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Alterations of the default mode network in functional dyspepsia patients: a resting-state fmri study

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Abstract

Background *Increasing brain imaging studies have emphasized the role of regional brain activity abnormalities in functional dyspepsia (FD) during the resting state. The goal of this study was to investigate the default mode network (DMN) in FD patients and healthy controls (HCs).* ***Methods*** *Resting-state functional magnetic resonance imaging (fMRI) scanning was carried out on 49 patients and 39 HCs. Independent component analysis (ICA) was used to isolate the DMN in each subject. Group topography of the DMN was compared to study significant alteration in FD. A correlation analysis was then performed in the FD group to investigate the effects of symptom severity and the psychological factors on the DMN.* ***Key Results*** *Significant spatial differences with the DMN in FD patients, compared with HCs, were mainly found in the dorsomedial prefrontal cortex (dmPFC), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), pregenual anterior cingulate cortex (pACC), thalamus, parahippocampal gyrus, precuneus, parietal cortex, and temporal pole. Meanwhile, Nepean Dyspepsia Index (NDI) scores were positively correlated with the pACC, and was negative correlated with the OFC. However, both the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores were not correlated with any regions of interest showing differences between the FD patients and the HCs.* ***Conclusions & Inferences*** *These findings suggested that the DMN might indeed undergo dysfunctional changes due to the abnormal persistent activity in FD patients. To a certain extent, the changes in the DMN were related to the FD-related symptom severity.*

Keywords *fMRI, functional dyspepsia, independent component analysis, resting-state.*

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INTRODUCTION

Functional dyspepsia (FD), defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease likely to explain the symptoms,[1] has a high prevalence rate world-wide. It is not well known what causes the symptoms of FD. Furthermore, FD has significant influence on the health-related quality of life and high health-care costs. Researchers thereby are paying more attention to investigating certain factors which may induce FD. To date, altered brain—gut interactions on processing of visceral afferent information have been proposed as an important mechanism for FD.[2–5]

By using a gastric distension paradigm, recent neuroimaging studies have provided evidence that abnormal brain regions and circuit activities play a crucial role in the alterations. For example, Vandenberghe *et al.* applied positron emission tomography (PET) to investigate the role of hypersensitivity to proximal gastric distention in FD, and found that proximal gastric distension activated the bilateral sensorimotor cortices, bilateral orbitofrontal cortex (OFC), bilateral gyrus frontalis medialis, bilateral gyrus temporalis superior, bilateral cerebellar hemisphere and left gyrus temporalis inferior.[6] Van Oudenhove *et al.* also investigated functional abnormalities in patients with FD using PET.[4] These findings revealed dysfunctions in the brain processing painful visceral stimulations in FD patients.

However, studies on resting brain activity in pathological conditions are providing insight into the

organization of intrinsic activity in the human brain associated with the pathogenesis of the disease.[7] Recently, more and more attention has been paid to abnormal brain activity during the resting state in the FD patients. Van Oudenhove *et al.* investigated the influence of psychosocial factors on FD brain activity during resting state. They reported that the large cingulated cortex [the pregenual anterior cingulate cortex (pACC) and anterior middle cingulated cortex (aMCC)] were negatively correlated with anxiety, while anxiety was positively correlated with the dorsal pons during the baseline.[4] Furthermore, Van Oudenhove *et al.* reported the influence of gastric hypersensitivity and abuse in patients with FD during the resting state. Abuse history was found to be associated with brain activity differences in the insula, prefrontal, and hippocampus (HIPP)/amygdala regions.[8] Our group focused on the differences in resting brain activity in FD and the relationship between abnormal brain activity with symptom severity.[5] These studies mentioned above show that, except for the experimental paradigms for gastric distension, naturalistic FD studies would be likely to be another optimal point for understanding the neurophysiological mechanisms underlying FD associated with the resting state.

The default mode network (DMN), identified as a resting state of brain function, is of particular interest in the field of neuroscience.[9] Although the exact role of the DMN remains unknown, it has been related to attending external and internal stimuli, as well as self-referential and reflective activity. In gut-brain-related imaging studies, the prefrontal cortex (PFC), ACC, posterior cingulate cortex (PCC), HIPP/papraHIPP, and amygdala were often reported to present (de)activated patterns during rectal or gastric distension. Moreover, the overall pattern was in line with the DMN. However, to date, brain imaging evidence on the FD resting-state is still lacking, and less is known about whether or not the DMN would be abnormal in patients with FD.

