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Sex-specific brain microstructural reorganization in irritable bowel syndrome

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INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by the presence of chronically recurring abdominal pain and altered bowel habits[5]. While IBS has previously been viewed as a disorder of the gut, the new definition by the Rome Foundation is a disorder of gut-brain interactions. It is generally accepted that the pathophysiology of IBS symptoms includes a combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, dysbiosis and altered central nervous system (CNS) processing[11]. Ongoing reciprocal communication between the gut and the brain is achieved via the nervous, immune and neuroendocrine systems. As part of this communication, the brain receives continuous, extensive interoceptive signaling about the homeostatic state of the gut, primarily via vagal afferent pathways and the brain exerts “top down” influence of the on the gut via the branches of the autonomic nervous system.[32]

Multimodal brain imaging studies have demonstrated that individuals with IBS compared to healthy controls (HCs) have structural (gray matter) and functional alterations in the core regions of the emotional arousal[16,18,21,25,32,40,52,55], central executive[1,18–

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Conflicts of Interest Statement

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20], sensorimotor processing[16,20,21,32,55], default mode[20,27,39,41,58,59], and salience[16–18,55] networks[26,32]. These disease-relevant brain networks are all involved in the processing and modulation of visceral and non-visceral sensory information[32].

In addition to alterations in signaling along the brain-gut axis in IBS, there are also sex-specific differences in both the clinical presentation and brain function including higher overall prevalence[6,33], healthcare utilization, hypersensitivity to intestinal and non-intestinal stimuli [7,53] along with reporting more extraintestinal comorbidities in females[42,56], Female compared to males exhibit greater functional remodeling within sensorimotor, salience, emotional arousal, and executive control brain networks[15,26,32]. When viewed together, these findings support the hypotheses that the etiology and maintenance of symptoms for females with IBS is driven by greater multisystem sensory sensitivity.

While much is known about functional changes within the brain in IBS[26,31], less is known about the accompanying microstructural white matter changes that may occur. Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that is sensitive to the underlying microstructure of the brain, and preliminary evidence from studies using this technique has shown IBS-related sex differences[12]. Consistent with differences in functional brain networks, IBS females compared to IBS males and HC females show increased strength of axonal or dendritic projections and increased myelination within and between sensorimotor, corticothalamic, and basal ganglia circuits involved in pain processing and integration of sensorimotor information[12].

The current study examined whole brain DTI images in a large sample of well-phenotyped IBS and HC participants to rigorously investigate sex-dependent differences both in brain microstructural organization and in clinical phenotypes. Voxel-wise comparisons in DTI measurements (i.e., fractional anisotropy, mean, radial and axial diffusivity, fiber tract density) were used to test the main hypothesis, based on previous research[12], that females with IBS show evidence for greater axonal strength and myelination within and between sensorimotor, corticothalamic, and basal ganglia circuits, compared to IBS males and these differences extend beyond sex-differences observed in HCs. We also hypothesized that females would show greater levels of somatic awareness and sensory sensitivity consistent with multisystem sensory sensitivity.

METHODS

Subject Population

The study cohort consisted of 252 male and female subjects, including 152 subjects who met Rome III symptom criteria for IBS[28] and 100 healthy controls (HCs). These patients were prospectively enrolled in a cross-sectional study involving observational MRI and evaluation of IBS from 2013–2019. A gastroenterologist or gastrointestinal nurse practitioner obtained histories and conducted physical examinations. All procedures complied with the principles of the Declaration of Helsinki and were approved by the Institutional Review Board at our institution, and all analyses were performed in compliance with the Health Insurance Portability and Accountability Act.

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Exclusionary criteria for all subjects included pregnancy or lactation, substance abuse, tobacco dependence (smoked half a package of cigarettes or more daily), abdominal surgery other than appendectomy or cholecystectomy, current or past psychiatric illness, extreme strenuous exercise (exercise more than one hour per day), and major medical or neurological conditions. In addition, subjects with current regular use of analgesic drugs (including narcotics, opioids, and α2-δ ligands) were excluded. Use of medications such as antidepressants (low-dose tricyclic anti-depressants, selective serotonin uptake inhibitors, nonselective serotonin reuptake inhibitors) was only allowed if subjects had been on a stable dose for a minimum of 3 months. We did not exclude subjects who used NSAIDS such as diclofenac. Instead, subjects were asked to refrain from taking this medication 12 hours prior to their scanning visit. All subjects were premenopausal confirmed by self-report and were scanned during the follicular phase of the menstrual cycle.

Study Questionnaires

IBS symptom severity was measured using the IBS Severity Scoring System (IBS-SSS)[13]. The IBS-SSS is a 5-item instrument which assesses abdominal pain intensity and frequency, distention, dissatisfaction with bowel habits, and impact of IBS on quality of life over the past 10 days. The IBS-SSS questionnaire uses a 500-point scale ranging from 0 (no symptoms) to 500 (the most severe symptoms). IBS severity is categorized as mild (75–175), moderate (175–300), or severe (>300), while a score less than 75 indicate absence of IBS or in remission.

For IBS, questionnaires were completed before scanning to determine IBS symptom type, severity, duration of symptoms, and abdominal symptoms (Bowel Symptom Questionnaire) [51]. Overall gastrointestinal (GI) symptom severity and abdominal pain in the past week were assessed using a 21-point Numerical Rating Scale (scale=0–20, 0=no pain and 20=the most intense symptoms imaginable). Usual symptom severity was assessed on an ordinal scale where 1=None, 2=Mild, 3=Moderate, 4=Severe, and 5=Very Severe. IBS patients also completed questionnaires to measure for GI-symptom specific anxiety (Visceral Sensitivity Index [VSI])[24]. The Complex Medical Symptom Inventory(CMSI) was used to determine the presence of common somatic symptoms of discomfort or pain (e.g. abdominal pain, headache) as well as sensory sensitivity to nonpainful environmental stimuli (e.g. bright light or odors) for 3 month out of the past year[57]. From this, scores on the somatic awareness and sensory sensitivity subscales were derived.[44] All subject completed an assessment of trait anxiety (State Trait Anxiety Inventory; STAI)[49].

