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Original Article

Inter-hemispheric Functional Connections Are More Vulnerable to Attack Than Structural Connection in Patients With Irritable Bowel Syndrome

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Background/Aims

Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disease characterized by recurrent abdominal pain and bowel dysfunction. However, the majority of previous neuroimaging studies focus on brain structure and connections but seldom on the inter-hemispheric connectivity or structural asymmetry. This study uses multi-modal imaging to investigate the abnormal changes across the 2 cerebral hemispheres in patients with IBS.

Methods

Structural MRI, resting-state functional MRI, and diffusion tensor imaging were acquired from 34 patients with IBS and 33 healthy controls. The voxel-mirrored homotopic connectivity, fractional anisotropy, fiber length, fiber number, and asymmetry index were calculated and assessed for group differences. In addition, we assessed their relevance for the severity of IBS.

Results

Compared with healthy controls, the inter-hemispheric functional connectivity of patients with IBS showed higher levels in bilateral superior occipital gyrus, middle occipital gyrus, precuneus, posterior cingulate gyrus, and angular gyrus, but lower in supplementary motor area. The statistical results showed no significant difference in inter-hemispheric anatomical connections and structural asymmetry, however negative correlations between inter-hemispheric connectivity and the severity of IBS were found in some regions with significant difference.

Conclusions

The functional connections between cerebral hemispheres were more susceptible to IBS than anatomical connections, and brain structure is relatively stable. Besides, the brain areas affected by IBS were concentrated in default mode network and sensorimotor network.
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Key Words

Brain; Default mode network; Irritable bowel syndrome; Neuroimaging

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Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disease which is characterized by abdominal pain and disordered defecation.[1] Global studies that recorded the prevalence of IBS is about 5-22%,[2] and this number is about 5-10% in China.[3,4] In the general population, IBS is more prevalent in women compared with men.[5] The subtypes of IBS were distinguished depend on predominant stool pattern, including constipation-predominant IBS, diarrhea-predominant IBS, mixed IBS alternating constipation and diarrhea, and an unsubtyped IBS. The pathogenesis of IBS appears to be multifactorial, including diet, an altered neuroendocrine system, abnormal intestinal microbiota, genetics, and mucosal low-grade inflammation.[6] Hitherto, the underlying pathophysiological mechanisms of IBS are still incompletely understood.

The majority of IBS patients were discovered with psychological abnormalities, such as fatigue, anxiety, and depression.[7-10] The human gut and brain interact complexly through the gut-brain axis (GBA), which includes the central nervous system, autonomic nervous system, enteric nervous system, and hypothalamic pituitary adrenal (HPA) axis.[11] The enteric microbiota is widely distributed in the human gastrointestinal tract, although individuals' gut microbiota may not be identical, the relative abundance and distribution of these bacterial phylotypes are similar to healthy controls (HCs). IBS is considered an exemplary disorder of gut-brain communication. An increasing number of studies suggested that gut microbiota is an environmental factor that can regulate the brain through the GBA.[12,13] In recent years, some studies have reported a relationship between neuropsychiatric and GBA,[14-16] and suggested that the modulation of gut microbiota may be a viable strategy for the treatment of mental diseases.[13]

Noninvasive neuroimaging has become a popular method to identify neurophysiologic abnormalities in several diseases of the brain. Meanwhile, multimodal brain imaging has promoted a better understanding of brain diseases. Previous studies have reported significant brain abnormalities in patients with pain or mental diseases.[17-19] For example, abnormal rest-state functional connectivity (rsFC) was reported in adults with major depressive disorders.[20] Stress-related mental disorders such as major depressive disorders and anxiety disorders are associated with the change of brain structure,[21] and over time these diseases can lead to more severe changes in the brain. Simultaneously, different types of chronic pain showed unique anatomical reorganization of brain.[22]

The human brain is remarkably asymmetrical and which increases throughout life.[23] Despite the left and right halves of the brain resembling each other, the 2 hemispheres also display significant anatomical and functional differences.[24] There is an advantage to bihemispheric processing, provided that each hemisphere participates in specific functions. Besides, the interaction of perception, cognition, and behavior between 2 brain hemispheres is important for brain functioning.[25] Several studies have suggested stress-related mental disorders displayed the disruption of inter-hemispheric structural connectivity and the loss of functional connectivity (FC),[26,27] accompanied by significant changes in structural asymmetry.[28]

