Research article

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Increased interhemispheric resting-state functional connectivity in functional dyspepsia: a pilot study

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Recent brain imaging studies have emphasized the role of regional brain activity abnormalities in the pathophysiology of functional dyspepsia (FD). However, whether the functional connectivity between brain regions is changed, especially between the cerebral hemispheres, in patients with FD remains unknown. Thus, the present study aimed to examine the interhemispheric resting-state functional connectivity (RSFC) changes in patients with FD. Resting-state functional MRI (fMRI) was performed in 26 patients with FD and in 20 matched healthy controls. An interhemispheric RSFC map was obtained by calculating the Pearson correlation (Fisher *Z* transformed) between each pair of homotopic voxel time series for each subject. The between-group difference in interhemispheric RSFC was then examined at global and voxelwise levels separately. The global difference in interhemispheric RSFC between groups was tested using the independent two-sample *t*-test. Voxelwise comparisons were carried out using a permutation-based nonparametric test, and multiple comparisons across space were corrected using the threshold-free cluster enhancement (TFCE) method. The results showed that patients with FD had higher global interhemispheric RSFC than healthy controls ($p < 0.01$). Furthermore, voxelwise analysis revealed that patients with FD had increased interhemispheric RSFC in brain regions including the anterior cingulate cortex, insula and thalamus ($p < 0.01$, TFCE corrected). Our findings provide preliminary evidence of interhemispheric correlation abnormalities in patients with FD and contribute to a better understanding of the pathophysiology of the disease. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: functional dyspepsia; functional MRI; interhemispheric; functional connectivity

INTRODUCTION

Functional dyspepsia (FD), which is characterized by persistent or recurrent upper abdominal pain or discomfort, including early satiety, abdominal fullness, bloating or nausea (1), has a high prevalence rate world-wide (2). The pathophysiology of FD remains incompletely understood, although several mechanisms, such as gastric motility or accommodation abnormalities, visceral hypersensitivity, *Helicobacter pylori* infection, acid and psychosocial dysfunction, have been suggested to play a role (2). Nowadays, dysfunction of the brain–gut axis has been widely accepted to be a key mechanism underlying the pathogenesis of the symptoms of functional gastrointestinal disorders, such as FD (3). More specifically, the role of functional abnormalities at the level of the central nervous system in the pathophysiology of FD has been emphasized by recent brain imaging studies (2,4–6). However, these investigations have focused on the study of regional brain activity abnormalities in patients with FD during visceral stimuli or the resting state. Whether the functional connectivity between brain regions is changed, especially between the cerebral hemispheres, in patients with FD remains unknown. As noted by Vandenberghe *et al.* (6), patients with FD show a more symmetrical activation pattern than healthy controls (7) during gastric distension. Thus, it has been speculated that the interactions between hemispheres might be changed in patients with FD.

Resting-state functional MRI (fMRI) (8) has provided a way to characterize directly the functional connectivity between brain regions (9–13). Functional homotopy, the high degree of synchrony of activity between homologous areas in opposite hemispheres, which can be quantified by interhemispheric resting-state functional connectivity (RSFC), is one of the most fundamental characteristics of the brain's intrinsic functional

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Abbreviations used: *ACC, anterior cingulate cortex; FD, functional dyspepsia; fMRI, functional magnetic resonance imaging; FWHM, full width at half-maximum; NDI, Nepean Dyspepsia Index; PDS, postprandial distress syndrome; QOL, quality of life; RSFC, resting-state functional connectivity; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; TFCE, threshold-free cluster enhancement.*

architecture (10–12). Alterations in interhemispheric RSFC have been found in normal ageing (10), psychiatric disorders (9) and substance dependence (13). These findings suggest that interhemispheric correlations may be of great importance in brain function and may be sensitive to the disruption of functional circuitry in disease (13). To our knowledge, no studies on the interhemispheric RSFC changes in patients with FD have been published.

Therefore, this study aimed to examine the changes in functional connectivity between hemispheres in patients with FD using fMRI. We compared the interhemispheric RSFC in patients with FD with those of matched healthy controls and hypothesized that patients with FD have increased interhemispheric RSFC.