Diffusion Tensor Imaging (DTI)

DTI scans were collected using a standard spin-echo echo planar imaging on a Siemens Prisma 3T MRI scanner (Siemens Healthcare, Erlangen, Germany) with a repetition time (TR)=9500ms; echo time (TE)=88ms; field-of-view (FOV) of 256×256mm with an acquisition matrix of 128×128 for a voxel size of 2×2×2mm. Diffusion weighting was distributed along 64 directions using b-value of 1000 s/mm^2. Additionally, a single reference b=0 s/mm^2 image was used as a reference.

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Image Processing

All DTI scans were first denoised using the MRtrix3 software package (Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/mrtrix)[4], then corrected for eddy currents and motion using the eddy correct functionality of the FSL Diffusion Toolbox (FDT) as part of FSL (FMRIB; Oxford, UK; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). Following skull extraction using the Brain Extraction Tool (BET), fractional anisotropy (FA) and mean (MD), radial (RD) and axial diffusivity (AD) maps were calculated from the diffusion tensor. All FA, MD, RD, and AD images for each participant were registered to the Johns Hopkins University DTI atlas (ICBM-DTI-81 1mm FA atlas) using the linear (12 directions via FLIRT) and non-linear (FNIRT) commands in FSL. Voxel-wise comparisons in FA, MD, RD, and AD were performed within a mask consisting of both cortical white matter and deep gray matter regions of interest, including the basal ganglia and thalamus, defined by their respective locations from the Harvard-Oxford subcortical atlas, as defined previously[12].

Probabilistic DTI tractography was performed using the MRtrix3 software package. After seeding 1 million voxels randomly throughout brain, the number of fiber tracts passing through each image voxel was counted. Resulting fiber track density (TD) images of each participant were also registered to the Johns Hopkins University DTI atlas (ICBM-DTI-81 1mm FA atlas) using FLIRT and FNIRT commands in FSL.

Image Statistical Analysis

Following image preprocessing, a general linear model (GLM) was implemented through AFNI (Analysis of Functional NeuroImages)[9] to evaluate significant voxel-wise differences in FA, MD, RD, AD and TD 1) between IBS female and HC female, 2) between IBS male and HC male, 3) between IBS female and IBS male, and 4) between HC female and HC male. Additionally, an interaction contrast or the difference of differences [IBS (female- male) - HC (female -male)] was specified to determine whether the sex differences in FA, MD, RD, AD, and TD differed based on diagnosis. The GLM was also applied to determine the association of the observed sex differences in IBS with somatic awareness and sensory sensitivity scores.

The GLM was implemented using the AFNI *3dttest++* command and specifying age and body mass index as covariates in the models. To control false discovery rate (FDR), significant clusters from *3dttest++* were filtered through the spatial autocorrelation function implemented in *3dFWHMx*, and appropriate cluster-based thresholds based on permutation testing were determined using *3dClustSim* using a level of significance, $p<0.05$, and FDR $q<0.05$. To identify the overlap between the significant clusters identified in the IBS female - IBS male contrast and the interaction contrast, the cluster mask from the interaction contrast was overlayed on IBS female-IBS male contrast cluster mask. Areas of overlap were then retained based on a minimum cluster size of 200uL.

Group differences in demographic, psychosocial and symptom measures were assessed using the independent t-tests in SPSS software version 22.0 (SPSS Inc.) applying a threshold for significance at P<.05. To elucidate significant mean differences, we report the absolute

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value of the standardized mean change, Cohen's effect size d. As a rule of thumb, small effect d=.20, medium, d=.50, and large d=.80. We also performed correlational analyses to examine the influence age and symptom duration on the clinical outcomes in IBS.

RESULTS

The sample consisted of 100 HC (61 Female) and 152 IBS (107 females) participants. The characteristics of the sample by diagnosis is provided in Table 1. All participants had a body mass index <30, with HC having a slightly higher mean body mass than IBS (mean difference=2.4). Healthy controls were also slightly older (30y compared to 28y). As shown in Table 2, within IBS, female compared to males were younger (26.7y v 31.8) and reported shorter pain duration 8.7y v 12.9y). However, after controlling for age, differences in duration were no longer significant. There was no difference in age of disease onset. IBS females compared to IBS males also reported greater IBS symptom severity as measured by the IBS-SSS, GI-specific anxiety, somatic awareness, and sensory sensitivity. There were no differences observed in trait anxiety between male and female IBS patients. Age and IBS symptom duration were not associated with the clinical outcomes.

Sex-Specific Microstructural Differences

Compared with healthy controls, female IBS patients demonstrated regional differences in FA, MD and TD measurements along multiple white matter pathways that are associated with sensory perception, integration of sensory information and pain modulation (Fig. 1). Notably, increased FA and decreased MD was observed in female IBS patients within the corticospinal tracts passing through the internal capsule, projecting to the primary as well as supplementary motor and sensory cortices (Fig. 1A–B). In addition to these projections, a similar increase in FA and decrease in MD was observed in white matter projecting to the frontal lobe, including the forceps minor, inferior fronto-occipital fasciculus, and uncinate fasciculus within female IBS patients compared to female HCs. Measurements of AD and RD in these participants suggests the increase in FA observed in female IBS patients was driven by a decrease in RD (Supplemental Fig. S1B), suggestive of increased myelination or axon caliber within these patients[45–47]. TD measurements showed higher track density in IBS females within and adjacent the basal ganglia, including the putamen and globus pallidus, including projections to the insula and frontal lobe (Fig. 1C). Additionally, TD was reduced in female IBS patients in superior and inferior longitudinal fasciculi when compared to female HCs. In stark contrast, however, male IBS patients only showed subtle differences in FA and no differences in MD, AD, RD, or TD (Fig. 2). Similar to female IBS patients, some basal ganglia regions (left putamen) showed higher FA in male IBS patients. Additionally, small regions within body and genu of the corpus callosum, the superior corona radiata and the superior longitudinal fasciculus of the right hemisphere showed lower FA values in male IBS patients compared to male HCs.

Diagnosis-Specific Microstructural Sex Differences

Next, regional differences in FA, MD and TD measurements between females and males within the IBS group (Fig. 3–5A) were examined, as well as the interaction between sex and diagnosis (Fig. 3–5B) and areas of overlap between these two comparisons (Fig. 3–5C).

