharing the similar hemodynamic time course. Seed-based and ICA typically give very similar networks. (*C*) In parcellation-based connectivity matrix analysis, the connectivity patterns between a set of predefined brain regions (eg, functional parcellations[171]) are represented as a matrix and subject to statistical analysis. (*D*) In graph theoretic analysis, topological measures that describe different properties of the organization of the connectivity strength (edges) across multiple regions (nodes) or networks (nodes of the same color), that is, connectome, are examined. Abstraction of the brain as a graph also allows informative visualization, such as connectogram (modified from Nieto-Castanon[172] under the Creative Common License). BOLD, blood oxygenation level dependent; DMN, default mode network; ECN, executive control network; ICA, independent component analysis; SN, salience network.

Graph theoretic approach (see **Fig. 1**D) is highly useful in capturing and visualizing complex brain interactions embedded in these high dimensional matrices. In a brain graph, each ROI is a node and the functional connectivity between a pair of ROIs is an edge. Nodes and edges may be clustered and segregated such that nodes can belong to the same or different networks and edges can indicate within-network or between-network connectivity. Graph theoretic measures then capture these systematic organizations at nodal, network, and whole-brain levels.[32,33] By modeling connectivity as complex networks, graph theoretic analyses provide a new avenue to characterize macroscopic brain topology and reveal disease mechanisms.[34–36] As detailed later in this article, Zhou and colleagues[37] derived functional connectivity matrices based on 1128 ROIs (635,628 ROI pairs) and used graph theoretic measures on such huge functional connectome matrices to derive topological parameters to examine the network-based neurodegenerative hypothesis.

With these methods, rsfMR imaging provides a novel network-sensitive, immediately repeatable, noninvasive tool to examine human functional connectome. Importantly, these methods are broadly applicable to both static and time-varying functional connectivity, the latter of which

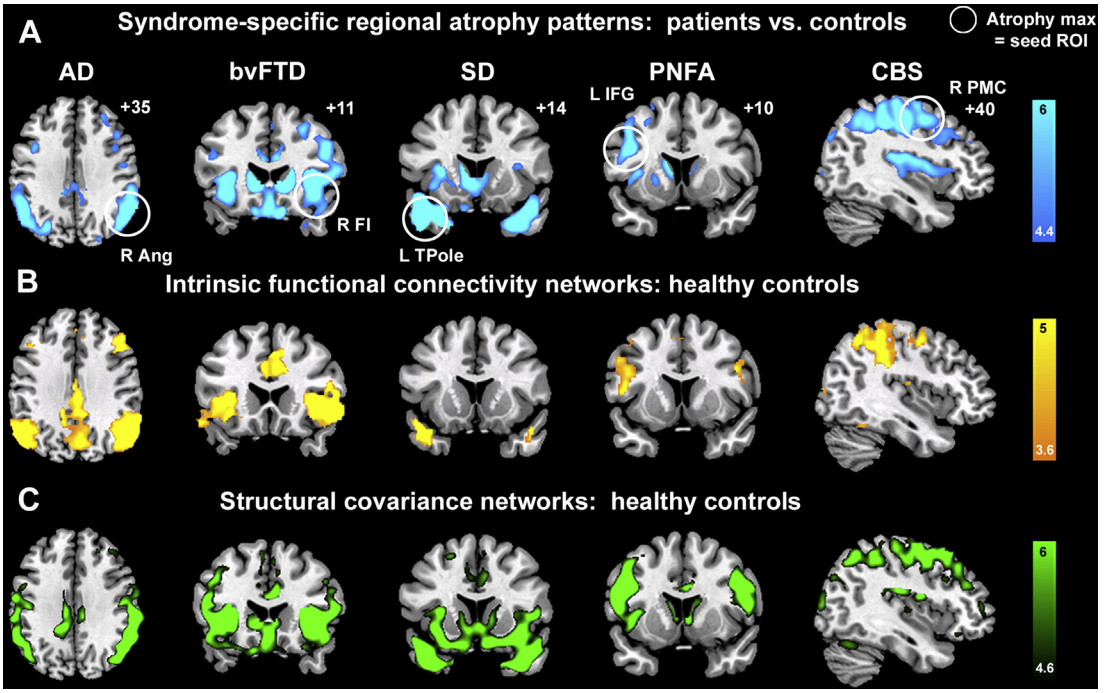

Fig. 2. Convergent syndromic atrophy, healthy ICN, and healthy structural covariance patterns. (*A*) Five distinct clinical syndromes showed dissociable atrophy patterns, whose cortical maxima (*circled*) provided seed ROIs for ICN and structural covariance analyses. (*B*) ICN mapping experiments identified 5 distinct networks anchored by the 5 syndromic atrophy seeds. (*C*) Healthy subjects further showed GM volume covariance patterns that recapitulated results shown in (*A*) and (*B*). Color bars indicate *t*-scores. In coronal and axial images, the left side of the image corresponds to the left side of the brain. ANG, angular gyrus; FI, frontoinsula; IFGoper, inferior frontal gyrus, pars opercularis; PMC, premotor cortex; TPole, temporal pole. (*Adapted from* Seeley WW, Crawford RK, Zhou J, et al. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009;62(1):42–52.)

better captures neural dynamics at a finer time scale and is shown to be of clinical utility.[38]

CAN RESTING-STATE FUNCTIONAL MR IMAGING–BASED CONNECTIVITY ANALYSES REVEAL SYNDROME-SPECIFIC NETWORK CHANGES?

To date, rsfMR imaging has been widely used to chart normal human functional connectivity architecture[24,39,40] and predict individual differences in human behavior and cognition.[41–43] Such typical architecture provides important framework to understanding diseases. Seeley and colleagues[27] confirmed that spatial atrophy patterns in 5 distinct neurodegenerative syndromes, including AD and variants of FTD, mirror normal human ICNs derived from rsfMR imaging (see **Fig. 2**, rows 1 and 2). Specifically, AD causes atrophy within a posterior hippocampal-cingulo-temporal-parietal network, which resembles the "default mode network" (DMN) in health.[39,44,45] BvFTD, in contrast, features atrophy in anterior insula, anterior cingulate cortex (ACC), and subcortical and thalamic regions, mirroring the "Salience Network" (SN) in health.[43,46,47] The SN is often activated in response to social-emotionally significant internal and external stimuli,[48,49] whereas elements of the DMN are usually involved in episodic memory and visuospatial imagery.[44,50,51] Notably, although the anterior SN degenerates in bvFTD, posterior cortical functions survive or even thrive, at times associated with emergent visual creativity.[52,53] AD, in contrast, maintains socioemotional functions and features episodic memory loss and visuospatial dysfunction.