EXPERIMENTAL DETAILS

Patients with FD

The recruitment criteria and symptom evaluation were similar to those in a previous study (2). In the present study, 26 patients with FD were recruited after careful history taking, clinical evaluation and laboratory examinations. All patients were right handed. The examinations included upper abdominal ultrasound, upper gastrointestinal endoscopy, renal function, hepatic function, routine analysis of blood, electrocardiogram, urine and stool examinations, etc. According to the Rome III criteria, all patients were classified as having 'postprandial distress syndrome (PDS)'. Patients were included if they met the following criteria: (i) between 20 and 30 years of age; and (ii) fulfilled the Rome III criteria for PDS.

Patients were excluded if they met one of the following criteria: (i) pregnant or lactating; (ii) suffered from or had a history of any serious cardiovascular, respiratory, renal, neurological or psychiatric disease or head trauma with loss of consciousness; (iii) experienced acid regurgitation, heart burn or upper abdominal pain as a predominant symptom; (iv) suffered from gastric atrophy, esophagitis or erosive gastroduodenal lesions detected by endoscopy, cholecystitis or gallstones; and (v) prior to 2 weeks before recruitment, had used steroids, aspirin, selective serotonin reuptake inhibitors, phenothiazines, nonsteroidal anti-inflammatory drugs or medication affecting gastrointestinal motility.

Healthy controls

Twenty right-handed age-matched healthy controls were also recruited. All subjects were free from any gastrointestinal symptoms. A basic evaluation, including a review of medical history, physical examination, electrocardiogram, upper abdominal ultrasound and gastrointestinal endoscopy, was taken for each healthy subject to exclude anyone with organic disease. Other exclusion criteria included: (i) pregnancy or lactation; (ii) suffered from or had a history of any serious cardiovascular, respiratory, renal, neurological or psychiatric disease or head trauma with loss of consciousness; and (iii) had been taking drugs, such as those mentioned above, that might affect gastrointestinal motility prior to 2 weeks before recruitment.

Symptoms and psychosocial evaluations

The severity of the symptoms and health-related quality of life (QOL) were assessed using the Nepean Dyspepsia Index (NDI) (14). The symptom index of the NDI includes 15 dyspepsia-related physical signs: frequency (0–4), intensity (0–5) and bothersomeness (0–4). A score of zero represents no symptoms and higher numbers indicate more severe symptoms. The QOL index in NDI consists of four domains: interference (13 items), know/control (seven items), eat/drink (three items) and sleep/disturb (two items). A higher score indicates a better QOL. The translated version of NDI has been found to be a reliable and valid measurement of the severity of symptoms and QOL in Chinese patients with FD (15).

The Zung Self-Rating Anxiety Scale (SAS) (16) and the Zung Self-Rating Depression Scale (SDS) (17) were used to quantify the anxiety/depression-related symptoms of the participants. Both of the scales consisted of 20 items, each of which was scored in the range 1–4. The final score of SAS/SDS was calculated by multiplying the raw score by 1.25. A score of less than 50 or 53, for SAS and SDS separately, was taken to be in the normal range according to the Chinese norm (18,19).

Written informed consent was provided by each participant. The entire study procedure was approved by the Ethics Committee at Chengdu University of Traditional Chinese Medicine.

Data acquisition

The imaging data were collected using a 3-T Siemens scanner (Allegra, Siemens Medical System, Erlangen, Germany) at the Huaxi MR Research Center, West China Hospital at Sichuan University, Chengdu, China. A standard birdcage head coil was used together with a restraining foam pad to minimize head motion and diminish scanner noise. The axial three-dimensional T_1-weighted image was obtained with a spoiled gradient recall sequence (TR = 1900 ms; TE = 2.26 ms; flip angle, 9°; in-plane matrix resolution, 256 × 256; slices, 176; field of view, 256 mm; voxel size, 1 × 1 × 1 mm^3). Functional images were acquired using a gradient-echo echo planar imaging sequence (TR = 2000 ms; flip angle, 90°; in-plane matrix resolution, 64 × 64; slices, 30; voxel size, 3.75 × 3.75 × 5 mm^3). The subjects were instructed to lie in the scanner with their eyes closed. A total of 180 volumes was acquired for each subject.