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Specifically, the body and the genu of the corpus callosum, the external capsules, along with white matter fibers extending through the anterior part of internal capsules, corona radiata, and bilateral superior longitudinal fasciculi, demonstrated higher FA values (Figs. 3A and Fig. 3B) and lower MD values (Figs. 4A and Fig. 4B) in female IBS patients, suggesting reinforced white matter projections to sensorimotor and frontal lobe regions. The interaction effects between sex and disease strongly influenced the results (Figs. 3B and 4B), confining changes to slightly smaller subregions within these broader anatomical locations and suggesting female IBS patients (Figs. 3C and 4C, Table 3 and Table 4), more than male IBS patients, are the primary driver for the observed brain differences. This increased FA in IBS females observed while quantifying interaction effects was driven largely by a decrease in RD along the same white matter tracts (Supplemental Fig. S2C).

When examining the diagnosis-specific differences in TD measurements, interestingly, whole brain TD values were found to be systematically higher in female IBS patients compared with male IBS patients (Fig. 5A) as well as for female HCs compared with male HCs (Fig. 5B). In the genu of the corpus callosum, for example, there was around a 10% higher TD in females compared with males in both cohorts of patients (Fig. S3), but no difference in TD within sex between IBS and HCs for either males (*P=0.9018*) or females (*P=0.9557*). The interaction effects between sex and disease showed a significantly larger differences in TD within IBS females and males compared to HC males and females within the basal ganglia, including but not limited to regions of the putamen and globus pallidus, some thalamic regions, and medial frontal lobe regions (Fig. 5C–D, Table 5).

Linking IBS sex-specific brain alterations and multisystem sensory sensitivity.—In IBS, the observed sex-specific differences in white matter pathways were associated with either somatic awareness or sensory sensitivity subscales with little overlap in anatomical locations (Supplemental Tables S1–5, Supplemental Tables Figs. S4–S5). With one exception (See Supplemental Table S1, Fig. S4A), many of the increases in FA and TD and decreases observed in female compared to male IBS were associated with increases levels of sensory sensitivity or increased somatic awareness.

DISCUSSION

The main findings of the current study showed increased white matter density in female compared to male IBS participants within tracks projecting to the frontal lobe and sensorimotor regions, as evidenced by increased FA and decreased MD, as well as increased density and projections within the basal ganglia, and from the striatum to the thalamus, insular and frontal cortical regions. Some of these sex-related differences were also observed between healthy female and males. Significant “sex-by-disease” interactions in the microstructural reorganization of the brain were observed, providing important evidence that these changes are both sex-dependent and specific to IBS. Importantly, the findings indicate that most of the white matter changes previously observed in individuals with IBS compared to HCs[12] are driven by brain alterations in female with IBS. In contrast, few microstructural differences were observed between male IBS and HCs. As hypothesized, females with IBS reported greater levels of somatic awareness and sensory sensitivity, and these were associated with the observed sex-specific microstructural differences in

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IBS, namely an increase in FA, decrease in MD, decrease in RD, and increase in TD. When viewed together with the greater reports of symptom severity and GI-specific anxiety in female compared to male IBS participants, these findings support the hypothesis that the etiology and maintenance of IBS symptoms in females is driven by reinforcement of projections, or increased myelination,[45–47] in white matter tracks involved in pain and sensory processing and modulation regions that comprise cortico-basal ganglia-thalamic pathways. These findings are also consistent with the greater prevalence of wide-spread pain and visceral hypersensitivity[34] in female IBS, and provide strong evidence for sex-specific clinical phenotypes in IBS with potentially different neurophysiological underpinnings responding to different therapeutic approaches.

Converging evidence from a number of brain imaging studies in IBS patients is consistent with functional changes in several brain networks, including the emotional arousal[16,18,21,25,32,40,52,55], central executive[1,18–20], default mode[20,27,39,41,58,59], salience[16–18,55], and sensorimotor processing networks[16,20,21,32,55]. While previous studies, including one report from our group have suggested these functional changes also may be accompanied by remodeling of microstructural white matter connections between these same brain areas[12], the influence and dependence of these structural changes on sex has not been adequately explored.

Alterations in cortico-basal ganglia-thalamic loops

The basal ganglia are considered an important hub for the processing and integration of multisensory signals, as well as a major site for adaptive neuroplasticity[2]. The parallel processing of different types of ascending sensory information in the basal ganglia is thought to increase the chances of detecting and responding to salient sensory events. A critical process in the differentiation of salient from benign sensory signals requires a selective downregulation of non-salient multimodal sensory signals. Through their cortical and thalamic connections (i.e., the cortico-basal ganglia-thalamic loop) the basal ganglia are thought to be involved in the modulation of pain signaling via the integration of sensory, motor, emotional, cognitive, and autonomic signals[3,8]. The observed increased density and projections within the basal ganglia and the reinforced ascending white matter projections between basal ganglia, sensorimotor and frontal regions [posterior mid-cingulate (pMCC) and anterior cingulate (ACC), and medial prefrontal cortex(mPFC)] in female compared to male IBS subjects may provide the anatomical substrate for compromised processing of multisensory signals, and failure to inhibit non salient visceral and somatic signals.

Female IBS showed differences in primary and secondary sensorimotor areas (S1/S2, M1, SMA, pMCC[54]) consistent with increased ascending signaling to these sensory brain regions. Before reaching the brain, nociceptive signals are modulated at the dorsal horn level by descending endogenous pain modulation pathways originating in the periaqueductal gray (PAG). The PAG receives inputs from several regions within the emotional arousal network, involving the anterior cingulate, insular, amygdalar and prefrontal cortices, ultimately influencing the balance between inhibitory and facilitatory descending modulation. In addition to playing a crucial role in endogenous pain modulation, these regions also send

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information about the emotional and hedonic aspects of the sensory information to the basal ganglia and have previously been implicated in the development of chronic pain[36].