Recently analyses have identified regional and network alterations in the brain of patients with IBS.[29,30] Compared to HCs, alterations in rsFC of the default mode network (DMN), central executive network, and sensorimotor network have been observed in patients with IBS.[31,32] A recent study reported IBS had lower fractional anisotropy (FA) and higher mean diffusivity in the thalamic regions, the basal ganglia, and the sensory/motor association/

integration regions.[33] However, there is a lack of consistency with regard to the morphologic abnormalities of the brain reported in patients with IBS,[34-36] which is probably influenced by the gender and IBS subtypes of patients.[37,38] Although a number of researches on patients with IBS have investigated the abnormalities in specific brain areas and connections, few studies focus on the inter-hemispheric connections and asymmetry.

We hypothesized that patients with IBS would display aberrant inter-hemispheric functional and anatomical connections compared with healthy adults. Five types of MRI features, including voxel-mirrored homotopic connectivity (VMHC) from functional MRI (fMRI), asymmetry index (AI) from structural MRI, FA, fiber length, and FN from diffusion tensor imaging (DTI), were analyzed in this study. To the best of our knowledge, this is the first attempt to evaluate the asymmetry and inter-hemispheric connectivity of patients with IBS.

Materials and Methods

Participants

Thirty-four participants with IBS (24 diarrhea-predominant IBS, 4 constipation-predominant IBS, and 6 mixed IBS) and 33 age-, gender-matched HCs were recruited from Lanzhou University Second Hospital (see Table 1 for details). All participants were right-hand. The diagnosis was based on the Rome IV criteria by a gastroenterologist who is experienced in the evaluation of IBS.[39] Exclusion criteria included psychiatric disease, other severe disease, and history of drug or alcohol abuse. Written informed consent to participate was obtained from each participant. All procedures were in accordance with the guidelines. Ethical approval (2019A-176) was obtained from the medical ethics committee of Lanzhou University Second Hospital.

Table 1. Demographics and Psychological Assessments Between Irritable Bowel Syndrome and Healthy Controls

	IBS (n = 34)	HC (n = 33)	*P*-value
Gender (F/M)	16/18	22/11	0.105
Age (yr)	27.35 ± 4.40	25.67 ± 4.56	0.128
BMI (kg/m^2)	22.56 ± 4.08	20.36 ± 2.24	0.008
Education (yr)	17.35 ± 1.92	17.00 ± 2.02	0.466
IBS-SSS	247.06 ± 39.04	120.00 ± 23.98	< 0.001
IBS-QOL	83.33 ± 10.97	96.88 ± 3.57	4.683e-9
PCS	10.15 ± 8.39	2.24 ± 4.51	1.034e-5
PHQ-15	11.06 ± 7.49	0.00 ± 0.00	4.055e-12
HAMA	10.82 ± 7.79	2.18 ± 2.95	1.074e-7
HAMD	9.41 ± 6.82	2.82 ± 4.82	2.332e-5
SF-MPQ	8.59 ± 5.65	0.00 ± 0.00	1.453e-12

IBS, irritable bowel syndrome; HC, healthy control; F, female; M, male; BMI, body mass index; IBS-SSS, IBS Severity Scoring System; IBS-QOL, IBS-quality of life; PCS, Pain Catastrophizing Scale; PHQ-15, Patient Health Questionnaire; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SF-MPQ, short-form McGill Pain Questionnaire.
Values are expressed as n or mean ± SD.