Based on the inversely correlated relationship between the salience and DMNs in the healthy brain[54,55] and the opposing symptom-deficit profiles of AD and bvFTD, Seeley and colleagues[56] proposed a "reciprocal networks" model in which each network exerts an inhibitory influence on the other. This model has led to the hypothesis of divergent functional connectivity changes in AD and bvFTD. Zhou and colleagues[57] later tested this hypothesis by comparing AD and bvFTD to age-matched healthy controls using task-free fMR imaging ICN technique. As predicted, the SN connectivity was disrupted in bvFTD but enhanced in AD, whereas the DMN connectivity

was disrupted in AD but enhanced in bvFTD (Fig. 3). The findings were largely consistent with previous studies on the DMN connectivity reductions in AD.[58–60] Several studies using other imaging modalities supported the divergent patterns in AD and bvFTD.[61,62] The reciprocal model is further supported by a fornix/hypothalamus deep brain stimulation (DBS) study on patients with AD.[63] All patients with AD after 1 month and 12 months of DBS showed consistent increased metabolism in the DMN regions along with improvements and/or slowing in the rate of cognitive decline; more interestingly, they also presented robust decreased metabolism in the SN regions (ACC and medial frontal cortex).

Graph theoretic analyses on functional connectivity revealed decreased clustering coefficient and characteristic path length closer to the theoretic values of random networks in patients with AD,[64] in parallel with findings using other imaging modalities.[59,62,65,66] Weakening of intermodular connectivity was outspoken and strongly related to cognitive impairment in AD.[64] This observation was in line with a global reduction of functional long-distance links between frontal and caudal brain regions.[65] Taken together, the randomization of the brain functional networks in AD suggested a loss of global information integration through degeneration in a distributed network. The opposite trend exhibited by bvFTD toward an overly

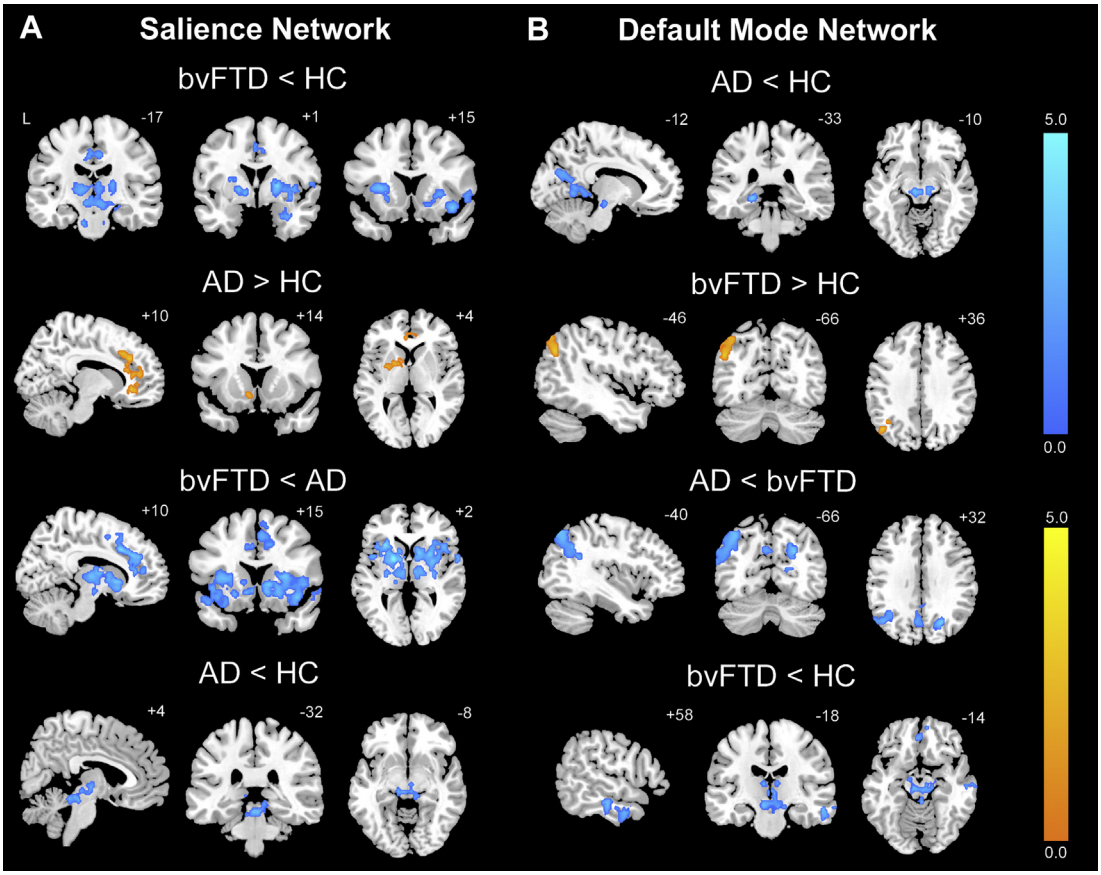

Fig. 3. BvFTD and AD feature divergent SN and DMN dynamics. Group difference maps illustrate clusters of significantly reduced or increased connectivity for each ICN. In the SN (*A*), patients with bvFTD showed distributed connectivity reductions compared with healthy controls (HCs) and patients with AD, whereas patients with AD showed increased connectivity in ACC and ventral striatum compared with healthy controls. In the DMN (*B*), patients with AD showed several connectivity impairments compared with HCs and patients with bvFTD, whereas patients with bvFTD showed increased left angular gyrus connectivity. Patients with bvFTD and AD further showed focal brainstem connectivity disruptions within their "released" network (DMN for bvFTD, SN for AD). Results are displayed at a joint height and extent probability threshold of $P<.05$, corrected at the whole-brain level. Color bars represent t-scores, and statistical maps are superimposed on the Montreal Neurologic Institute template brain. (*Adapted from* Zhou J, Greicius MD, Gennatas ED, et al. Divergent network connectivity changes in behavioral variant frontotemporal dementia and Alzheimer's disease. Brain 2010;133(5):1352–67.)

ordered topology in electroencephalogram (EEG) data might imply the divergent effect of the disease on distributed large-scale networks.[62]

A significant portion of patients with AD does exhibit nonmemory deficits in language, executive function, and higher visual functions.[67] These patients make up 3 major types of AD variants, namely the early-onset AD (EOAD), the logopenic variant of primary progressive aphasia (lvPPA), and the posterior cortical atrophy (PCA). Structural imaging studies found that these AD variants share common atrophy in the DMN, especially the posterior cingulate cortex.[68,69] PET studies examining glucose metabolism found hypometabolism in distinct brain regions that were associated with executive function, language, or visual functions corresponding well to the variant-specific deficits.[70] Recent rsfMR imaging study compared functional connectivity at the atrophy regions either common across and specific to AD variants and found common connectivity in posterior DMN and precuneus, suggesting DMN involvements were shared among AD variants.[70] For variant-specific atrophy region, intrinsic networks related to variant-specific cognitive deficits were identified. Atrophy specific to the lvPPA was seated in the language network,[70] which was similarly found in another study comparing lvPPA and amnesic patients with AD matched on amyloid deposition.[71] Anterior SN and right executive-control network were specific to the EOAD.[70,72] Atrophy regions specific to the PCA were linked with the higher visual network,[70] where disrupted functional connectivity was also reported in a later study examining dorsal and ventral visual networks separately in PCA[73] (**Fig. 4**). The topographic similarity between the variant-specific atrophy and the deficit-related functional networks support the network-based propagation of the neurodegenerative diseases, in which similar local pathologic changes and disease-related aggregate spread in different brain networks may underline the clinico-anatomical variations in AD.