Image preprocessing

Preprocessing of the functional images was composed of the following steps: dropping the first four TRs; slice time correction; three-dimensional motion correction; temporal despiking; spatial smoothing [full width at half-maximum (FWHM), 6 mm]; mean-based intensity normalization; temporal bandpass filtering (0.009–0.1 Hz); linear and quadratic detrending; and regression of the nuisance signal (motion parameters, global signal, white matter and cerebrospinal fluid). All subjects had a maximum translation of less than 1 mm in all directions and rotation around the three axes measuring 1°. The resulting functional images were normalized to the MNI152 template with a resolution of 2 × 2 × 2 mm^3 through the following steps: registration of functional images to structural images; registration of structural images to the MNI152 template; and the two transformations were combined to generate a third which was used for the registration of the functional images to the MNI152 template. All registrations were performed using the affine registration tool FLIRT (20,21). The preprocessing steps were completed using AFNI (22) and FSL (23), and the corresponding script can be found at http://www.nitrc.org.

Interhemispheric RSFC and statistical analysis

The interhemispheric RSFC map of each subject was generated by calculating the Pearson correlation (Fisher *Z* transformed) between each pair of homotopic voxel (with opposite MNI space *x* coordinate) time series (9). The mean interhemispheric RSFC of each subject was calculated by averaging the Fisher *Z*-transformed

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correlations across all gray matter voxels. The gray matter mask was created by thresholding the MNI152 gray matter tissue prior at a threshold of 25% tissue-type probability. Group comparison of the mean interhemispheric RSFC was performed using a two-tailed independent two-sample *t*-test after the age and gender effects had been regressed out. A difference was considered to be significant at a $p < 0.01$.

Regional-specific between-group differences in interhemispheric RSFC were examined using a permutation-based nonparametric test (Randomise v2.1; 10 000 permutations; covariates, age + gender). The statistical analysis was performed on one hemisphere, and the results were projected to the other. Multiple comparisons across space were corrected using the threshold-free cluster enhancement (TFCE) method (24). A difference was taken to be significant at a corrected $p < 0.01$. To address the smoothing effect on the results, we smoothed the images with variant sizes of the kernel (FWHM of 4 and 8 mm) and re-performed the statistical analysis.

RESULTS

Clinical and demographic results

The clinical and demographic results are shown in Table 1. Healthy controls and patients with FD showed no significant difference in demographic data, including gender and age ($p > 0.1$). Patients with FD had higher SAS and SDS scores than did healthy controls ($p < 0.01$). One patient showed mild anxiety, whilst three showed mild depression.

Spatial distribution of interhemispheric RSFC

The interhemispheric RSFC map showed reproducible patterns of spatial distribution at a single-subject level in both healthy controls and the FD group. The FD and healthy control group-level interhemispheric RSFC maps which showed similar spatial heterogeneity are given in Figure 1. Gray matter appears to have higher interhemispheric RSFC than white matter (Fig. 1). The interhemispheric RSFC appeared to be higher in voxels closer to the midline, especially in the middle frontal, parietal and occipital lobes, and cerebellum (Fig. 1). However, a higher interhemispheric RSFC was not uniquely observed in brain areas closer to the midline. For example, brain regions such as the insula, putamen and sensorimotor cortices were observed to have greater correlation values than other areas with the same distance to the midline (Fig. 1).

Increased Interhemispheric RSFC in patients with FD

Patients with FD showed significantly higher mean interhemispheric RSFC than did healthy controls (healthy controls, 0.550 ± 0.058; FD, 0.604 ± 0.052; $p = 0.002$). Voxelwise analysis showed that patients with FD had higher interhemispheric RSFC in brain regions including the anterior cingulate cortex (ACC), insula and thalamus ($p < 0.01$, TFCE corrected) (Fig. 2). The effective size and peak coordinates of significant clusters are summarized in Table 2. The differences in these regions were still significant when variant sizes of smoothing kernels were adopted in the preprocessing step (Fig. 3).

In order to elucidate the most robust between-group differences in interhemispheric RSFC, we adopted a stringent significance threshold value. However, increased interhemispheric RSFC in patients with FD was found in other widespread brain regions, such as subregions of the prefrontal cortex, pre-/post-central gyrus, brainstem, cerebellum and subdivisions of the temporal and occipital lobes, at a lower significance threshold value of corrected $p < 0.05$ (See Supporting information Fig. S1 and Table S1).