Psychological Assessment

All participants underwent a battery of standardized psychological assessments before MRI scanning. Body mass index (BMI),[40] IBS Severity Scoring System (IBS-SSS, range = 100-500),[41] Pain Catastrophizing Scale (PCS, range = 0-52),[42] Patient Health Questionnaire (PHQ-15, range = 0-30),[43] and short-form McGill Pain Questionnaire (SF-MPQ, range = 0-60)[44] were used to evaluate the severity of health problems. Anxiety and depression states were measured using the Hamilton Anxiety Scale (HAMA, range = 0-56)[45] and Hamilton Depression Scale (HAMD, range = 0-54).[46] IBS-quality of life (IBS-QOL, range = 0-100) assessed the influence of bowel habit on daily life.[47] BMI, IBS-SSS, PCS, PHQ-15, SF-MPQ, HAMA, and HAMD assessed the level of obesity, severity of IBS symptoms, degree of pessimism about pain, somatic symptom burden, overall intensity of pain, and severity of anxiety and depression, respectively. The higher score means the higher level of these symptoms. Besides all that, IBS-QOL is a valuable scale to reflect the impact of physical and psychological in IBS patients, and the higher score indicate better QOL.

Image Acquisition

All MRI data were acquired on a 3.0 T Siemens scanner using the standard 8-channel head coil at Lanzhou University Second Hospital. High-resolution 3-dimensional T1-weighted data were acquired with the following parameters: repetition time (TR) = 2000 msec, echo time (TE) = 2.67 msec, voxel size = 1.0 × 1.0 × 1.0 mm, slice thickness = 1.0 mm, field of view (FOV) read = 256 mm, FOV phase = 87.5%, flip angle = 12°, inversion time (TI) = 900 msec. All of the images were checked to rule out structural abnormalities. Resting-state fMRI images were acquired using an echo-planar-imaging sequence with the following parameters: TR = 2000 msec, TE = 30 msec, voxel size = 3.4 × 3.4 × 3.0 mm, slice thickness = 3.0 mm, FOV read = 220 mm, FOV phase = 100.0%, flip angle = 90°. DTI images were performed with echo-planar-imaging sequence with the following parameters: TR = 7600 msec, TE = 90 msec, voxel size = 2.0 × 2.0 × 3.0 mm, slice thickness = 3.0 mm, FOV read = 256 mm, FOV phase =

100.0%, Throughout scans, all subjects were instructed to relax, keep their eyes closed and avoid thinking of anything in particular.

Data Preprocessing

Functional MRI preprocessing was performed using the data processing assistant for resting-state fMRI[48] with statistical parametric mapping (https://www.fil.ion.ucl.ac.uk/spm).[49] The first 10 images of each functional time series were discarded to allow signal stabilization and adaptation of the participants to the scanning environment. Slice timing correction, head motion correction, spatial normalization to the Montreal Neurological Institute template, and spatially smoothed with 6 mm full width at half maximum Gaussian kernel were applied to the remaining volumes. Subsequently, linear detrending and band-pass-filter (0.01-0.08 Hz) were performed to reduce the effect of low-frequency drift and high-frequency physiological noise. Nuisance covariates including 6 head motion parameters, cerebrospinal fluid signals, global mean, and white matter were removed by linear regression.

The 3-dimensional T1 images were processed using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu), which include a set of automatic sequences to reconstruct the surface of whole brain.[50,51] Details of this pipeline were described in previous studies.[50,52] A 2-dimensional cortical surface was calculated and we divided the whole brain into 45 anatomically labeled areas for each hemisphere using the Automated Anatomical Labeling template.

For the DTI data, we first converted the format of images from DICOM into 4-dimensional nifti-1 format file. Data processing was executed by using the pipeline for analyzing brain diffusion images (PANDA; http://www.nitrc.org/projects/panda/),[53] which is based on FSL (http://fsl.fmrib.ox.ac.uk/fsl)[54] and Diffusion Toolkit.[55] The approach of processing included correction for simple head motion and eddy current distortions using affine transformation to the b0 image. After correction, we obtained the FA maps of each subject. Fiber assignment by continuous tracking algorithm was subsequently performed to obtain the whole-brain fiber tractography. Path tracking procedure started from the deep white matter regions and terminated at a voxel with a turning angle greater than 45° or reached a voxel with an FA of < 0.2. The DTI metrics were calculated for each subject, followed by spatial standardization and Gaussian smoothing.