Similarly, emerging studies used rsfMR imaging to assess distinct network disruptions in FTD variants. SvPPA was associated with extensive functional connectivity disruption between the anterior temporal lobe and multiple speech-processing areas.[74] To our knowledge, functional connectivity of nfaPPA has not yet been examined, but it might be related to the network anchored by the inferior frontal gyrus.[75] More importantly, a link between specific functional connectivity changes and behavioral impairment in FTD variants is established. Farb and colleagues[76] found that high level of behavioral dysfunction was associated with enhanced prefrontal connectivity in bvFTD, whereas low level of behavioral dysfunction was associated with reduced lateral prefrontal connectivity in svPPA. Recent studies using graph theoretic analyses on whole-brain functional connectome revealed distinct abnormal network topology in bvFTD and svPPA. Notably, patients with bvFTD featured loss of hubs in frontal lobes involving ACC, orbitofrontal cortex, and caudate nucleus, which were associated with executive dysfunction[77] (**Fig. 5**), whereas patients with svPPA had loss of hubs and reduced nodal degree in the inferior and ventral temporal regions and occipital cortices.[78] Additionally, the network centrality combined with social-executive behavioral measures had been applied to distinguish patients with bvFTD from healthy controls and frontoinsular stroke with a high classification rate.[79] Taken together, disruption of optimal brain connectome configurations were driven by specific symptom-associated networks, supporting the network breakdown mechanism in neurodegeneration.

CAN RESTING-STATE FUNCTIONAL MR IMAGING–BASED CONNECTIVITY ANALYSES UNCOVER DISEASE MECHANISM AND THE UNDERLYING NEUROPATHOLOGY?

That each neurodegenerative syndrome reflects a large-scale network breakdown has been established, as discussed previously, through a variety of convergent approaches. But what do we know about how disease progresses to create a network-related spatial pattern? At least 4 disease-general hypotheses have been put forth and can be summarized: (1) "nodal stress," in which regions subject to heavy network traffic (ie, "hubs") undergo activity-related "wear and tear" that gives rise to or worsens disease[80,81]; (2) "transneuronal spread," in which some toxic agent propagates along network connections, perhaps through "prionlike" templated conformational change[82–89]; (3) "trophic failure," in which network connectivity disruption undermines internodal trophic factor support, accelerating disease within nodes lacking collateral trophic sources[90–92]; and (4) "shared vulnerability," in which networked regions feature a common gene or protein expression signature[93] that confers disease-specific susceptibility, evenly distributed throughout the network. These non–mutually exclusive candidate network degeneration mechanisms make competing predictions about how healthy network architecture should influence disease-associated regional vulnerability. Notably, although "network degeneration" is often understood to mean "network-based spread," only the "transneuronal

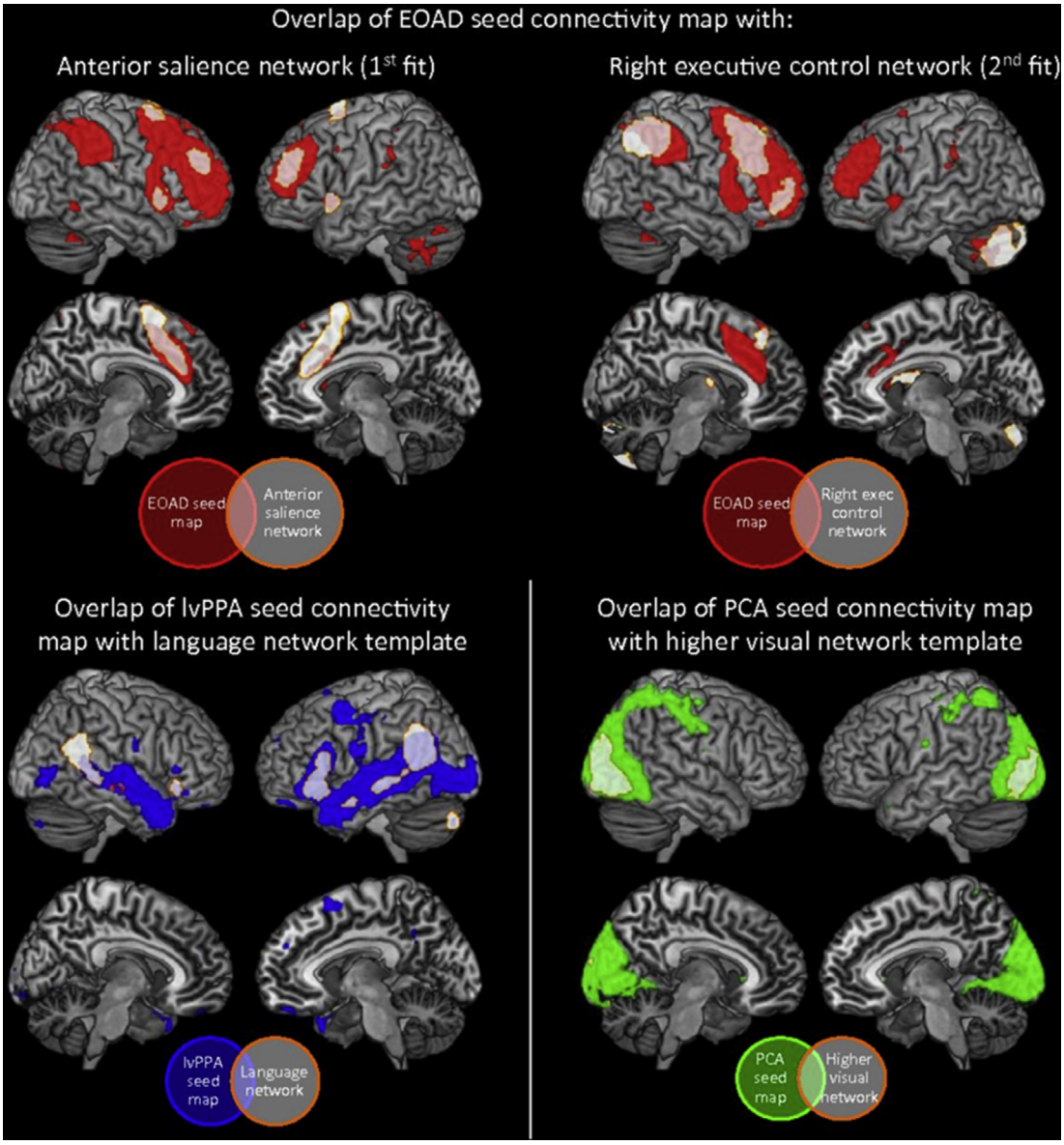

Fig. 4. Overlap of seed-based connectivity networks of specifically atrophied ROIs with best-fitting functional network templates. The EOAD seed connectivity map showed 2 strong fits: the anterior salience network showed the best fit with the left hemisphere connectivity map, and the right executive-control network showed the best fit with the right connectivity map. The lvPPA seed and PCA seed connectivity maps showed the best fit with the language and higher visual networks, respectively. (*Adapted from* Lehmann M, Ghosh PM, Madison C, et al. Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease. Brain 2013;136(Pt 3):844–58.)

spread" model proposes that progression represents physical spreading of a pathologic process along axons connecting individual neurons.

