

Fractional amplitude of low-frequency fluctuation changes in functional dyspepsia: A resting-state fMRI study

Guangyu Zhou ^{a,1}, Peng Liu ^{a,1}, Jingjing Wang ^a, Haixia Wen ^a, Mengbo Zhu ^a, Ruixia Zhao ^a, Karen M. von Deneen ^a, Fang Zeng ^b, Fanrong Liang ^b, Qiyong Gong ^d, Wei Qin ^a, Jie Tian ^{a,c,*}

^a Life Sciences Research Center, School of Life Sciences and Technology, Xidian University, Xi'an, Shaanxi 710071, China

^b Acupuncture and Tuina School/The 3rd Teaching Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 610075, China

^c Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

^d Department of Radiology, The Center for Medical Imaging, Huaxi MR Research Center (HMRC), West China Hospital of Sichuan University, Sichuan 610075, China

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ABSTRACT

Recently, there is an increasing interest in the study of the role of brain dysfunction in the pathogenesis of symptoms of functional dyspepsia (FD). More specifically, abnormal brain activities in patients with FD during the resting state have been proven by several positron emission tomography (PET) studies. Resting-state functional magnetic resonance imaging (fMRI) is also a valuable tool in investigating spontaneous brain activity abnormalities in pathological conditions. In the present study, we examined the amplitude of low-frequency fluctuations (ALFF) and fractional (f)ALFF changes in patients with FD by using fMRI. Twenty-nine patients with FD and sixteen healthy controls participated in this study. Between-group differences in ALFF/fALFF were examined using a permutation-based nonparametric test after accounting for the gender and age effects. The results revealed a significant between-group difference in fALFF but not in ALFF in multiple brain regions including the right insula, brainstem and cerebellum. Seed-based resting-state functional connectivity analysis revealed that FD patients have increased correlations between the right cerebellum and multiple brain regions including the bilateral brainstem, bilateral cerebellum, bilateral thalamus, left para-/hippocampus, left pallidum and left putamen. Furthermore, fALFF values in the right insula were positively correlated with the severity of the disease. These findings have provided further evidence of spontaneous brain activity abnormalities in FD patients which might contribute to our understanding of the pathophysiology of the disease.

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1. Introduction

Functional dyspepsia (FD), which is defined as the presence of symptoms including chronic or recurrent postprandial fullness, early satiation, and epigastric pain or burning in the absence of any organic, systemic, or metabolic disease that might explain the symptoms [1], is a common functional gastrointestinal disorder (FGID). The reported prevalence rate of the disease is high world-wide [2–6] and it has an important impact on health-related quality of life (QOL) [7]. For example, in a Swedish population-based study, the reported prevalence rate of FD was 20% [3]. The prevalence rate of FD for the residents in the United States was 29% [4]. In a Chinese-based epi-

demology investigation, 23.5% of the study population was found to suffer from FD [6]. Furthermore, the healthcare cost of the disease is high [8,9]. However, the pathophysiology of the disease is still not clear [1].

Helicobacter pylori infection, visceral hypersensitivity, gastric motility or accommodation abnormalities, acid and psychosocial factors have all been suggested to play a role in the pathogenesis of the symptoms of FD [10,11]. Recently, dysfunction of the bidirectional brain–gut interactions has been widely accepted as a key mechanism [12–15]. More specifically, brain imaging studies have found different brain activation during gastric distension in patients with FD compared with healthy controls suggesting abnormal processing of visceral stimuli at the level of the central nervous system (CNS) [16–18]. Compared with a large resting energy consumption, task-related increase in neural metabolism is small (<5%) [19]. Thus, the study of spontaneous neural activity changes in disease might provide additional information of brain dysfunctions in FD patients [10]. In fact, abnormal brain activity during the resting state has been observed

* Corresponding author. Life Sciences Research Center, School of Life Sciences and Technology, Xidian University, Xi'an, Shaanxi 710126, China. Tel.: +86 29 81891070; fax: +86 29 81891060.

E-mail address: tian@ieee.org (J. Tian).

¹ These authors contributed equally to this work.

in patients with FD by several positron emission tomography (PET) studies [10,17,18]. Spontaneous neural activity could also be studied using resting-state functional magnetic resonance imaging (fMRI) [20] which has the advantage of no radiation exposure over PET. To our knowledge, resting-state fMRI studies in patients with FD are rare.