Calculation of Voxel-mirrored Homotopic Connectivity

The VMHC was obtained to quantify the rsFC between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere.[56] We computed the value of VMHC using resting-state fMRI data analysis toolkit (REST V1.8; http://www.restfmri.net/forum/REST_V1.8).[57] The procedure of computation included the follow steps: (1) creating a mean normalized T1 image and averaged it with left-right mirrored version to generate a group-specific symmetrical template, (2) registering the T1 image of each subject to the symmetrical template and applying this transformation to the corresponding functional data, (3) computing the Pearson's correlation coefficient between each voxel and its symmetrical interhemispheric counterpart, (4) applying the Fisher's z transformation to improve normality. The resultant values constituted the VMHC maps and were used in group-level analyses.

Voxel Based Morphometry-based Volumetric Analysis

For each subject, the volume of each region of interest (ROI) and intracranial volume were obtained with FreeSurfer software (https://www.freesurfer.net/). To evaluate the possible structural abnormalities of hemispheric asymmetry produced by IBS, we calculated the AI using the following formula:

$$AI = [(L - R)/(L + R)]/2$$

where L and R represent the corresponding volume on the left and right hemisphere respectively. The absolute value of AI ranges from 0.0 to 0.5. Thus, positive and negative AI values indicate leftward (left larger than right) and rightward asymmetry respectively.

Statistical Methods

Statistical analyses were performed using REST V1.8. To test the group differences in age, years of education, psychological assessments, FA, FN, and fiber length, data was analyzed with Student's *t* test. The chi-square test was employed to compare gender distributions between groups. A value of $P < 0.05$ was considered significant. To examine the differences in AI between IBS and HCs, we used one-way ANOVA with intracranial volume as covariate. Individual-level VMHC maps were entered into a group-level voxel-wise *t* test analysis. AlphaSim was used to correct for multiple comparisons, and significance threshold was defined as $P < 0.05$. Lastly, Pearson correlation analyses were performed to assess the relationships between metrics and the severity of IBS. Significant correlation was defined as $r > 0.3$ and $P < 0.05$.

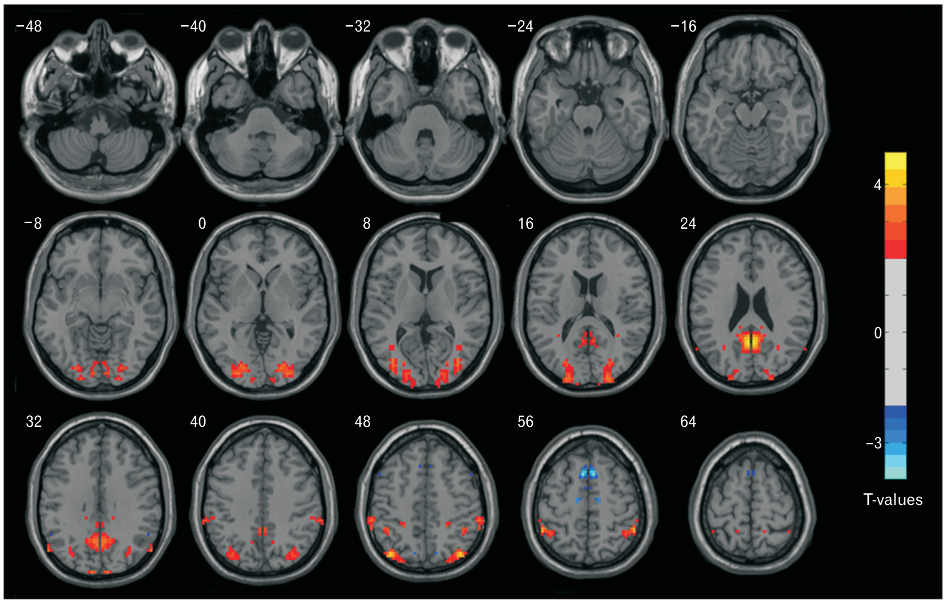

Figure 1. Statistical maps showing voxel-mirrored homotopic connectivity (VMHC) differences between irritable bowel syndrome (IBS) and healthy controls (HCs; $P < 0.05$, corrected with Alphasim). IBS patients showed much higher VMHC in superior occipital gyrus, middle occipital gyrus, precuneus, posterior cingulate gyrus, and angular gyrus (red), while lower in supplementary motor area (blue). The color bar indicates the T-value from *t* test between groups.