The ideal approach for examining disease progression and predicting neurodegeneration from brain connectivity would be to follow individuals from health to disease, exploring connectivity-vulnerability interactions within single subjects. Although this approach may prove challenging for the FTD syndromes, longitudinal analyses of this type are beginning to be pursued for AD-type dementia through large, ongoing, collaborative longitudinal studies. To date, efforts to investigate disease progression mechanisms have mainly relied on cross-sectional data. As discussed in relation to disease onset, for each of 5

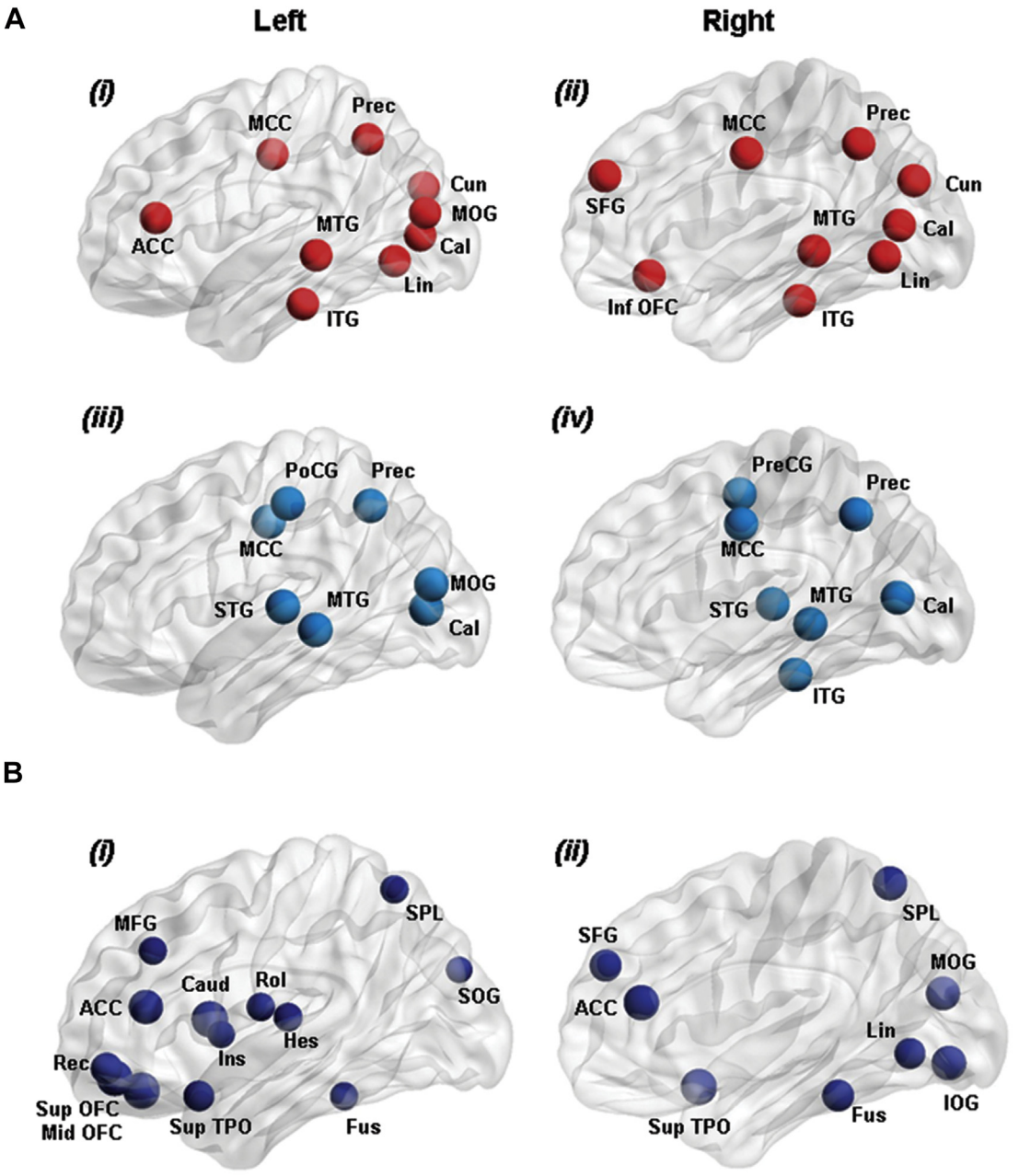

Fig. 5. Graph theoretic analysis reveal reduced nodal degree in bvFTD patients. (*A*) Cortical hubs of the functional networks of healthy controls (i, ii) and patients with the behavioral variant of frontotemporal dementia (bvFTD) (iii, iv). Hubs were identified as brain regions having either integrated nodal degree or betweenness centrality 1 SD greater than the network average. (*B*) Regions showing decreased integrated nodal degree (i, ii) in patients with bvFTD compared with healthy controls. Node size is proportional to the difference in the value of the integrated nodal parameters between the 2 groups. Cal, calcarine cortex; Caud, caudate nucleus; Cun, cuneus; Fus, fusiform gyrus; Hes, Heschl gyrus; Ins, insula; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; Lin, lingual gyrus; MCC, middle cingulate cortex; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PoCG, postcentral gyrus; Prec, precuneus; PreCG, precentral gyrus; Rec, gyrus rectus; Rol, rolandic operculum; SFG, superior frontal gyrus; SOG, superior occipital gyrus; SPL, t superior parietal lobule; STG, superior temporal gyrus; TPO, temporal pole. (*Adapted from* Agosta F, Sala S, Valsasina P, et al. Brain network connectivity assessed using graph theory in frontotemporal dementia. Neurology 2013;81(2):134–43.)

syndromes Zhou and colleagues[37] identified critical network epicenters whose normal connectivity profiles most resembled the syndrome-associated atrophy patterns. Graph theoretic analyses in healthy subjects revealed that regions with higher total connectional flow and, more consistently, shorter functional paths to the epicenters, showed greater syndrome-associated vulnerability (**Fig. 6**). Across all 5 syndromes, network nodes subject to greater intranetwork total information flow were found to undergo greater atrophy. This observation raised the possibility that activity-dependent mechanisms, such as oxidative stress, local extracellular milieu fluctuations, or glia-dependent phenomena, influence regional vulnerability; this influence might be a key factor in determining sites of initial onset or secondary onset (ie, progression). Second, nodes with shorter connectional paths to an epicenter showed greater vulnerability, suggesting that transneuronal spread represents one of the key factors driving early target network degeneration, most likely by physical transmission of toxic disease proteins or other agents along axons. In other words, epicenter infiltration by disease may provide privileged but graded access across the network that determines where the disease will arrive next. Although trophic factor insufficiency or a shared gene or protein expression profile may help to determine sites of onset, the findings of this study were difficult to reconcile with predictions made by these models regarding the graded vulnerability seen within the target networks. To extend the anatomic scope of the analyses, the investigators further examined