The amplitude of low-frequency fluctuations (ALFF) has been proven to be a valuable characteristic of spontaneous neural activity [21–23]. The ALFF is defined as the total power of the low frequency range, typically 0.01–0.1 Hz, and can be affected by various physiological factors such as cardiac and respiratory-related processes [23]. In addition, state factors such as arousal level also affect ALFF [23]. In contrast, fractional ALFF (fALFF) which is calculated as the ratio between total power within the low-frequency range and total power in the entire frequency range is a more specific measurement of low-frequency neural activity [22,23]. Whether ALFF/fALFF is changed in patients with FD still remains elusive.

Thus, the present study was aimed to examine ALFF and fALFF changes in patients with FD compared with healthy controls. Furthermore, we investigated the resting-state functional connectivity (RSFC) changes of brain regions showed significant between-group differences in ALFF/fALFF. We also examined correlations between ALFF/fALFF/RSFC of significant clusters and clinical symptoms in the patient group.

2. Materials and methods

2.1. Participants

Twenty-nine right-handed FD patients were recruited for the present study. The recruitment criteria and symptom evaluation were similar to those in our previous study [10]. Careful history taking, clinical evaluation and laboratory examinations were performed for each patient. The examinations included upper abdominal ultrasound, upper gastrointestinal endoscopy, renal function, hepatic function, routine analysis of blood, electrocardiogram, urine and stool exams. All patients were classified as having postprandial distress syndrome (PDS) according to the Rome III criteria. The inclusion criteria of a patient included: 1) between 20 and 30 years of age; 2) meeting the Rome III criteria for PDS.

The patient was excluded if he/she met one of the following criteria: 1) being pregnant or lactating; 2) having had gastric atrophy, esophagitis, or erosive gastroduodenal lesions detected by endoscopy, cholecystitis, or gall-stones; 3) having experienced acid regurgitation, heart burn or upper abdominal pain or heart pain as a predominant symptom; 4) having suffered from or having a history of any serious cardiovascular, respiratory, renal, neurological, psychiatric diseases or head trauma with loss of consciousness; or 5) having been taking steroids, aspirin, selective serotonin reuptake inhibitors, phenothiazines, non-steroidal anti-inflammatory drugs, or medication affecting gastrointestinal motility two weeks prior to the recruitment.

Sixteen age and gender matched healthy controls (all right-handed) who were free from any gastrointestinal symptoms were also recruited. Each healthy subject underwent a basic evaluation including a review of medical history, physical examination, electrocardiogram, and upper abdominal and gastrointestinal endoscopy to exclude any organic disease.

2.2. Symptoms and psychosocial assessment

The Nepean Dyspepsia Index (NDI) was adopted to evaluate the severity of the symptoms and health-related QOL [24]. The symptom index of the NDI includes fifteen dyspepsia-related physical signs: frequency (0–4), intensity (0–5) and bothersomeness (0–4). A higher score indicates more severe symptoms. The QOL index of the

NDI consists of four domains: interference (13 items), know/control (7 items), eat/drink (3 items) and sleep/disturb (2 items). The severity of the symptoms of the disease was measured using the Chinese-translated version of NDI [25].

The anxiety and depression related symptoms of the participants were quantified using the Zung Self-Rating Anxiety Scale (SAS) and the Zung Self-Rating Depression Scale (SDS) separately. Both of the scales consisted of 20 items each which were scored from 1 to 4. The final score was calculated as the summation of all of the items which was then multiplied by a factor of 1.25 [26,27].

Each participant provided a written informed consent. This study was approved by the Ethics Committee at Chengdu University of Traditional Chinese Medicine.

2.3. Image acquisition

All image data were collected on a 3 T Siemens scanner (Allegra; Siemens Medical System) equipped with a standard birdcage head coil at the Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, China. The head movement was minimized by using a restraining foam pad. For each participant, a sagittal 3D T1-weighted image was obtained with a spoiled gradient recall sequence (TR = 1900 ms, TE = 2.26 ms; flip angle = 9°; field of view = 256 mm × 256 mm; matrix size = 256 × 256; in-plane resolution: 1 mm × 1 mm; slice thickness = 1 mm; slices with no gap = 176). Then, a 6 min resting scan was performed for each participant using a gradient-echo echo planar imaging sequence (TR = 2000 ms; flip angle = 90°; field of view = 240 mm × 240 mm; matrix size = 64 × 64; in-plane resolution = 3.75 mm × 3.75 mm; slice thickness = 5 mm; axial slices with no gap = 30). The participants were instructed to lie in the scanner with their eyes closed and stay awake.