In this study, there were two main goals: (i) to investigate the possible alteration of the DMN in FD, and (ii) to investigate the interaction between the abnormal activity in the DMN and the symptom severity and to examine the relationship between the abnormal activity in the DMN and the psychological factors in FD. Independent component analysis (ICA), a data-driven or model-free approach, can separate brain imaging data mixed together into spatially independent and temporally synchronous brain areas. Independent component analysis is being increasingly applied to fMRI data. As a promising analysis method, ICA has been extensively applied in studying the DMN patterns in healthy subjects and patients with certain diseases.[10–13] We thereby applied ICA for selecting the DMN component for each subject in this study. Here, we hypothesized that the DMN might show abnormal spatial patterns of activity in FD patients as compared with healthy controls (HCs).

MATERIALS AND METHODS

Participants

Forty-nine FD patients (18 males, 31 females; ages ranging from 20 to 27 years) were recruited for this study. All of the included patients met the Rome III criteria on FD and postprandial distress. Meanwhile, each patient underwent a careful basic evaluation including upper gastrointestinal endoscopy, upper abdominal ultrasound, electrocardiogram, hepatic function, renal function and routine analysis of the blood, urine, and stool. The following patients were excluded if he/she met any of the following criteria: (i) being pregnant or lactating, (ii) having been taking medications that affect gastrointestinal motility such as selective serotonin reuptake inhibitors, non-steroidal anti-inflammatory drugs, aspirin, phenothiazines and/or steroids for over 2 weeks before enrollment, (iii) having a history of gastrointestinal surgery, (iv) having suffered from serious cardiovascular, neurological, psychiatric, renal, or respiratory diseases, (v) having been experiencing acid regurgitation, heart burn, or upper abdominal pain as the predominant symptom, (vi) having had gastric atrophy or erosive gastroduodenal lesions, and (vii) having had cholecystitis, gall-stones, or esophagitis. Furthermore, all of the FD patients were forbidden to take medications, which potentially influence gastrointestinal motility and sensitivity (such as prokinetic and anti-nausea drugs) at least 24 h before study participation.

Thirty-nine HCs (14 males, 25 females; ages ranging from 20 to 27 years) were also recruited in this study. They had no history of neurological or psychiatric disorders and had refrained from alcohol or drug consumption in the previous week, and underwent similar basic evaluations mentioned above.

All of the FD patients and HCs gave their informed written consents and the study was approved by the Ethics Committee of Chengdu University of Traditional Chinese Medicine.

Behavioral measures

In this study, the Zung Self-Rating Depression Scale (SDS)[14] and the Zung Self-Rating Anxiety Scale (SAS)[15] were adopted to quantify the depression-/anxiety-related symptoms. Both the SDS and SAS consisted of 20 items, each of which was scored from 1 to 4. The final scores of the SDS and SAS were calculated by multiplying the raw score by a factor of 1.25. A score less than 53 (SDS) or 50 (SAS) was considered to be in the normal range.

The Nepean Dyspepsia Index (NDI) was applied for measuring both the symptom severity and the quality of life (QOL).[16] The translated version of the NDI was certified to be reliable and valid in evaluating the symptom severity and QOL of Chinese FD patients.[17] In detail, the symptom index of the NDI was based on 15 dyspepsia-related physical signs rated for frequency (0–4), intensity (0–5), and bothersomeness (0–4). The number 0 represented no symptoms, and higher numbers paralleled worsening of the symptoms. The QOL index of the NDI included four domains, namely interference (13 items), know/control (seven items), eat/

drink (three items), and sleep/disturb (two items). Higher scores indicated a better QOL.

Imaging data acquisition

After an overnight fast of at 12 h and 2 h before scanning,[6] all subjects, without any symptoms of FD, underwent a 5-min resting-state scan. During scanning, they were asked to remain relaxed, to keep their eyes closed, and to remain still.

Images were collected using a 3T Siemens scanner (Allegra; Siemens Medical System, Erlangen, Germany) at the Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, China. To minimize the head motion to diminish scanner noise, a standard birdcage head coil was used along with a restraining foam pad. Five-minute functional images were then acquired with a single-shot gradient-recalled echo planar imaging sequence (TR/TE: 2000 ms/30 ms, field of view: 240 mm × 240 mm, matrix size: 64 × 64, flip angle: 90°, in-plane resolution: 3.75 mm × 3.75 mm, slice thickness: 5 mm thick with no gaps, 30 axial slices). High-resolution T1-weighted images were then collected with a volumetric three-dimensional spoiled gradient recall sequence (TR/TE: 1900 ms/2.26 ms, field of view: 240 mm × 240 mm, matrix size: 240 × 240, flip angle = 9°, in-plane resolution: 1 mm × 1 mm, slice thickness = 1 mm, 176 sagittal slices). All of the subjects completed the image acquisition procedure.