The observed alterations in the ACC and mPFC together with the increased perception of threat indexed by increased GI-specific anxiety in female IBS participants could be a consequence of dysfunctional multisensory processing leading to increased emotional signaling (ACC) and increased but failed attempts to downregulate signals by mPFC resulting increased PAG signaling (and chronic changes in sensorimotor cortices). Alteration in the connectivity of these key salience regions with basal ganglia and thalamus as a part of the cortico-basal ganglia-thalamic loop has been observed in several psychiatric disorders marked by reduced ability to exert cognitive control over maladaptive thoughts, and attention to appropriate salient internal and external stimuli[22,37,38,50]. Although highly speculative, the shared alterations in sensory processing and modulation between these disorders suggest a shared endophenotype explaining not only the frequent comorbidity with other chronic overlapping pain conditions but also symptom responsiveness to different brain-gut therapeutic modalities, such as tricyclic antidepressants, cognitive behavioral therapy and mindfulness-based stress reduction.

Shared pathways with other chronic pain conditions

Neuroimaging studies have shown that compared to HCs, individuals with IBS (comprised primarily of female participants) have resting state connectivity and gray matter morphometry alterations in the regions innervated by the tracts showing differences in this study including basal ganglia, sensorimotor and prefrontal cortex, and thalamus[26,31,52]. Similar changes have been observed in other disorders that are female predominant and often found comorbid with IBS including fibromyalgia and urological chronic pelvic pain syndrome[14,23,35,48]. Greater levels of sensory sensitivity and somatic awareness and higher rates of comorbidity in females compared to males have also been reported in the majority of chronic pain conditions[30]. The similar sex differences observed in this study between healthy female and males, is consistent with the concept that alterations in sensory integration and modulation systems are not only an important component of IBS pathophysiology, but that they increase the vulnerability of females to develop chronic pain conditions. It has been speculated that the altered modulation of multisensory input in female subjects may in part be explained by the regular experience of visceral pain associated with the menstrual period and delivery, and the greater salience assessment of visceral and somatic stimuli.

Alterations in sensory integration and modulation systems is also consistent with the observation that patients with certain somatic and visceral chronic pain syndromes, also show increased sensitivity to other sensory modalities, including visual, auditory and olfactory stimuli[10,44]. Also, increased brain responses to such stimuli in visual and auditory processing regions, including the basal ganglia have been shown to be discriminate female subjects with fibromyalgia from female HCs to a greater degree than brain responses to a painful stimulus[29]. This multisensory signature in fibromyalgia was associated with higher somatic pain ratings highlighting the role of compromised processing of nonpainful multisensory signals in FM. The observed microstructural differences in the basal ganglia in

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conjunction with higher reports of somatic awareness, symptom related anxiety and greater widespread pain symptoms in women with IBS highlight a potentially shared mechanism between these conditions.

In principle, the observed brain alterations in the cortico-basal ganglia-thalamic loop could be the result of altered descending influences from cortical regions, from chronically increased ascending signaling from the spinal cord, or ultimately from some peripheral, yet unknown process in the gut. The fact that similar sex related differences in cortico-basal ganglia-thalamic microstructure were observed in healthy subjects without any gut symptoms, and in patients with other chronic somatic and visceral pain disorders, makes a specific peripheral source highly unlikely. However, we are unable to rule out the possibility of chronic engagement of the endogenous descending pain facilitatory pathways (associated with GI specific anxiety), amplifying normal sensory signals from the gut reaching the dorsal horn which then generate amplified sensory signals reaching the thalamus and the basal ganglia loop.

Strengths and Limitations

In comparison to previous studies examining sex differences[12], the significantly increased sample size in the current study provides greater statical power to assess difference within IBS subjects as well as in HCs, and to formally test “sex-by-disease” interactions in brain microstructural reorganization, providing strong evidence for sex and disease-specific alterations. The cross-sectional nature of the study and DTI assessments do not permit an assessment of directionality (i.e., top-down or bottom-up processing). A more fine-grained seed-based connectivity is needed to assess anatomical connectivity. Also, the etiology of the observed microstructural alterations cannot be assessed without a longitudinal experimental design as well as concurrent and complimentary multi-omics assessment (e.g., metabolomics including sex hormones, microbiome, genetics, and epigenetics) to gain new insights into genetic and molecular influences on the observed brain alterations. Lastly, it is important to point out the technical limitations of DTI and tractography, particularly as it relates to crossing fibers and propensity for false positives when using probabilistic methods[43]. Future studies utilizing a combination of approaches to mitigate these limitations are necessary to fully appreciate potential sex-differences between IBS patients.