2.4. Data analysis

The functional images were processed using the Functional MRI of the brain (FMEIB) Software Library (FSL) [28] and Analysis of Functional NeuroImaging (AFNI) [29]. The preprocessing steps consisted of: 1) dropping the first four volumes; 2) slice time correction; 3) three-dimensional motion correction; 4) temporal despiking; 5) linear detrending; and 6) spatial smoothing (full width at half maximum [FWHM] = 6 mm). The resulting images were normalized to the MNI152 template with a resampling resolution of 2 × 2 × 2 mm using the affine registration tool FLIRT [30,31]; functional images were aligned to the structural image, and the structural image was aligned to the MNI152 template.

The ALFF and fALFF maps (standardized by transforming each individual data to Z-score) of each participant were calculated using FSL [22]. The fALFF qualifies the ratio of power of low-frequency fluctuations (0.01–0.1 Hz) to that of the entire frequency range and has been suggested to be more sensitive in detecting spontaneous brain activity than ALFF [21,22]. Group voxelwise comparisons were carried using a permutation-based non-parametric test (Randomise v2.1; 5,000 permutations; covariates: age and gender). Multiple comparisons across space were corrected using the threshold-free clustering enhancement (TFCE) method [32].

Then, we performed seed-based RSFC analysis [33] by using clusters that showed significant between-group difference in ALFF/fALFF as regions of interest (ROI). Specifically, mean time series of each ROI was extracted, then whole brain RSFC maps were obtained by calculating the Pearson correlation between the time series of each voxel and that of each ROI. Finally, all subjects' Fisher Z-transformed connectivity maps were fed into group-level voxelwise comparison using permutation-based non-parametric test

Table 1
Demographics and clinical data of the subjects.

| Item | Healthy controls | FD patients | <i>p</i> value |
|------------------------------|------------------|---------------|----------------|
| Sex distribution (% Male) | 43.75% | 34.48% | 0.62 |
| Age (years) | 21.94 ± 0.85 | 22.41 ± 1.86 | 0.50 |
| SAS | 33.36 ± 36.73 | 43.06 ± 8.60 | < 0.005 |
| SDS | 34.06 ± 7.81 | 44.57 ± 10.21 | < 0.005 |
| NDI | – | 48.93 ± 12.28 | – |
| QOL | – | 77.98 ± 8.65 | – |
| Duration of disease (months) | – | 33.72 ± 20.20 | – |

Data are presented as mean ± std. FD, Functional Dyspepsia; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; NDI, Nepean Dyspepsia Index; QOL, quality of life.

(Randomise v2.1; 5,000 permutations; covariates: age and gender) with multiple comparisons corrected using the TFCE method.

In order to examine the correlations between brain functional abnormalities and clinical symptoms, we extracted mean ALFF/fALFF or RSFC values within a 4-mm radius centered at the peak of significant clusters. Next, the correlations between these values and the NDI scores as well as the duration of disease were examined using Spearman correlation analysis. The significant level was set at $p < 0.05$ with Bernoulli corrected for multiple correlations.

3. Results

The demographics and clinical data of the subjects are shown in Table 1. The healthy controls and FD group showed no significant between-group differences in demographics data including gender and age ($p > 0.5$). Higher SAS and SDS scores were observed in the patient group ($p < 0.05$). The average duration of disease in the patient group was 33.7 months (standard deviation: 20.2 months).

Between-group voxelwise comparison analysis revealed no significant differences in ALFF ($p > 0.05$). In contrast, significant between-group difference in fALFF was observed in multiple brain regions including the right insula and bilateral brainstem and cerebellum ($p < 0.05$, corrected) (Fig. 1, Table 2). In no regions did healthy controls showed higher fALFF than patients with FD ($p > 0.05$, corrected).