Imaging data preprocessing

Data preprocessing was performed with SPM5 (Neurology, London, UK, http://www.fil.ion.ucl.ac.uk). The first five time points were discarded to avoid the instability of the initial MRI signal. Images were realigned to the first image. If translation and rotation were more than 1.5 mm or 1.5°, the subject was excluded. The images were normalized to the Montreal Neurological Institute (MNI) template and then smoothed using a Gaussian kernel with 6 mm full width at half maximum (FWHM). Before data were entered into the ICA, a voxel-wise transformation was applied on the time course data Vijk(t), Vijk′(t) = [Vijk (t) − <Vijk>]/σijk (t, time; i, j, k, three directions in space; <Vijk>, mean; σijk, standard deviation). The procedure might remove any systematic, between-group differences with respect to BOLD amplitudes, similar to the studies from Sorg *et al.*[10]

Component Identification

Independent component analysis analysis was performed using a group ICA algorithm[18] with Group ICA of the fMRI Toolbox (GIFT, http://icatb.sourceforge.net/) to identify spatial independent and temporally coherent networks in three stages: (i) data reduction, (ii) application of the ICA algorithm, and (iii) back reconstruction. In more detail, all of the data from 49 FD patients and 39 HCs were decomposed into 20 components. The number of components was determined using the minimum description length criteria modified to account for spatial correlation.[19] Data were first reduced to 20 dimensions with principal component analysis (PCA) followed by an independent component estimation using the informax algorithm.[20] During the final stage of back-reconstruction to the original dimensionality, individual subject imaging maps and time courses were estimated using the group solution.[18]

As resting-state connectivity can be found in the low-frequency range, the components whose time courses showing characteristics within a high-frequency range (>0.1 Hz) would be omitted. After ICA separation, the 'best-fit'[21] DMN component of each subject was identified by spatially correlating all components with a DMN mask. The brain regions involved in the DMN mask were described in previous studies.[10,21,22]

At the second-level analysis, one- and two-sample *t*-tests were adopted to show DMN-related differences between FD patients and HCs. Results were thresholded at $P < 0.05$, fall discovery error corrected (FDR-corrected) and with a cluster size >5 voxels. A mask was created to be associated with differences in (de) activated brain regions between FD patients and HCs. The mask would be used further to extract several regions of interest (ROIs) and correlate behavioral data with DMN regions showing differences between FD and HCs.

The ROIs were defined from the two-sample *t*-tests mentioned above. The center of the Talairach coordinates of the 6 mm sphere was on the base of the peak *t* score and each voxel of the ROIs restricted in the mask was applied for further correlation analyses.

Correlation of DMN regions with symptoms and psychological factors

To identify potential interactions of DMN abnormalities in patients with FD and symptom severity, the mean z-score of the voxels in the ROIs of each patient was extracted and correlated with NDI scores. The age and gender were seen as covariances of no interest. To identify potential interactions of DMN abnormalities in patients with FD and the anxiety factor, the mean z-score of the voxels in the ROIs of each patient was extracted and correlated with the SAS scores. The age and gender were seen as covariances of no interest. Similarly, to identify the association between DMN abnormalities of patients with FD and the depression factor, the mean z-score of voxels in the ROIs of each patient was extracted and correlated with the SDS scores. The age and gender were seen as covariances of no interest. Adjustment for multiple comparisons was made with the Bonferroni correction.

RESULTS

Behavioral data

Table 1 shows the comparison of behavioral data between patients with FD and HCs. The mean NDI and QOL scores were 46.49 ± 15.13 and 51.37 ± 12.27 in the FD group, and the mean SDS and SAS scores reported by patients were 43.27 ± 10.04 and 42.07 ± 8.01, respectively. All of these behavioral scores were larger than the ones for HCs. Meanwhile, there were no significant statistical differences in the demographics related to age and gender.