Table 2. Regions With Significant Differences in Voxel-mirrored Homotopic Connectivity ($P < 0.05$, AlphaSim Corrected)

Brain region	Peak MNI coordinate			Peak T-value
	x	y	z	
Bilateral superior occipital gyrus	±24	−99	18	3.678
Bilateral middle occipital gyrus	±24	−99	20	2.903
Bilateral precuneus	±3	−57	27	4.882
Bilateral posterior cingulate gyrus	±3	−57	29	4.854
Bilateral supplementary motor area	±6	15	57	−3.998
Bilateral angular gyrus	±39	−75	45	4.327

MNI, Montreal Neurological Institute.

Results

Characteristics of Participants

The demographics and psychological assessments of participants were presented in Table 1. There was no significant difference in gender, age or education level between IBS patients or HC adults. IBS patients had a significant higher BMI, IBS-SSS, PCS, PHQ-15, HAMA, HAMD, and SF-MPQ scores than that in HCs, whereas IBS-QOL declined significantly.

Table 3. Correlation Analyses Between Voxel-mirrored Homotopic Connectivity and Irritable Bowel Syndrome Severity Scoring System Score

Brain region	Peak MNI coordinate			Peak *r*-value
	x	y	z	
Bilateral middle occipital gyrus	±45	−87	15	−0.600

MNI, Montreal Neurological Institute.

Functional Connectivity Differences Between Groups

Figure 1 and Table 2 show the group comparisons of VMHC values. Patient with IBS had higher VMHC than the control group in the superior occipital gyrus (SOG), middle occipital gyrus (MOG), precuneus, posterior cingulate gyrus (PCG), and angular gyrus (ANG). Supplementary motor area (SMA) exhibited lower VMHC in the IBS than HC ($P < 0.05$, Alphasim correction).

We also examined the correlation between VMHC in each pair of ROIs and IBS-SSS scores, but a significant negative correlation between VMHC and the severity of IBS were found only in the bilateral middle occipital gyrus ($r = -0.600$, $P < 0.05$) (Table 3).

Anatomical Connection Differences Between Groups

We performed a between-group analysis for the AI, FA, fiber

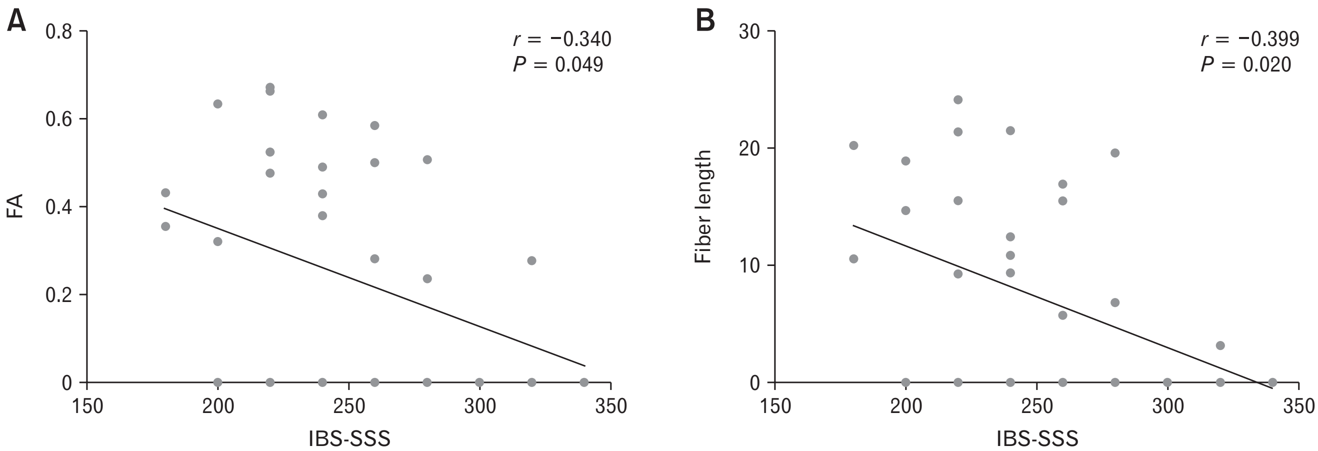

Figure 2. Correlation analyses between fractional anisotropy (FA)/fiber length and irritable bowel syndrome severity scoring system (IBS-SSS) score in posterior cingulate gyrus.