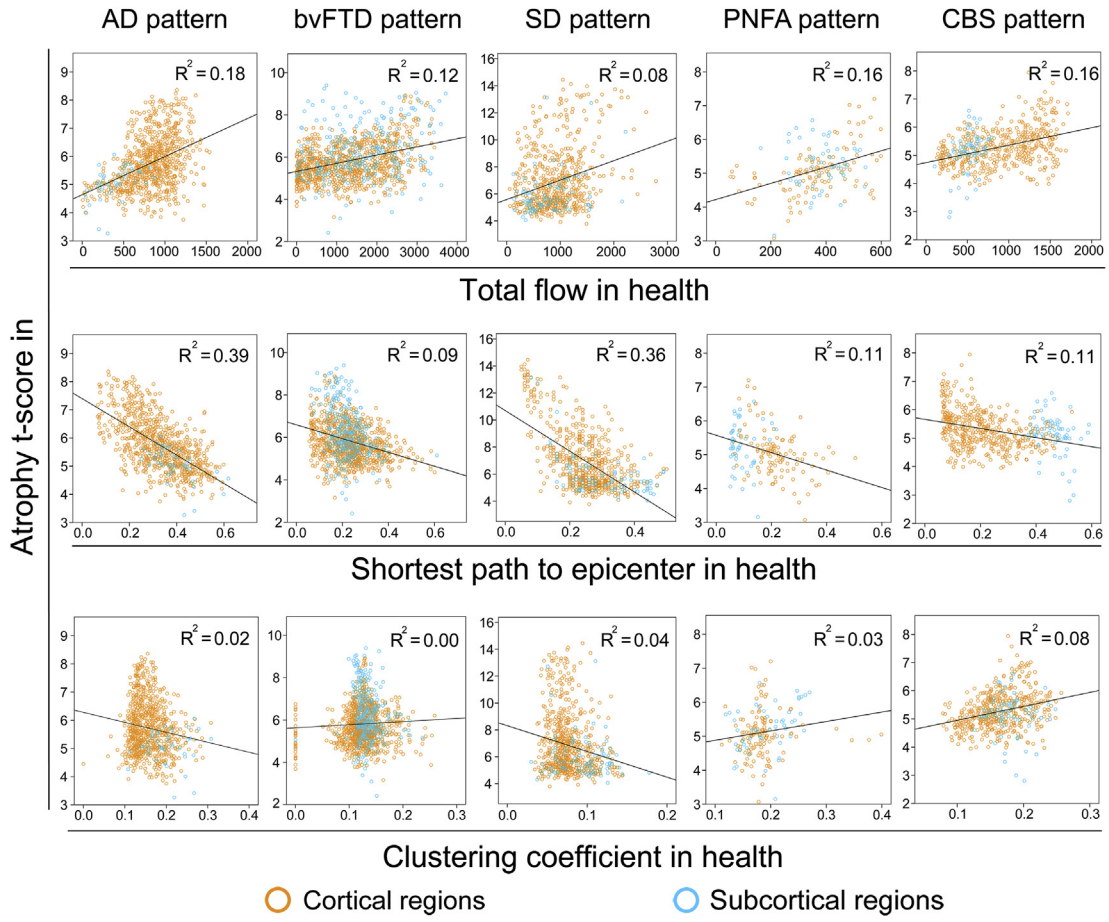

Fig. 6. Intranetwork graph theoretic connectivity measures in health predict atrophy severity in disease. Regions with high total connectional flow (row 1) and shorter functional paths to the epicenters (row 2) showed significantly greater disease vulnerability ($P<.05$ familywise error corrected for multiple comparisons in AD, bvFTD, SD, PNFA, and CBS), whereas inconsistent weaker or nonsignificant relationships were observed between clustering coefficient and atrophy (row 3). Cortical regions, blue circles; subcortical regions, orange circles. (*From* Zhou J, Gennatas ED, Kramer JH, et al. Predicting regional neurodegeneration from the healthy brain functional connectome. Neuron 2012;73(6):1216–27; with permission.)

connectivity-vulnerability relationships within the "off-target" networks to determine how nodal characteristics influence downstream vulnerability. Here, overwhelmingly, the evidence supported the transneuronal spread model. In summary, the findings best fit a model in which initial vulnerability may reflect a node's centrality (ie, "hubness") within the target network, whereas downstream vulnerability more closely related to a node's connectional proximity to the most vulnerable "epicenter" regions.

Maps of functional connectivity provide a means to understand why certain lesions and connectional abnormalities are particularly disruptive. One step further, it may predict the underlying AD or FTD pathology. Using task-free fMR imaging, Buckner and colleagues[80] showed that functional connectivity hubs in the healthy brain were mainly located in the DMN areas. More importantly, by mapping in vivo Aβ deposition with Pittsburg Compound B PET in patients with AD and controls, they found that the DMN cortical hubs in health resembled the high Aβ accumulation in AD compared with controls. This finding suggested that hubs, while acting as critical way stations for information processing, may also augment the underlying pathologic cascade in AD. Disruption of functional connectivity between the DMN regions may represent an early functional consequence of Aβ pathology before clinical AD. A recent study found significant disruptions of whole-brain connectivity in amyloid-positive patients with mild cognitive impairment in typical cortical hubs (posterior cingulate cortex/precuneus), strongly overlapping with regional hypometabolism.[94]

Intriguingly, subtle connectivity disruptions and hypometabolism were already present in amyloid-positive asymptomatic subjects and both connectivity and metabolism measures had positive correlation with each other and a negative correlation with amyloid burden (also see Brier and colleagues[95]). Two studies have indicated that the amount of Aβ deposits was negatively correlated with the DMN connectivity (ventral medial prefrontal cortex, angular gyrus, and medial posterior regions), and the lower connectivity was associated with poorer working memory performance in normal aging.[96,97] Gili and colleagues[98] found similar functional connectivity disruption of the DMN in AD and mild cognitive impairment (MCI), prodromal stage of AD, compared with controls. Interestingly, the posterior cingulate cortex showed reduced connectivity in patients with MCI in the absence of gray matter (GM) atrophy, which was, in contrast, detectable at the stage of fully developed AD. This study indicated that functional disconnection precedes GM atrophy during AD pathologic process.