Brain imaging data

None of the subject was excluded for ICA and the statistical analysis because of head motion. Although the default mode signal is actually negatively correlated with the task, we referred to it as 'activity' in this study.[22] Therefore, DMN activations observed in

Table 1 Comparison of behavioral data between FD patients and healthy controls

Items	FD (mean ± SD)	HCs (mean ± SD)	*P*-value
Age (years)	22.55 ± 1.78	22.18 ± 0.85	0.29[b]
Gender (Female/ Male)	31/18	25/14	0.94[a]
NDI	46.49 ± 15.13	1.95 ± 2.87	<0.001[b]
QOL	51.37 ± 12.27	27.08 ± 3.77	<0.001[b]
SDS	43.27 ± 10.04	34.81 ± 7.43	<0.001[b]
SAS	42.07 ± 8.01	33.85 ± 6.40	<0.001[b]
DD (months)	36.12 ± 26.89		

FD, Functional Dyspepsia; HCs, Healthy Controls; SD, Standard Deviation; NDI, Nepean Dyspepsia Index; QOL, Quality of Life; SDS, Zung Self-Rating Depression Scale; SAS, Zung Self-Rating Anxiety Scale; DD, Duration of disease.
[a]The *P*-value was obtained by Chi-squared test.
[b]The *P*-value was obtained by a two-sample two-tailed *t*-test.

patients with FD and HCs are shown in Fig. 1A. These activated brain regions included the medial prefrontal cortex (mPFC), OFC, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus (PC), cuneus, middle and superior frontal gyri, angular gyrus (AG), temporal pole (TP), paraHIPP, HIPP, amygdala and caudate. Compared with the HCs, significant spatial differences in FD patients mainly revealed increased activations in the left dorsomedial prefrontal cortex (dmPFC), left ventromedial prefrontal cortex (vmPFC), bilateral pACC, left thalamus, and right precuneus. Decreased activations were detected in the right OFC, left paraHIPP, right parietal cortex and right temporal pole in FD patients compared with HCs (Fig. 1B and Table 2).

It was shown in Fig. 2A that a significantly positive correlation ($r = 0.61$, $P < 0.001$, corrected) was observed between the NDI scores and the pACC, and a significantly negative correlation ($r = 0.60$, $P < 0.001$, corrected) was detected between the NDI scores and the OFC (Fig. 2B). When it came to psychological factors, no significant correlations were found between the SAS and SDS scores and any ROIs which could show spatial differences between FD patients and HCs. Furthermore, the correlations were also not found in the HCs group, involved in the symptom severity (the NDI scores) or the psychological factors (the SAS and SDS scores) at a threshold of $P < 0.05$.

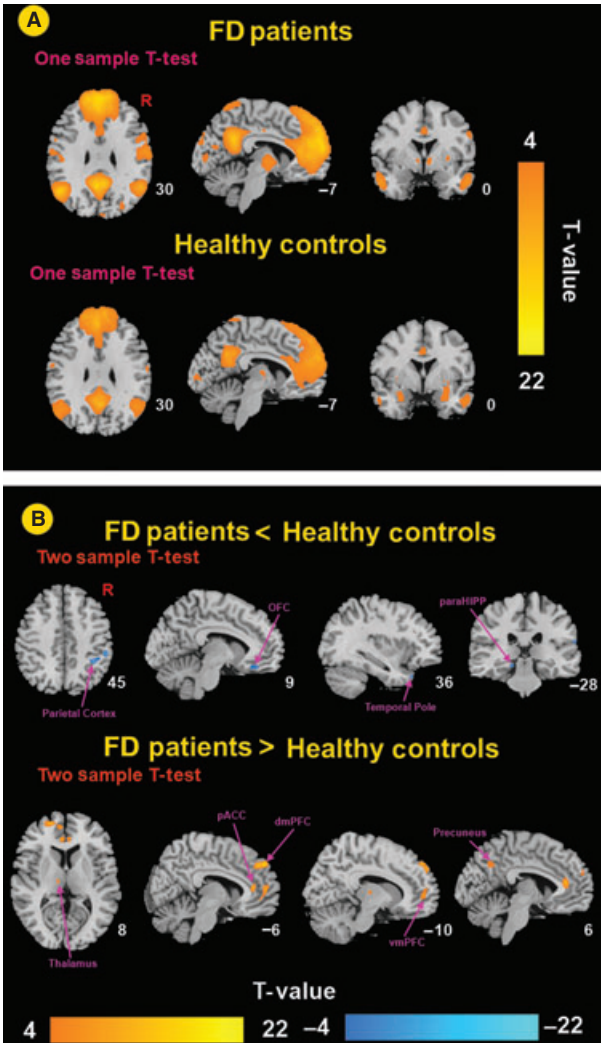

Figure 1 (A) Activated brain regions of the default mode network (DMN) for FD patients and healthy controls using ICA. (B) Brain regions showing significant spatial differences in DMN-related regions in FD patients *vs* healthy controls. The 2nd level analyses were thresholded at $P < 0.05$ (FDR corrected) and the cluster size was >5. Compared with healthy controls, increased DMM activations in FD patients are shown in a warm color, and decreased DMM activations are shown in a cool color.