DISCUSSION

In this study, we found increased global interhemispheric RSFC in patients with FD, when compared with healthy controls, using resting-state fMRI. More specifically, patients with FD had higher interhemispheric RSFC in brain regions including the ACC, insula and thalamus. These findings may provide further evidence of brain dysfunction in patients with FD.

Brain activity abnormalities in patients with FD during visceral stimuli and the resting state have been observed in several brain imaging studies (2,4–6). For example, Vandenberghe *et al.* (6) found that painful gastric distension activated the sensorimotor cortices, orbitofrontal cortex, gyrus frontalis medialis, temporalis superior and cerebellar hemisphere bilaterally and left-sided gyrus temporalis superior, but failed to activate brain structures of the medial pain system, such as the ACC, insula and thalamus. The authors noted that patients with FD showed a more symmetrical activation pattern, as the bilateral gyrus frontalis medialis and right gyrus temporalis superior were found to be significantly activated only in patients with FD (6) rather than healthy controls (7). These findings are likely to suggest that there are abnormal interactions between hemispheres in patients with FD. However, the focus of previous studies was mainly on regional brain activity abnormalities in patients with FD. Inter-regional correlations in spontaneous activity, which are also an important feature of the brain's

Table 1. Clinical and demographic characteristics

Item	Healthy controls	Functional dyspepsia	*p*
Gender (male/female)	7/13	8/18	0.81
Age (years)	22.05 ± 0.89	22.69 ± 1.89	0.31
SAS	35.19 ± 6.39	42.02 ± 6.53	0.002
SDS	34.12 ± 7.19	42.36 ± 9.30	0.003
NDI	–	44.92 ± 12.73	–
QOL	–	77.68 ± 8.31	–
Duration of disease (months)	–	27.15 ± 21.97	–

Data are presented as mean ± standard deviation; group difference was tested using two-tailed Mann–Whitney–Wilcoxon *U*-test. NDI, Nepean Dyspepsia Index; QOL, dyspepsia-specific health-related quality of life; SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale.

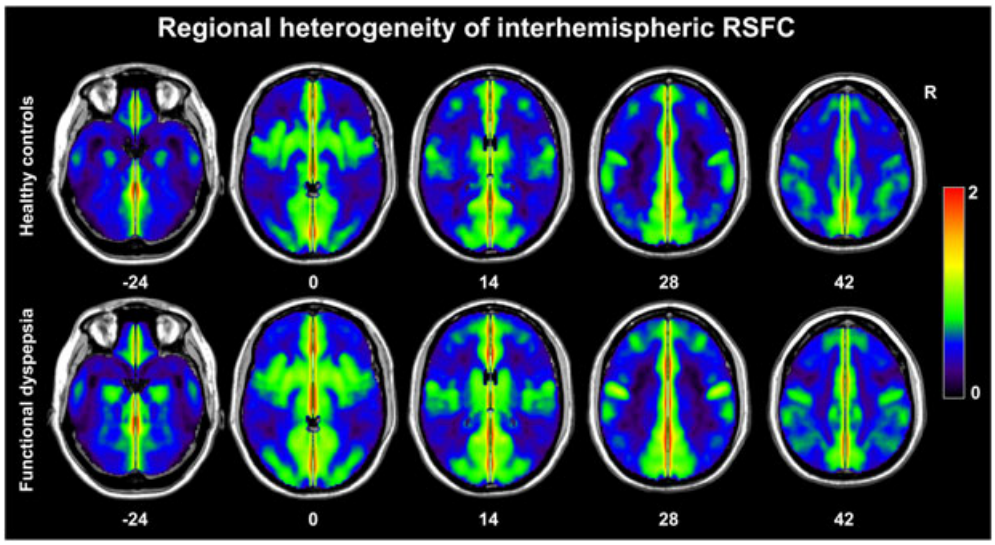

Figure 1. Group-level interhemispheric resting-state functional connectivity (RSFC) for healthy control and functional dyspepsia groups. The color bar shows the Fisher *Z*-transformed correlation. R, right.

functional architecture (10) and play an important role in understanding brain function in disease (25), have not been examined directly in patients with FD.