More recent studies on early AD and cognitively healthy older adults point to a more complex picture regarding the association between amyloid and functional connectivity. On the one hand, a lack of association between Aβ and DMN functional connectivity was reported[99]; on the other hand, the relationship between the DMN and cerebrospinal fluid (CSF) Aβ biomarker was found in a subnetwork of the DMN with a hub in the right dorsal ACC; this subnetwork was distinct from another one that was more associated with the tau biomarker and had a hub in the right anterior entorhinal cortex.[100] Such divergent associations with the DMN functional connectivity between Aβ and tau markers are consistent with, and may help understand, the known discrepancies between the 2 pathologies (eg, locus of deposition, symptoms predictive power[95,101]).

Furthermore, the influence of Aβ deposition may extend beyond DMN into functional connectivity within the fronto-parietal network, within the attentional networks, and the "anticorrelation" between these networks.[102,103] Some of these correlations are surprisingly positive, which might reflect compensatory reorganization to combat neural and cognitive decline.[102,104] Koch and colleagues[105] examined the relationship among Aβ pathology, functional connectivity, and cognitive performance in patients with prodromal AD and healthy controls. They extracted brain networks from rsfMR imaging and task fMR imaging during a demanding visuo-motor dual task (**Fig. 7**). Consistent with other studies, Aβ accumulation was negatively correlated with DMN connectivity. Furthermore, although the resting-state functional connectivity in the posterior DMN was lower in patients than in controls, the task connectivity in the same region showed the reversed pattern, and such higher task connectivity was associated with poorer task performance. Importantly, similar results were also found for the posterior right attentional network (rATN). However, only the DMN but not rATN resting-state functional connectivity statistically moderated the association between Aβ pathology and task performance. These findings prompt a network-based neurodegeneration hypothesis to account for how these changes "outside" of the epicenters may arise (for instance, through between-network connections[37,95]), and whether or how they are differentially associated with symptoms.

Based on the divergent functional connectivity patterns among patients with dementia and healthy controls, researchers have begun to

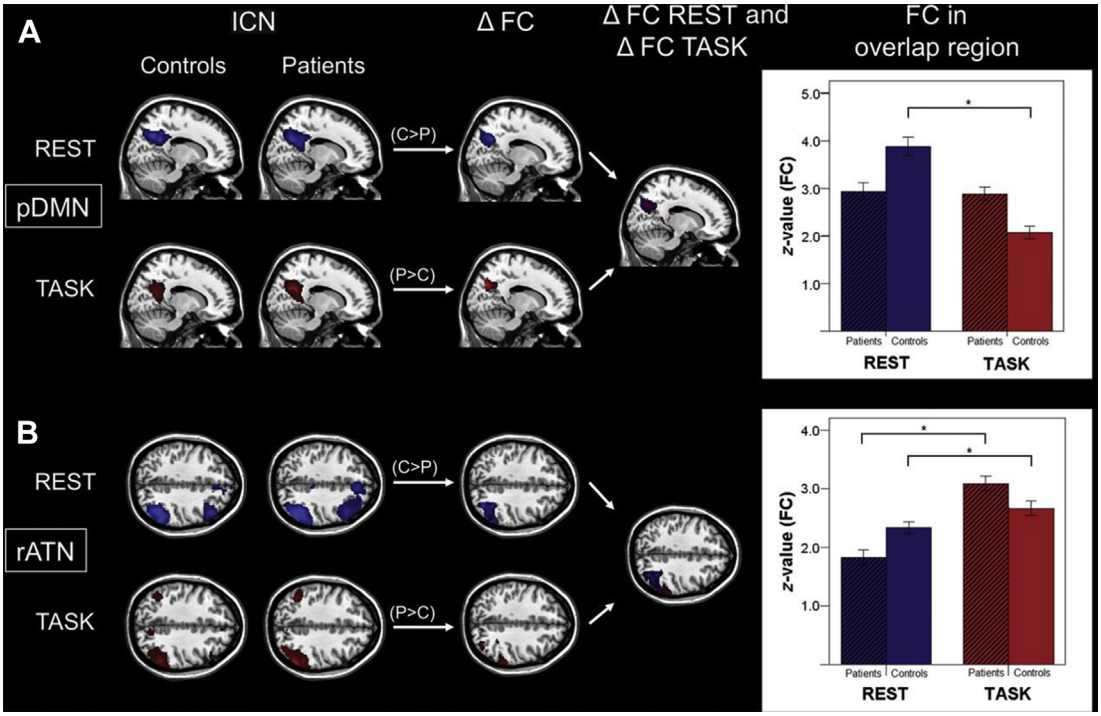

Fig. 7. Spatially consistent functional connectivity (FC) changes of posterior default mode network (pDMN) and right attentional network (rATN) across rest and task in patients. Columns 1 and 2: ICNs characterized by spatial patterns of FC during rest (*lines* 1 and 3) and task (*lines* 2 and 4) concerning the pDMN (*A*) and rATN (*B*). Columns 3 and 4: Results of the ICN group comparisons for FC maps between patients and controls (ΔFC) for rest and task condition as well as corresponding spatial overlaps of group differences (ΔFC Rest and ΔFC Task). Right side: Bar plots representing averaged FC values for overlapping group differences for each group, condition, and ICN. Paired *t* tests revealed FC differences across conditions ($P<.05$, * Significant result, pDMN T = 0.9 (patients)/7.7 (controls); rATN T = −7.8/−2.1). (*Adapted from* Koch K, Myers NE, Göttler J, et al. Disrupted intrinsic networks link amyloid-β pathology and impaired cognition in prodromal Alzheimer's disease. Cerebral Cortex 2015;25(12):4678–88.)

develop functional connectivity-based biomarkers to distinguish among dementia subtypes and controls. Using rsfMR imaging, Greicius and colleagues[58] calculated the goodness-of-fit score to the DMN at the individual level and achieved 85% of sensitivity and 75% of specificity differentiating AD from controls. The clustering coefficient derived from graph theoretic analyses of rsfMR imaging distinguished AD participants from the controls with a sensitivity of 72% and specificity of 78%.[59] A recent study computed whole-brain correlation-based connectivity among 116 ROIs and achieved 85% of sensitivity and 80% of specificity between the AD group and the non-AD group (MCI and controls).[106] Using graph theoretic measures, Khazaee and colleagues[107] were able to classify patients with AD or MCI and control individuals with 93.3% accuracy; furthermore, hub counting showed a progressive decrease from control to AD, suggesting that AD is characterized by aberrant network communication. Such classification success and implication on hub disruption is consistent with the findings of Dai and colleagues,[108] which also demonstrated hub-oriented impairment, in addition to disrupted internetwork connectivity, in AD compared with controls. Based on the observations that bvFTD and AD feature divergent connectivity effects on the SN and DMN, Zhou and colleagues[57] illustrated that a summary score incorporating both networks might better differentiate bvFTD from AD and each patient group from healthy controls, achieving the sensitivity of 92% and specificity of 96% in 3-group classification and 100% differentiation between AD and bvFTD. This suggested that functional network–based patterns, sensitive to decreases and increases, and divergent among syndromes, might prove more specific to predict disease diagnoses and predict the underlying pathology. Published work on differential diagnoses using functional networks in the language variants of FTD remains scarce. Current connectivity

approaches require replication in an independent clinical dataset and validation in pathologically verified clinical samples.