Conclusions

In summary, these results strongly suggest white matter changes previously observed in IBS compared to HCs are primarily driven by brain alterations in female patients. Specifically, female patients showed extensive microstructural alterations in sensorimotor, corticothalamic, and basal ganglia circuits involved in pain processing and integration of sensorimotor information. Together with the observed increases in IBS symptom severity, symptom related anxiety, and somatic awareness, and the greater prevalence of widespread pain in female IBS, these findings support the hypotheses that the etiology and maintenance of symptoms for females with IBS is driven by greater central sensitivity for multiple sensory stimuli.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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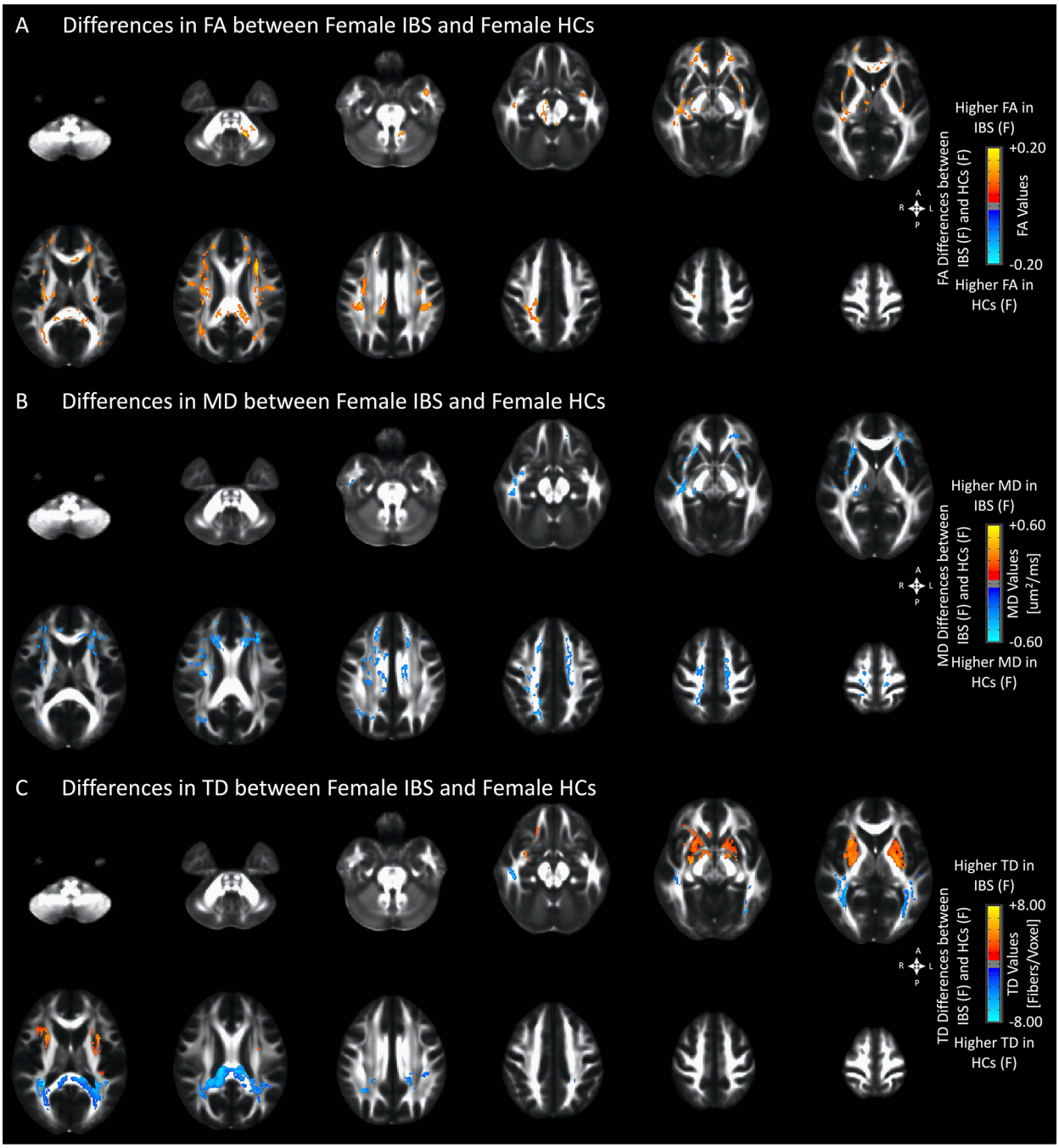

Fig. 1.

Anatomical localization of regional differences in (**A**) fractional anisotropy (FA), (**B**) mean diffusivity (MD), and (**C**) fiber track density (TD) between female IBS patients and female HCs. Significant clusters were determined by thresholding based on level of statistical significance ($p < 0.05$) and cluster size.

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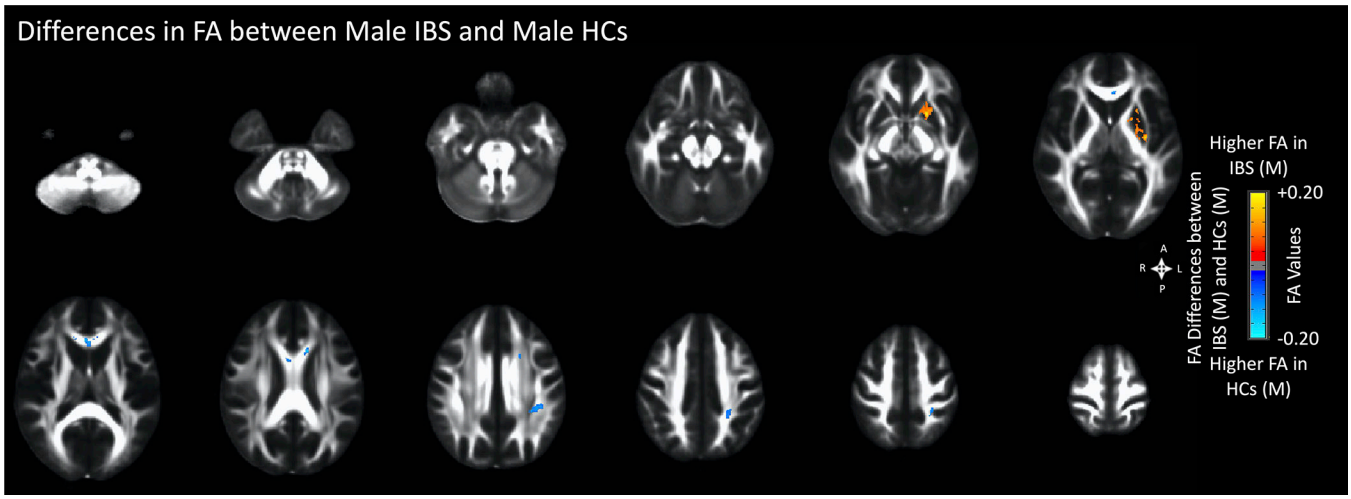

Fig. 2.

Anatomical localization of regional differences in fractional anisotropy (FA) between male IBS patients and male HCs. Significant clusters were determined by thresholding based on level of statistical significance ($p < 0.05$) and cluster size.