length, and fiber number. However, no significant differences were detected between IBS and HCs. As shown in Figure 2, we analyzed the correlations between FA/fiber length and IBS-SSS score using Pearson's correlation. The result showed that the FA ($r = -0.340, P < 0.05$) and fiber length ($r = -0.399, P < 0.05$) of the bilateral posterior cingulate gyrus showed significant negative correlation with the severity of IBS.

Discussion

In this study, we investigated the inter-hemispheric connection and structural asymmetry of IBS patients compared with HCs. Our results demonstrated that the FC of brain is the most sensitive to enteric disease, followed by anatomical connection, and the brain morphology of patients is the most stable. Compared with HCs, we found significant VMHC changes in the bilateral SOG, MOG, precuneus, PCG, SMA, and ANG. ROIs with abnormal changes may be related to the symptom manifestation of patients. Furthermore, we also found a negative correlation between inter-hemispheric FC and IBS-SSS in MOG. Although the differences of structural connectivity and asymmetry were not statistically significant, negative correlation was observed between anatomical connection and IBS-SSS. To our knowledge, this study is the first research aimed to evaluate inter-hemispheric connectivity and morphology of the brain in IBS patients.

Inter-hemispheric Functional Connectivity

VMHC describes the strength of FC between symmetric inter-hemispheric voxels. As shown in Figure 2 and Table 2, compared with HCs, inter-hemispheric FC significantly increased in precuneus, PCG, and ANG in IBS patients. Moreover, these areas are all important components of the DMN. An increase in VMHC means a significant increase in inter-hemispheric connectivity of IBS patients. Some previous studies interpreted higher VMHC as more inter-hemispheric coordinated processing among the corresponding neuronal communities.[58] The increase of VMHC in IBS patients may be related to the strengthened neural activity in ROIs associated with pain modulation and emotional processing. It has been shown that increased connectivity can be regarded as a sign of functional reorganization in early subtle brain damage.[59] FC has also been proposed as an objective marker of the impact of a brain injury.[60] Thus, significantly increased VMHC may reflect an early damage and reorganization of DMN in IBS patients. Topological reorganization of DMN have been reported in some previous studies of IBS.[61,62] The DMN is known to be altered in pain diseases and to participate in cognitive and memory-related aspects of pain modulation,[63] and is thought to be preferentially effected by the presence of chronic pain.[64] The significant increase of PCS and SF-MPQ scores also confirms this. Meanwhile, cognitive function in adult patients with IBS was found to be changed compared to HCs, especially in visuospatial episodic memory functioning, which is perhaps related to the cortisol levels.[65] Beyond this, PCG also plays a role in processing self-relevant emotional information. One study reported that there is increased processing of sad memories in depression.[66] Abdominal symptoms can affect the patients' mood disorder such as depression and anxiety through a bottom-up model with the GBA, but also psychological factors will influence motor functions, sensory threshold, and stress reactivity of the gut via vagal and sympathetic afferents (top-down model).[67] Other studies have found IBS patients display an increased recognition memory to words with negative emotional connotation or gastrointestinal symptoms,[68] which may mean that selective attention to gastrointestinal symptoms play a role in decreased pain thresholds and consequently increased symptom severity.

The precuneus in humans is functionally connected with the motor, sensorimotor, and visual cortices.[69] Our findings indicated that IBS patients showed increased inter-hemispheric FC in SOG and MOG. Meanwhile, as the severity increases, the VMHC of MOG is lower (Table 3). The SOF and MOF are near BA18 and BA19 that participate in various sensory inputs to the brain, such as somatosensory, visual, and auditory.[70] In addition to this, VMHC was significantly decreased in the SMA, which has been reported to be activated by pain and play an important role in functional processing of painful stimuli. A prior functional study focusing on intrinsic whole brain FC pattern reported higher long-range FC density in the occipital lobe and right SMA in patients with IBS.[71] Therefore, chronic abdominal pain may potentially affect the pain processing of SMA, which cause the abnormal FCs in these areas.