CAN RESTING-STATE FUNCTIONAL MR IMAGING–BASED CONNECTIVITY ANALYSES DETECT EARLY CHANGES AND TRACK DISEASE SEVERITY?

As neurodegeneration spreads from its initial target to the entire network accompanied by multidomain cognitive deficits, network-based breakdown measured by connectivity analyses could be a potential sensitive marker to detect onset and track disease severity at the individual level. By examining the functional connectivity cross-sectionally in healthy elderly controls and patients with mild, moderate, or severe AD by rsfMR imaging, Zhang's group[60] found that all patients with AD consistently disrupted the functional connectivity between posterior cingulate cortex and the DMN regions, including medial prefrontal cortex, precuneus, and hippocampus, which intensified as the stage of AD progression increased. However, this study did not take into account the global atrophy volume and regional atrophy at posterior cingulate cortex. Similar to AD, specific regions of connectivity disruption within the SN can track disease severity of FTD. BvFTD clinical severity (CDR-SB) correlated with loss of right frontoinsular SN connectivity and with biparietal DMN connectivity enhancement, demonstrating that not only connectivity reduction but also enhancement have potential to track disease progression.[57]

Characterizing the earliest stages of cognitive impairment is receiving increasing attention in the field of aging and dementia research. MCI is a transitional state between healthy elderly individuals and mild AD, which is at high risk for developing AD. Emerging evidence on MCI showed a similar AD pattern of reduced DMN connectivity, including posterior cingulate cortex, medial prefrontal cortex, precuneus, and hippocampus.[4,98,109–112] Functional connectivity strength also was correlated with cognitive performance and can discriminate MCI from healthy controls.[113] In a recent longitudinal study, the DMN connectivity score (derived from task fMR imaging) distinguished patients with MCI who underwent cognitive decline and conversion to AD from those who remained stable over a 2-year to 3-year follow-up period, independent of global atrophy and demographics.[114] Looking at resting-state instead of task functional connectivity, another longitudinal study came to similar conclusions. In particular, functional connectivity of precuneus at baseline showed high sensitivity and specificity in classifying amnesic MCI converting to AD against those nonconvertors.[115]

In parallel with consistent neuroimaging findings on symptomatic FTD and patients with AD, researchers recently became excited about studying the functional architecture changes in the high-risk population, aiming to develop disease-prevention strategies.[116,117] Genetic studies show unequivocally that the apolipoprotein ε4 (APOE ε4) allele is associated with an increased risk of EOAD and late-onset AD.[118,119] Functional connectivity studies on asymptomatic carriers of the APOE ε4 allele observed both decreased and increased connectivity at the DMN regions previously defined as having abnormal connectivity in AD[120–122] (see review by Seeley[123]). The connectivity changes in the DMN were observed before any manifestations of cognitive changes and in the absence of Aβ deposition[124] and white matter degradation.[125] Chen and colleagues[126] applied graph theoretic measures and found that ε4 carriers had lower nodal efficiency in bilateral hippocampus, right para-hippocampal gyrus, bilateral amygdala, and right Heschl gyrus (**Fig. 8**). To note, although these regions are generally implicated in memory-related processes, in this study it was their structural connectivity but not functional connectivity that was statistically associated with memory impairment, suggesting the usefulness of multimodal imaging. A recent task-free fMR imaging study revealed decreased connectivity between posterior cingulate cortex and regions of the posterior DMN while increased connectivity between ACC and the SN regions in the APOE ε4 carriers relative to noncarriers.[127] This finding was amazingly consistent with the reciprocal model between the SN and DMN. Results as such may therefore point to a genetic moderation of the network-based neurodegeneration.

What complicates the implication of the APOE-functional connectivity relationship is that compensatory reorganization[128] of brain networks may be prevalent in ε4 carriers to maintain cognitive performance. Functional connectivity that is higher in carriers compared with noncarriers is often interpreted as such. For instance, Matura and colleagues[129] reported higher functional connectivity between left posterior cingulate cortex (PCC) and left middle temporal gyrus in ε4 carriers compared with noncarriers. Using eignenvalue centrality (EC), a voxelwise measure computed as the sum of centralities of all neighbors connected to a given voxel, Luo and colleagues[130] found lower EC in left medial temporal lobe and left lingual gyrus and increased EC in left middle frontal gyrus for the ε4 carriers. Although the lower functional connectivity in the medial temporal regions was consistent with

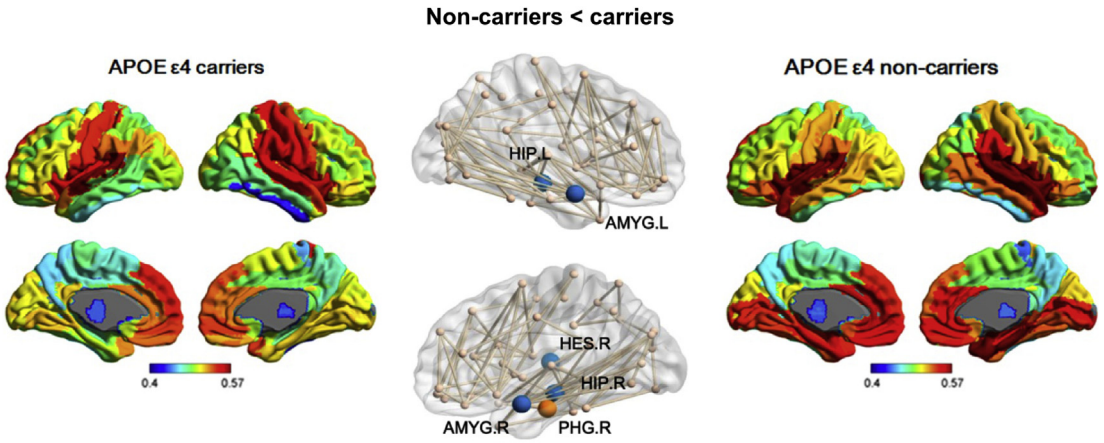

Fig. 8. Cognitively normal elderly APOE ε4 carriers showed lower nodal efficiency in the medial temporal lobe areas (middle panel). This lower nodal efficiency was consistent between functional and structural connectivity at the right parahippocampal gyrus (PHG.R; orange node). Age, gender, and education were considered as covariates in the analysis. Left and right panels show the topological distribution of mean nodal efficiency of ε4 carriers and noncarriers, respectively. AMYG, amygdala; HES, Heschl gyrus; HIP, hippocampus; L, Left; PHG, parahippocampal gyrus; R, Right. (*Adapted from* Chen Y, Chen K, Zhang J, et al. Disrupted functional and structural networks in cognitively normal elderly subjects with the APOE e4 allele. Neuropsychopharmacology 2015;40(5):1181–91. Figure 1b and Figure 2.)