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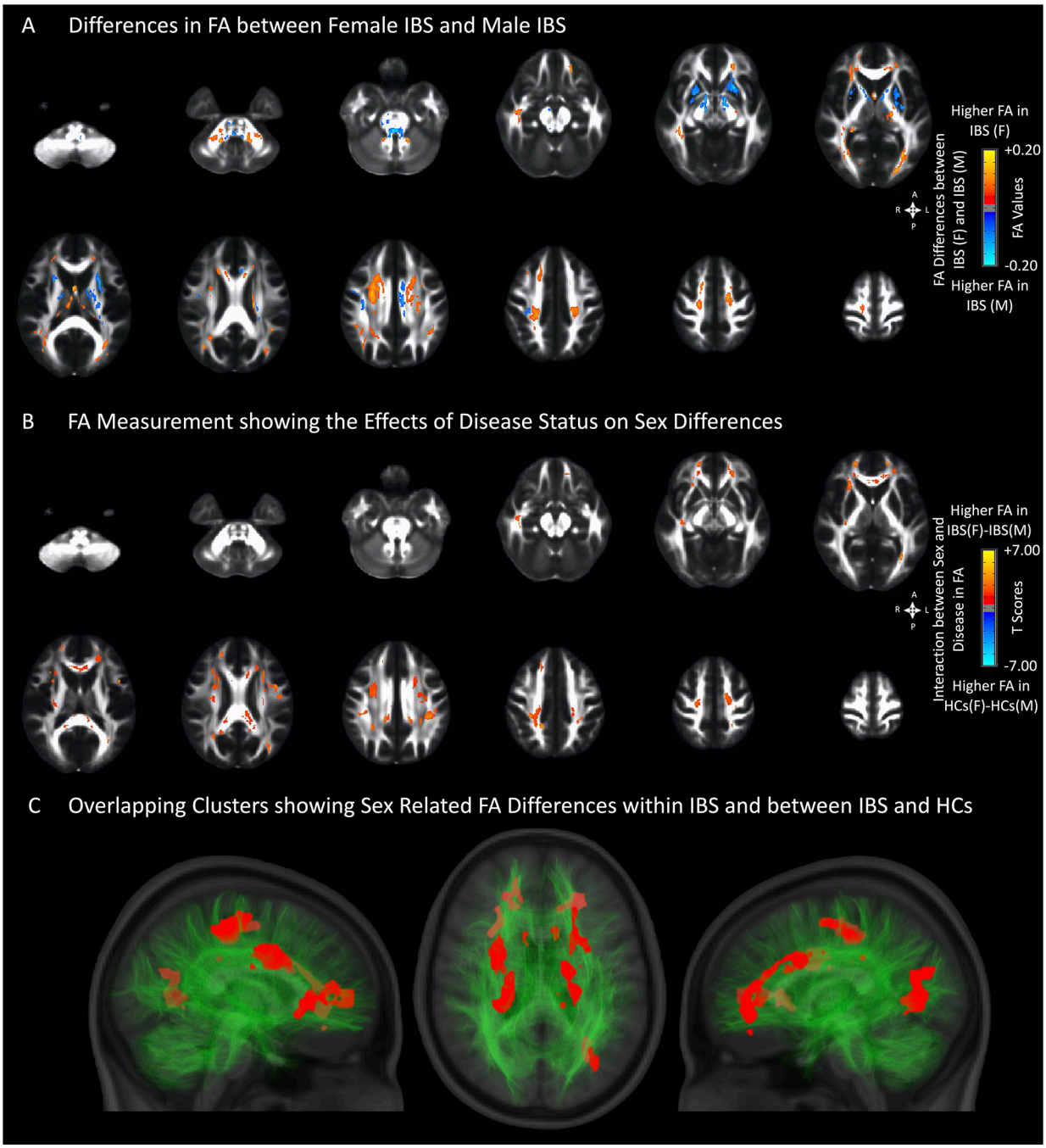

Fig. 3.

Anatomical localization of regional, sex-associated differences in fractional anisotropy (FA) (**A**) within IBS patients, (**B**) the interaction between sex and disease (*IBS[F-M] vs. HC[F-M]*), and (**C**) overlapping clusters between (**A**) and (**B**). Significant clusters were determined by thresholding based on level of statistical significance ($p < 0.05$) and cluster size.

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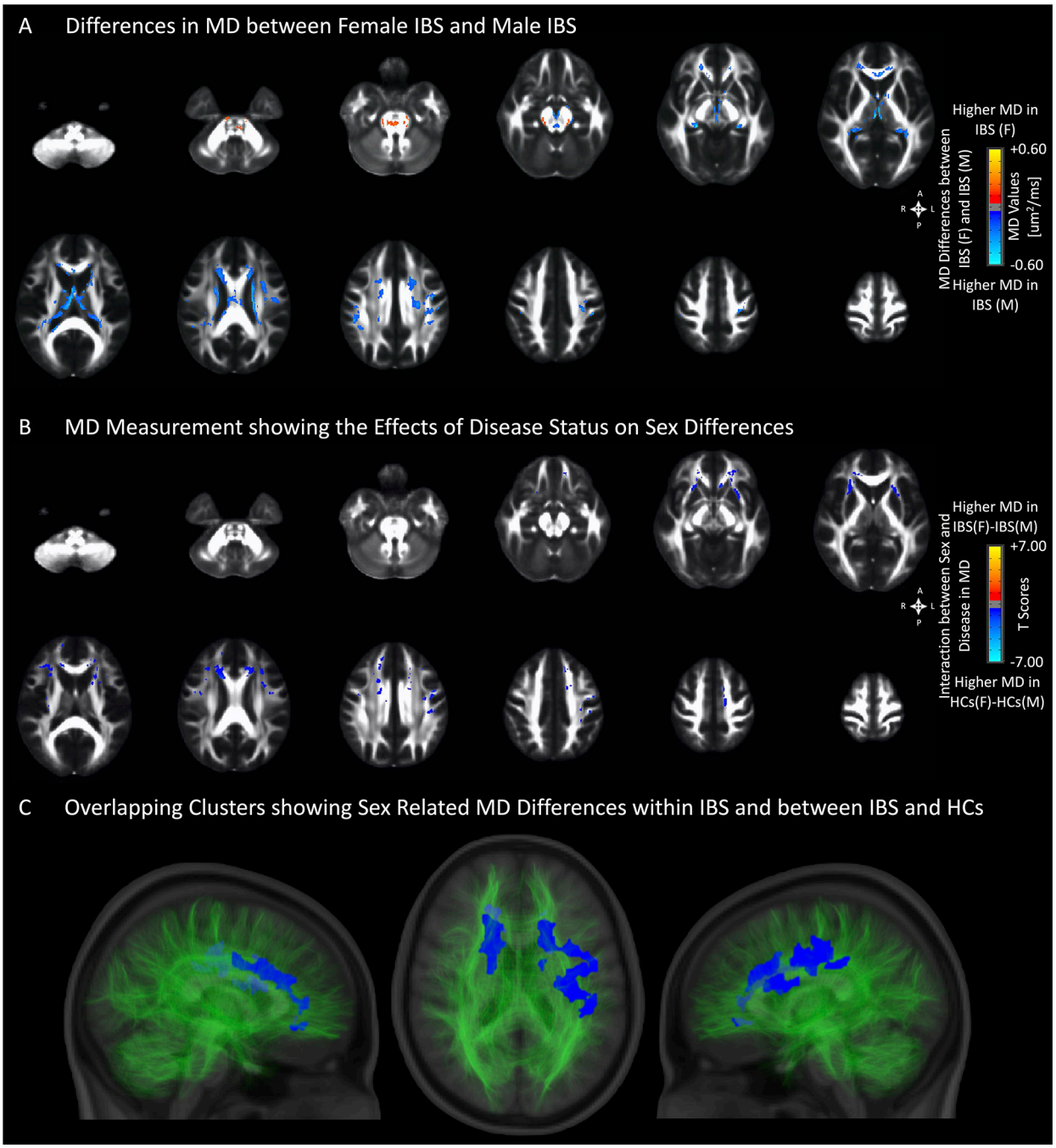