DISCUSSION

The goal of this study was to increase our understanding of the neural mechanisms in FD patients by examining disruption of DMN activity and the correlation between these abnormal brain regions in the DMN and symptom severity and psychological disturbances including depression and anxiety in patients with FD. We found that the major differences in the spatial pattern of DMN (de)activity between FD patients and HCs were observed in the dmPFC, vmPFC, OFC, pACC, thalamus, precuneus, parietal cortex, and temporal pole. We also found that the NDI scores, SAS scores, and SDS scores were associated with these abnormal DMN regions: NDI scores were positively correlated with the pACC, and was negatively correlated with the OFC. However, no significant correlations were found between the SAS and SDS scores and any regions of interest which could

Table 2 Main localizations of DMN maps by comparing FD patients *vs* healthy controls

Regions	Hem	BA	Talairach X	Y	Z	*T*-Value	Vol
Increased activations (FD patients > healthy controls)							
dmPFC	L	9	−6	51	36	4.89	15
	R						
vmPFC	L	10	−6	50	6	4.81	17
	R						
Precuneus	L						
	R	7/31	6	−60	33	5.52	14
pACC	L	24/32	−3	35	7	4.75	28
	R	24/32	6	32	7	4.92	17
Thalamus	L		−9	−17	6	4.77	14
	R						
Decreased activations (FD patients < healthy controls)							
Parietal cortex	L						
	R	40	42	−42	41	−4.91	15
OFC	L						
	R	11	6	26	−11	−5.01	12
Temporal pole	L						
	R	38	36	19	−31	4.76	9
paraHIPP	L	35/36	−18	−30	−9	−4.70	8
	R						

Hem, hemisphere; BA, Brodmann area; Vol, voxels; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; pACC, pregenual anterior cingulate cortex; OFC, orbitofrontal cortex; paraHIPP, parahippocampal gyrus.

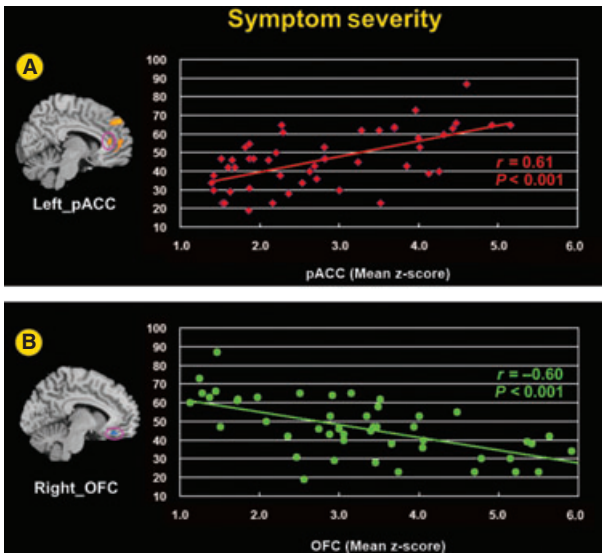

Figure 2 (A) The significantly positive correlation between the pACC and symptom severity. (B) The significantly negative correlation between the OFC and symptom severity. All of the correlation analyses were thresholded at $P < 0.001$.

show spatial differences between FD patients and HCs.

In this study, increased activation in the vmPFC was found in comparison to the HCs. The vmPFC, having reciprocal connections with a number of limbic regions including the amygdala and HIPP, is well suited to support functions involving the integration of information about emotion, memory, and environmental stimulation. In irritable bowel syndrome (IBS) studies, the engagement of the vmPFC could reflect affective responses to the distension and cortical modulation of bodily somatic reactions.[23] In FD studies, vmPFC activations were commonly found in distension and/or resting studies.[4,5] Activation in the dmPFC has been detected during anticipation of aversive stimuli and during tasks of emotional evaluations or integrations.[24,25] Furthermore, both the vmPFC and dmPFC are more involved in emotional regulation, especially in negative emotion processing.[26] Based on these previous reports, the present finding in the PFC-related regions could be explained by enhancing affective responses to sensations and abnormal emotional processing, which arose from the stomach in FD patients compared with HCs.