impaired episodic memory, the higher connectivity in the middle temporal gyrus was speculated to reflect compensation. Consistent with these observations, McKenna and colleagues[131] found lower functional connectivity in early mild cognitive impairment (EMCI) patients than healthy controls but these changes were not evident in carriers compared with noncarriers. One possibility would be that compensatory reorganization of brain networks have protected some ε4 carriers from advancing into EMCI. Finally, using a longitudinal dataset, Ye and colleagues[132] observed a genotype-by-diagnosis interaction of the longitudinal changes in functional connectivity between hippocampus and right frontal regions in preclinical control individuals and patients with MCI. Specifically, cognitively normal ε4 carriers showed an increased connectivity across time, whereas MCI ε4 carriers showed a decrease. The investigators postulated this reversed trend to reflect a compensatory reorganization of the brain dynamics that is exhausted eventually, leading to the onset of clinical conditions. Future research needs to establish what compensatory mechanisms may be in play, whether they also follow a network trajectory, and how ε4 genotype can influence such mechanisms, for instance by replenishing reduced temporal dynamics complexity between brain regions through altering hemodynamic synchrony.[133]

Despite its robustness in risk elevation, presence of the ε4 allele does not guarantee a fate to dementia. Studies also suggest that the influence of APOE genotype on brain network organization may not necessarily be pathologic per se.[134,135] Therefore, it is plausible that the APOE genotype interacts with other risk factors and demographic characteristics during the lifespan to make its host more vulnerable to late-onset dementia.[136–138] For instance, female ε4 carriers have long been shown to suffer higher risk of AD.[119] Using hippocampal seeds, Heise and colleagues[139] reported lower hippocampus-precuneus/PCC connectivity in female ε4 carriers compared with male carriers and female noncarriers; it was also the only group to show a cross-sectional association between age and hippocampal functional connectivity. Besides gender, APOE genotype may also interact with Aβ pathology to elevate susceptibility to pathologic neurodegeneration.[136,140,141]

Similarly, recent rsfMR imaging work moves toward characterizing the early functional connectivity changes in subjects with genetic risk for FTD. The SN functional connectivity abnormalities were found in presymptomatic C90rf72, GRN, and MAPT carriers,[142,143] which was consistently involved in bvFTD, demonstrating that the network changes exist decades before disease onset.[144] However, no agreement on the pattern of changes has been made yet.[142,143,145] To date, researchers have started to investigate the issue by considering technical factors,[146] the possible influence of different pathology,[147] and distinct temporal and spatial profiles,[146] Such validation is essential for validating rsfMR imaging functional connectivity as a biomarker of the prodromal changes.

Last, work on intervention has begun to use rsfMR imaging functional connectivity to evaluate intervention efficacy. For instance, Goveas and colleagues[148] applied such analysis to identify the neural correlates of cognitive improvement in subjects with mild AD after 12 weeks of donepezil treatment. After donepezil treatment, neural correlates of cognitive improvement measured by Mini-Mental State Examination scores were identified in the hippocampal connectivity with left parahippocampus, dorsolateral prefrontal cortex, and inferior frontal gyrus. Stronger recovery in the network connectivity was associated with cognitive improvement. This finding suggested that rsfMR imaging connectivity approach may be further developed to monitor and predict AD treatment response in clinical pharmacologic trials.

SUMMARY AND FUTURE DIRECTIONS

Characterizing brain networks, such as rsfMR imaging–based functional connectivity changes, can explain how an endophenotype of molecular pathologic changes, such as cortical amyloid and tau accumulation, has built up in an individual brain leading to symptoms. The hub characteristics of a brain region and the degree of their functional connectivity and structural integration explain why certain brain networks are more vulnerable than others to brain diseases such as AD. Network-based principles have begun to shed light on group-level changes across a host of neurodegenerative disease syndromes.[149] To aid in the search for treatments, however, these methods will need to be developed for use in tracking single subjects over time. We summarize the possible future directions in the following.

First, differential diagnosis is required to tease apart variance in neurodegenerative disease associated with individual differences in clinico-anatomical variations and treatment responses.[70,76,142,143] The clinical utility of rsfMR imaging–based functional connectivity, as well as other modalities, will certainly benefit from better appreciation of disease heterogeneity through, for instance, more refined population stratification based on genetic, demographic, and environmental factors.[150,151] Rapidly increasing access to large and shared databases across multiple sites[152] can help overcome drawbacks of small-sample studies on disease variants and improve the stability and reproducibility of rsfMR imaging data analysis.[153]

Second, the strength of rsfMR imaging to discover covert neural changes in asymptomatic population opens up the opportunities of early detection and intervention, where outcomes can be substantial.[117,139,149,151,154,155] A combination of rsfMR imaging functional connectivity, and multimodal data, such as structural MR imaging, diffusion MR imaging,[156,157] other noninvasive detection techniques,[158] and better understanding of disease heterogeneity will greatly improve the sensitivity and specificity of existing methods.[115,157]

Third, many of these advancements will be attributable to breakthroughs in computational and statistical techniques. Methodological improvement, such as deriving functional connectivity with higher tempo-spatial fidelity (eg, Bayesian network modeling,[159] dynamic functional connectivity[160,161]; multi-atlas approach[162]), and machine learning[107,108,163] on whole-brain functional connectome (static or dynamic) or nonlinear statistical methods, will allow us to discover more robust and valid features of the diseases, and thus promise higher accuracy and generalizability in the detection at the preclinical stage, predictions on disease onset, progression, and treatment response.

Finally, longitudinal design is essential for moving from group predictions of disease progression toward individual prospective. More longitudinal data could help validate or clarify the rich knowledge gained from cross-sectional studies, such as the critical role of increased functional connectivity in the precuneus in MCI conversion,[115] the different longitudinal patterns relating to the left and right frontoparietal networks between patients with bvFTD and patients with AD,[164] the differential manifestation of APOE ε4 effect on DMN connectivity between MCI converters and nonconverters,[165] and the change of rate of functional connectivity alternations at early and late stages of MCI,[166] to name but a few. There is a need to further develop the rsfMR imaging method to better map cognitive dysfunctions with neural changes.[167–170]

In summary, rsfMR imaging–based functional connectivity offers a flexible and powerful way to describe the interrelationship of the neural signals among various brain regions. Research in the healthy population has revealed the hierarchical and topological organizations of these connectivities as intrinsic networks supporting cognitive functions. Disruptions of typical organization and interactions within and between functional networks implicate abnormal cognition and behavior. This raised the plausibility of the same principle underlying neurodegenerative diseases, assaulting the brain in a systematic, network-oriented fashion. To date, network-sensitive neuroimaging work (using rsfMR imaging) supports this network-based neurodegeneration hypothesis.

This can serve as a significant first step toward predicting disease onset, variant manifestation, and progression. Future studies will continue to improve the working model to incorporate moderating factors, elucidate exception cases, and capitalize on translational opportunities.

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