In the present study, we specifically examined interhemispheric RSFC changes in patients with FD. Interhemispheric correlations have been proven to be region specific (11), normal ageing variant (10) and sensitive to functional circuitry disruptions in disease (9,13). The spatial distribution of interhemispheric RSFC in healthy controls observed in this study was consistent with that observed in other studies (9,10,13). In general, the correlation values were higher in gray matter than in white matter (Fig. 1). Voxels close to the midline, as well as other brain structures, such as the insula, putamen and sensorimotor cortices, appeared to have greater interhemispheric correlation (Fig. 1). Common inputs of sensory and motor signals from the thalamus are likely to contribute to the higher connectivity in sensorimotor cortices (9). Although patients with FD showed a similar spatial distribution pattern of interhemispheric correlations to that of healthy controls, the global interhemispheric RSFC was elevated significantly in the patient group.

Furthermore, patients with FD were found to have higher interhemispheric RSFC than healthy controls in brain regions including the ACC, insula and thalamus (Figs 2 and 3). Increased interhemispheric RSFC in patients with FD was found in much more widespread brain regions when a lower significance threshold value was used (Supporting information Fig. S1). However, as the present study was a pilot study aimed at the elucidation of the most robust interhemispheric correlation changes in patients with FD, we limit the discussion to brain regions showing a between-group difference at a more stringent significance level. The ACC, insula and thalamus are involved in the 'gastric sensation neuromatrix' (4,26,27) and 'homeostatic afferent network' (28). A previous study found that elevated levels of resting-state glycometabolism in these regions were associated with the severity of symptoms of FD (2). There is substantial evidence that the ACC is involved in attentional, emotional, cognitive and other dimensions of sensory and pain processing (29). The insula has been widely accepted as a key visceral sensorimotor area, integrating emotional and visceral sensory information (29), and has been consistently reported to

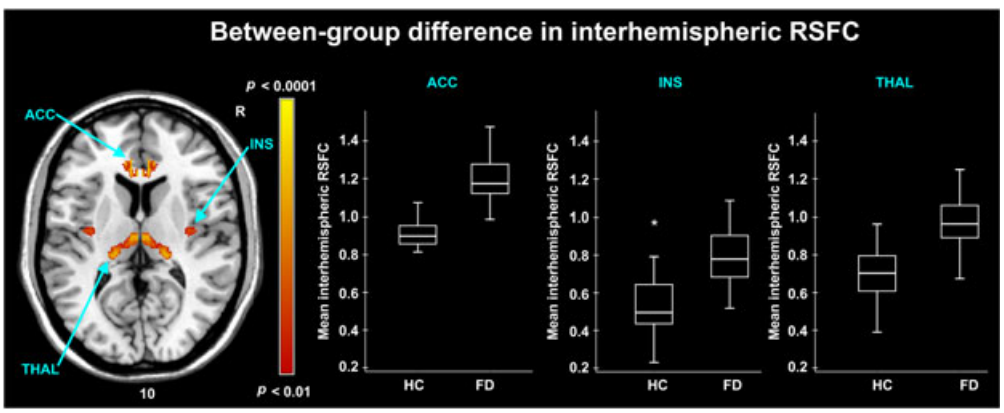

Figure 2. Brain regions in which patients with functional dyspepsia (FD) had higher interhemispheric resting-state functional connectivity (RSFC) than did healthy controls (HC). The boxplots show the mean Fisher *Z*-transformed correlation of significant clusters. The asterisks indicate outliers. ACC, anterior cingulate cortex; INS, insula; R, right; THAL, thalamus.

NMR IN BIOMEDICINE

Table 2. Peak coordinates of significant brain regions in which patients with functional dyspepsia showed higher interhemispheric resting-state functional connectivity than did healthy controls

Region	Number of voxels	Peak coordinates (MNI)			*p* (corrected)
		x (mm)	*y* (mm)	*z* (mm)	
ACC	339	±8	36	16	0.0012
Insula	130	±36	−10	12	0.0058
Thalamus	417	±18	−28	12	0.0025

ACC, anterior cingulate cortex.

be activated during visceral stimuli in healthy subjects (30). The failure of the activation of the insula during visceral stimuli, as discussed above, and the abnormal resting-state insular activity have been observed in patients with FD in previous studies (2,4,5). The thalamus is regarded as the 'gateway' to the cortex (2). It relays sensory and motor signals to the cortex and plays an important role in the regulation of alertness, consciousness and sleep. Abnormal thalamic activity may be related to the chronic or recurrent uncomfortable sensations suffered by patients with PDS. The ACC and thalamus are key regions involved in the medial pain modulation system (7). Our findings of functional abnormalities in these regions may further suggest the disruption of the homeostatic reflex system (3) at the level of the central nervous system in patients with FD. However, how our findings of aberrant resting-state interhemispheric correlation are related to abnormal brain activities in response to visceral stimuli requires further research.