Inter-hemispheric Anatomical Connectivity

Although no group differences were found in the structural asymmetry and inter-hemispheric anatomical connections, FA and fiber length were negatively related with the severity in PCG (Fig. 1). We speculate that the anatomical connection of IBS patients would be damaged, but the differences did not reach statistical significance. Several studies have reported microstructural white matter abnormalities in IBS patients,[33,72] but the region with significant differences were not consistent, including insula, thalamus, basal ganglia, and sensory/motor association/integration regions.[33] Our experimental results showed that the changes in brain structure have not occurred, which would also suggest the structure of the brain is not easily attacked by functional gastrointestinal disorders.

Numerous factors can clearly affect the GBA in each process, and bi-directional communication can together add significant complexity to the system. Bilateral brain abnormalities in IBS patients were analyzed through inter-hemispheric connectivity and structural asymmetry. Our results reflected that the FC is often more vulnerable to IBS than structural connection, and the morphology of brain is the most insensitive. Similar results regarding inter-hemispheric connectivity was reported in previous studies,[73,74] namely that the structural connectivity is relative stable.

In addition to these, we analyzed several common clinical scoring scales. As shown in Table 1, patients with IBS have significantly higher HAMD and HAMA scores compared with healthy adults, and the scores reached to mild depression ($8 < \text{HAMD} < 13$) and anxiety criteria ($\text{HAMA} < 17$), The results showed that patients with IBS are particularly susceptible to depressed or anxiety moods, which is consistent with the result of previous studies.[7,75,76] In this regard, stress-related emotion can exacerbate gastrointestinal symptoms via the GBA, as well as affecting the QOL.[77,78] Consistent with our speculation, statistical analysis results of IBS-QOL scores indicated the life quality declining of IBS patients. Gastrointestinal and psychological changes can interact and affect one another through the feedback mechanisms. Concomitantly, some clinical studies revealed that antidepressants have a continuous outcome for improvement of abdominal pain.[79,80] Although it is unrealistic to treat IBS with psychotropic drugs, the abdominal pain of patients can be partially relieved after psychotherapeutic interventions. By reducing signaling and enhancing downregulation at the level of the dorsal horn, noxious painful experiences can be reduced.[81]

Limitations

Limitations of the current study must be recognized. First, this study only considered a Chinese population, and the sample size was relatively small. It is well known that some variables may have no statistically significant differences between the 2 groups because of the small sample size, and the performance of correlation analysis would be affected.[82] Second, the use of cross-sectional data limits the interpretation, thus we cannot explore the causal relationship between brain alterations and intestinal symptoms. Third, the medication status of patients with IBS were not considered here, because different drugs or treatment modalities may affect the bidirectional brain-gut interactions. Consequently, future research may consider utilizing longitudinal imaging and enlarge the sample size to follow changes with symptom severity. Besides, inclusion of gut microbiota, serum, or stool metabolites in the analysis may further help us understand the pathological mechanisms of IBS.

Conclusion

In this study, through taking comprehensive analysis of the bilateral brain in patients with IBS, we speculate that inter-hemispheric FC is more vulnerable to IBS than anatomical connectivity, while the structural morphology of brain is the most stable. Meanwhile, the affected areas were concentrated in DMN and sensorimotor network. The results of our study are only preliminary, but it may provide theoretical basis for future research on the regulation of GBA and pathophysiology in functional intestinal diseases.

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Conflicts of interest: None.

Author contributions: Guangyao Liu, Shan Li, Dekui Zhang, Zhijun Yao, and Bin Hu were involved in study conception and design; Hong Liu and Jie Feng recruited patients and collected the data; Nan Chen, Ziyang Zhao, and Man Guo analyzed the data; Guangyao Liu and Shan Li wrote the manuscript; all authors were involved in the discussion of study result and critical revision of the manuscript, and approved the final draft of this paper, including the authorship list.

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