Fig. 4.

Anatomical localization of regional, sex-associated differences in mean diffusivity (MD) (**A**) within IBS patients, (**B**) the interaction between sex and disease (*IBS[F-M] vs. HC[F-M]*), and (**C**) overlapping clusters between (**A**) and (**B**). Significant clusters were determined by thresholding based on level of statistical significance ($p < 0.05$) and cluster size.

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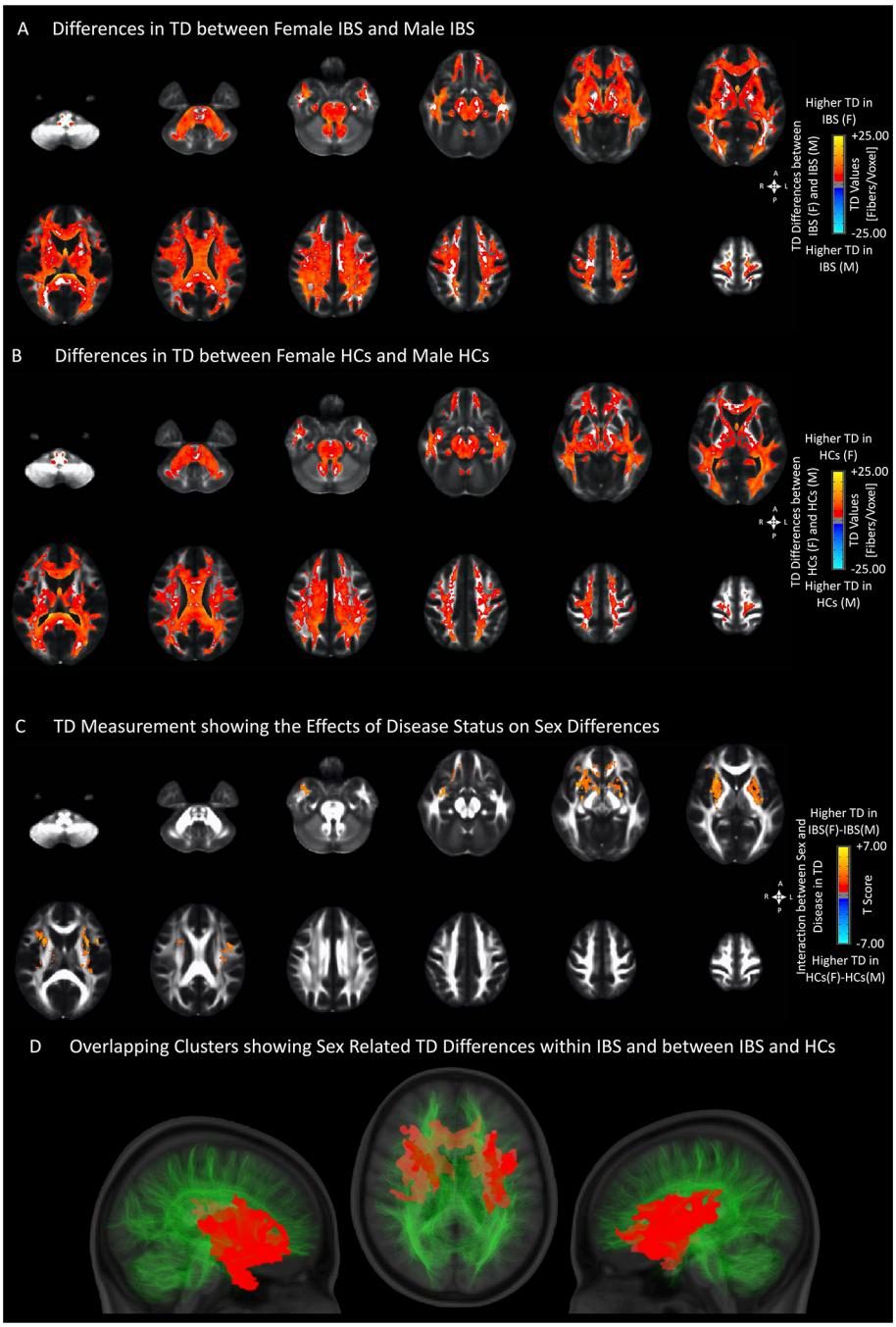

Fig. 5.

Anatomical localization of regional, sex-associated differences in track density (TD) (**A**) within IBS patients, (**B**) within HC participants, (**C**) the interaction between sex and disease (*IBS[F-M] vs. HC[F-M]*), and (**C**) overlapping clusters between (**A**) and (**C**). Significant clusters were determined by thresholding based on level of statistical significance ($p < 0.05$) and cluster size.

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Table 1.

Characteristics of the Sample

	HC (n=100) M(SD)	IBS(n=152) M(SD)	t(250), p-value	ES Cohen's d
Age	30.3(11.0)	28.2(9.8)	5.94, 0.13	0.20
Sex	39 Males/61 Females	45 Males/107 Females		
Body Mass Index	25.4(3.6)	23.0(2.8)	6.2, 2.6×10^{-9}	0.80
STAI Trait Anxiety	47.0(9.4)	53.9(11.4)	-5.03, 9.4×10^{-7}	−0.65
IBS-symptom severity scale [#]		221.6 (91.8)		
Overall symptom Severity last week (1–20) [*]		9.8 (4.3)		
Usual Symptom Severity (1–5) [*]		3.3 (.70)		
Symptom Duration (Years)*		9.9 (9.4)		
Bowel Habits (n)				
Constipation		50		
Diarrhea		62		
Mixed		13		
Unspecified		27		

[#] 3 missing data points

[*] 1 missing data point

Abbreviations: CMSI: HC=Healthy Control, ES=effect size, IBS=irritable bowel syndrome, M=mean, p=probability, SD =standard deviation, STAI=State Trait Anxiety Inventory

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Table 2.