There are several limitations of this study. First, the brain is asymmetrical. As suggested by Kelly *et al.* (13), functional homotopy could be considered to be defined using data-driven approaches, such as the clustering of interhemispheric voxels according to their RSFCs, in future studies. Moreover, factors such as the visceral hypersensitivity status have been found to be associated with brain activity abnormalities in patients with FD (5). Thus, potential effects of such factors on the interhemispheric RSFC changes seen here remain to be elucidated.

In conclusion, our findings provide preliminary evidence of increased interhemispheric RSFC in patients with FD compared with healthy controls. These findings add to our knowledge of

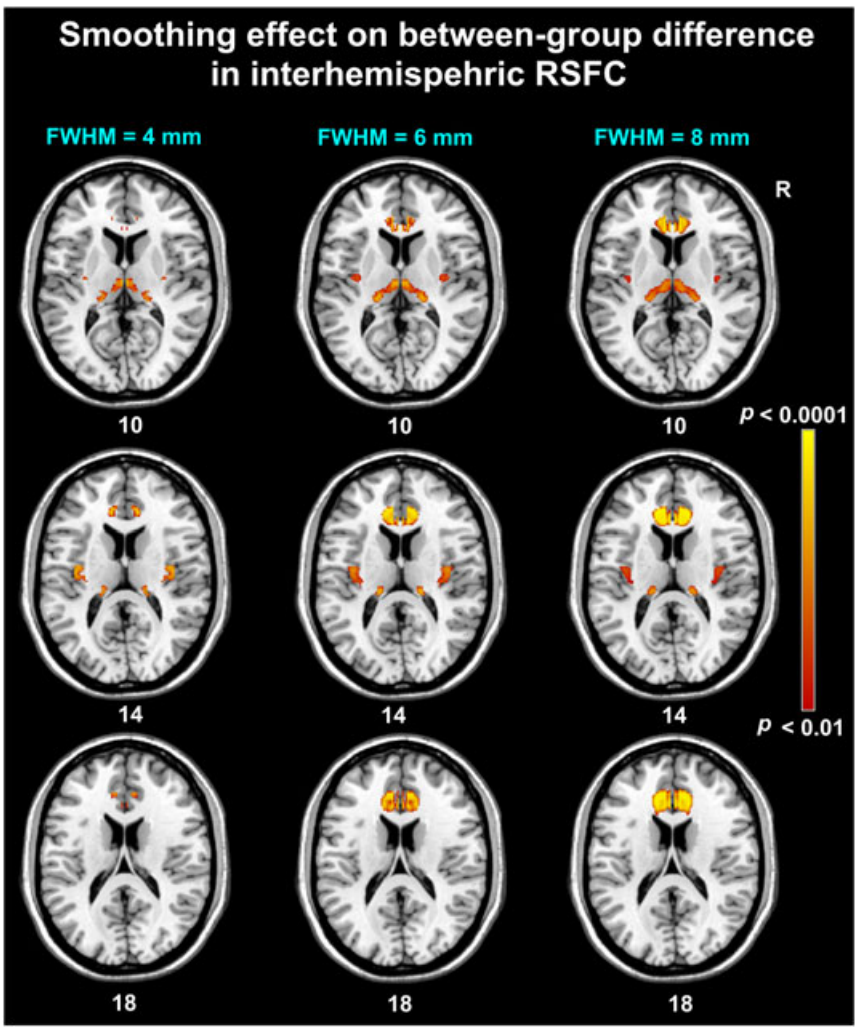

Figure 3. Brain regions in which patients with functional dyspepsia had higher interhemispheric resting-state functional connectivity than did healthy controls with variant sizes of smoothing kernels adopted. FWHM, full width at half-maximum; R, right.

the dysfunction of the brain–gut axis at the level of the central nervous system in patients with FD and contribute to a better understanding of the pathophysiology of the disease.

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