The pACC is suggested to be reciprocally connected to the insular cortex, engaging in visceral sensory processing. It is believed to receive large input from the amygdala and project the information to the viscero-motor centers.[27] Previously, electrical stimulation in the pACC could induce autonomic and visceromotor responses.[28,29] The crucial function of the pACC is involved in attentional, associative, and interpretational aspects of threat-related information processing. Meanwhile, the pACC was associated with pain processing, such as pain intensity.[30] Furthermore, we found a positive correlation between the pACC and the NDI scores, which was similar to the results of our previous PET-study.[5] There was a possible explanation for the abnormal activity in the pACC in this study. It presented that abnormal activation in the pACC was related to dysfunction in regulating autonomic and visceromotor responses, as well as pain processing in FD patients. The degree of dysfunction in the pACC might be more activated even during the resting state, following changes in symptom severity. Furthermore, it was possible that FD patients might be more hypersensitive to pain intensity. Although the reports about the activation of the pACC or lack of its activation in FD were not consistent,[4,5] increased activations in the pACC were found in this study. We suggested that the differences might arise from the imaging method (e.g. PET or fMRI) and data analysis method.

Another area of the brain that indicated significant differences between groups is the OFC. Neuroscience studies showed that the OFC is a nexus for sensory integration, monitoring and mapping visceral responses, and internal states, as well as appraising sensory reactions and modulating autonomic

responses.[6,31] Moreover, the OFC is implicated in a variety of functions, particularly higher- order executive functions. These executive functions include control and inhibition of inappropriate behavioral and emotional responses. For example, the OFC is viewed as a biomarker in studies of anxiety or depression disorders.[32,33] Our results showed that activation in the OFC was decreased in FD patients compared with the HCs, and was negatively correlated with the NDI scores. As the OFC plays a major role in the homeostatic afferent network, it might appear that the dysfunctional OFC activity disturbed homeostatic afferent processing, and OFC impairment was a persistent trait in the FD patients with the development of symptom severity. In addition, the OFC is involved in pain and pain modulation.[34,35] It was detected that OFC is induced to release endogenous opioids[36,37] which produce analgesia. We speculated that the decreased activity in the OFC was attributed to chronic and abnormal sensation arising from the stomach, which could yield a negative effect on analgesia.

Meanwhile, increased activations in the thalamus were found in this study. The thalamus has multiple functions, as a kind of a switchboard of information. It is generally believed to act as a relay between a variety of subcortical areas and the cerebral cortex. It relays sensory and motor signals to the cortex,[38] and the thalamus is an important part of the homeostatic afferent processing network. We speculated that dysfunction of the thalamus could lead to increasing sensory pathways and might bias FD patients toward unpleasant or painful perceptions from the viscera.

It is likely that psychological disturbances are suggested as one of the possible causes of functional gastrointestinal disorders, such as anxiety and depression.[39–41] Van Oudenhove *et al.* adopted PET to find the relationship between anxiety factors and the pACC, MCC, and dorsal pons during the baseline in westerners.[4] In this study, we also found that FD patients had higher SAS and SDS scores than HCs (Table 1). However, there was no correlation between the ROIs and psychological distress. We suggested that it was because of different racial/ethnic groups, different imaging methods, or data analysis approaches. Further studies on psychological factors in FD patients are needed.

The limitation in this study was that FD patients were not divided into hyper- and normosensitive groups. In a future study, we will try to investigate the different patterns of DMN activity among hyper-, normosensitive FD patients, and HCs.

Overall, our findings suggested that the DMN (e.g. PFC, ACC, and OFC) might indeed undergo dysfunctional changes due to abnormal persistent activity in patients with FD. To a certain extent, the changes in the DMN were related to FD-related symptom severity. The current results might provide neuroimaging evidence in support of the dysfunction of the brain—gut axis at the level of the central nervous system (CNS) in FD patients. The interaction between an aberrant DMN and FD warrants further investigation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTION

Wei Qin, Jie Tian, Fanrong Liang, Zeng Fang, and Peng Liu were responsible for the study concept and design; Wei Qin contributed to the acquisition of fMRI data; Peng Liu, Guangyu Zhou, and Jingjing Wang assisted with data analysis and interpretation of findings; Peng Liu drafted the manuscript; Karen M. von Deneen revised the draft for language expression; Peng Liu, Wei Qin, Fanrong Liang, and Jie Tian provided critical revision of the manuscript for important intellectual content; and all authors critically reviewed the content and approved the final version for publication.

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