Symptom and Psychosocial assessments stratified by sex as a biological factor in IBS

	IBS Females M (SD)	IBS Males M (SD)	t(df), p-value	ES Cohen's d
Age	26.7(8.8)	31.8(11.2)	t(150)=−3.02, p=0.003	−0.54
IBS-symptom severity scale (0–500) #	234.1(96.8)	191.8(71.3)	t(147)=2.61, p=0.01	0.47
Overall symptom severity last week (1–20) *	9.9 (4.2)	9.6(4.6)	t(149)=0.35, p=0.73	0.06
Usual Symptom Severity (1–5) *	3.4(.71)	3.1(.65)	t(149)=2.31, p=0.022	0.41
Symptom Duration (Years) *	8.7(8.8)	12.9 (10.0)	t(149)=−2.57, p=0.011	−0.47
Age onset *	17.9(6.9)	19.0 (6.8)	t(150)=−0.87, p=0.39	−0.16
STAI Trait Anxiety	52.9(11.7)	56.2 (10.4)	t(150)=−1.64, p=0.10	−0.29
Visceral Sensitivity Index	41.7(15.7)	34.7(15.6)	t(150)=2.51, p=0.013	0.45
CMSI-past 12 month &	8.6(7.7)	5.0(3.9)	t(146)=2.96, p=0.004	0.53
CMSI-life time &	10.1(8.4)	7.0(5.6)	t(146)=2.32, p=0.022	0.42
CMSI-Somatic Awareness &	3.1 (3.4)	1.8(1.8)	t(146)=2.56, p=0.011	.46
CMSI-Sensory Sensitivity &	.78(1.1)	.07(.26)	t(146)=4.38, p=2.2e−5	.79

missing 2 females, 1 male

* missing 1 female missing

& missing 3 females, 1 male

Abbreviations: CMSI: The Complex Medical Symptom Inventory df=degrees of freedom, HC=Healthy Control, ES=effect size, IBS=irritable bowel syndrome, M=mean, p=probability, SD =standard deviation, STAI=State Trait Anxiety Inventory

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Table 3.

Overlapping White Matter Clusters Showing Significant Sex Related Differences in Fractional Anisotropy (FA) in IBS patients, and between IBS Patients and HCs.

Clusters		Cluster Size (μL)	White Matter Pathways
Cluster #1	Higher in Female IBS Higher in IBS (F-M)	771	Anterior Corona Radiata (R) Body of the Corpus Callosum Genu of the Corpus Callosum Splenium of the Corpus Callosum Superior Corona Radiata (R) Superior Longitudinal Fasciculus (R)
Cluster #2	Higher in Female IBS Higher in IBS (F-M)	723	Body of the Corpus Callosum Cingulum Cingulate Gyrus (L) Superior Corona Radiata (L) Superior Longitudinal Fasciculus (L)
Cluster #3	Higher in Female IBS Higher in IBS (F-M)	238	Posterior Thalamic Radiation (R)
Cluster #4	Higher in Female IBS Higher in IBS (F-M)	200	Anterior Corona Radiata (L) External Capsule (L)

R=Right, L=Left, FA=Fractional Anisotropy

F=Female, M=Male, IBS=Irritable Bowel Syndrome, HC=Healthy Control

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Table 4.

Overlapping White Matter Clusters Showing Significant Sex Related Differences in Mean Diffusivity (MD) in IBS patients, and between IBS Patients and HCs.

Clusters		Cluster Size (μL)	White Matter Pathways
Cluster #1	Higher in Male IBS Higher in HC (F-M)	1,359	Anterior Corona Radiata (L) Anterior Corona Radiata (R) Body of the Corpus Callosum Genu of the Corpus Callosum Superior Corona Radiata (L)
Cluster #2	Higher in Male IBS Higher in HC (F-M)	1,253	Anterior Limb Internal Capsule (R) Anterior Corona Radiata (R) Body of the Corpus Callosum External Capsule (R) Genu of the Corpus Callosum Superior Corona Radiata (R) Superior Fronto-occipital Fasciculus (R) Superior Longitudinal Fasciculus (L) Superior Longitudinal Fasciculus (R)

R=Right, L=Left, MD=Mean Diffusivity

F=Female, M=Male, IBS=Irritable Bowel Syndrome, HC=Healthy Control

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Table 5.

Overlapping White Matter Clusters Showing Significant Sex Related Differences in Fiber Track Density (TD) in IBS patients, and between IBS Patients and HCs.

Clusters		Cluster Size (μL)	White Matter Pathways
Cluster #1	Higher in Female IBS Higher in IBS (F-M)	8,367	Anterior Limb Internal Capsule (L) Anterior Limb Internal Capsule (R) Anterior Corona Radiata (L) Anterior Corona Radiata (R) External Capsule (L) External Capsule (R) Fornix Stria Terminalis (L) Genu of the Corpus Callosum Posterior Limb Internal Capsule (L) Posterior Limb Internal Capsule (R) Posterior Corona Radiata (R) Retrolenticular Part Internal Capsule (L) Retrolenticular Part Internal Capsule (R) Sagittal Stratum (L) Superior Corona Radiata (L) Superior Corona Radiata (R) Superior Fronto-occipital Fasciculus (L) Superior Longitudinal Fasciculus (L) Superior Longitudinal Fasciculus (R) Uncinate Fasciculus (L) Thalamus

R=Right, L=Left, TD=Fiber Track Density

F=Female, M=Male, IBS=Irritable Bowel Syndrome, HC=Healthy Control

r=Right, l=Left, FA=Fractional Anisotropy, MD=Mean Diffusivity, TD=Fiber Track Density

IBS=Irritable Bowel Syndrome, HC=Healthy Control