RSFC analysis was performed using the right insula, bilateral brainstem and bilateral cerebellum as ROIs separately. The results showed that patients with FD have increased RSFC between the right cerebellum and multiple brain regions including the left para-/hippocampus, left pallidum, left putamen, bilateral brainstem, bilateral cerebellum and bilateral thalamus (Fig. 2). The cluster size

Table 2
Brain regions where patients with functional dyspepsia have higher fractional amplitude of low-frequency fluctuation than healthy controls.

| Region | Cluster Size | Peak Coordinates (MNI) | | | <i>p</i> value (corrected) |
|--------------|--------------|------------------------|-----|-----|----------------------------|
| | | x | y | z | |
| Insula R | 16 | 36 | 18 | –12 | 0.029 |
| Cerebellum L | 21 | –2 | –46 | –36 | 0.020 |
| R | 17 | 2 | –46 | –36 | 0.023 |
| Brainstem L | 59 | –6 | –44 | –34 | 0.022 |
| R | 26 | 6 | –42 | –36 | 0.032 |

NOTE: L, Left; R, Right.

and peaks coordinates of significant clusters are summarized in Table 3.

The correlation analysis showed that only fALFF of the right insula was positively correlated with the NDI scores in the patient group (Spearman $\rho = 0.51$, $p < 0.05$, Bernoulli corrected for multiple correlations) (Fig. 3). No significant correlation between fALFF and the duration of disease was observed ($p > 0.05$, corrected). The RSFC was found to correlate with neither NDI scores nor the duration of disease ($p > 0.05$, corrected).

4. Discussion

In the present study, we examined the ALFF and fALFF changes in patients with FD compared with healthy controls by using resting-state fMRI. The results revealed that patients with FD had increased fALFF in multiple brain regions including the insula, brainstem and cerebellum. Furthermore, RSFC analysis showed that correlations between the right cerebellum and bilateral brainstem, bilateral cerebellum, bilateral thalamus, left para-/hippocampus, left pallidum and left putamen were increased in patients with FD. Finally, the fALFF of the right insula was found to be positively correlated with the severity of the disease in the patient group. Our findings might have provided further evidence of abnormal resting state spontaneous brain activity in patients with FD and contribute to our better understanding of the pathophysiology of the disease.

Resting-state fMRI, ever since its first proposal by Biswal et al. [34], has become a powerful tool in the investigation of brain disorders. The amplitude information of the low-frequency oscillation, although examined infrequently compared with temporal correlations between brain regions (i.e., functional connectivity), has been proven to be useful in differentiating normal from disease conditions [23]. As noted above, ALFF directly measures the power of the

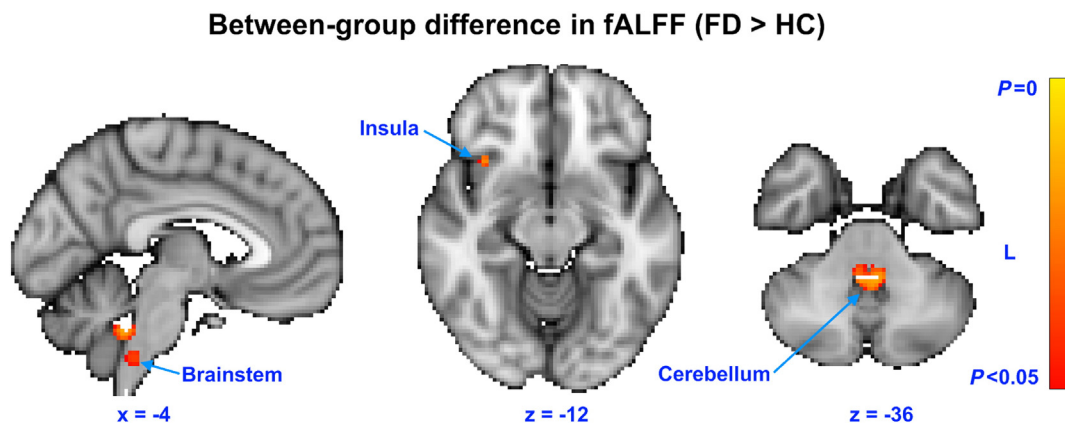


Fig. 1. Brain regions where patients with functional dyspepsia (FD) have higher fractional amplitude of low-frequency fluctuations (fALFF) than healthy controls (HC). The resulting images are overlaid on the MNI152 template. L, Left.

Between-group difference in RSFC of the right cerebellum (FD > HC)

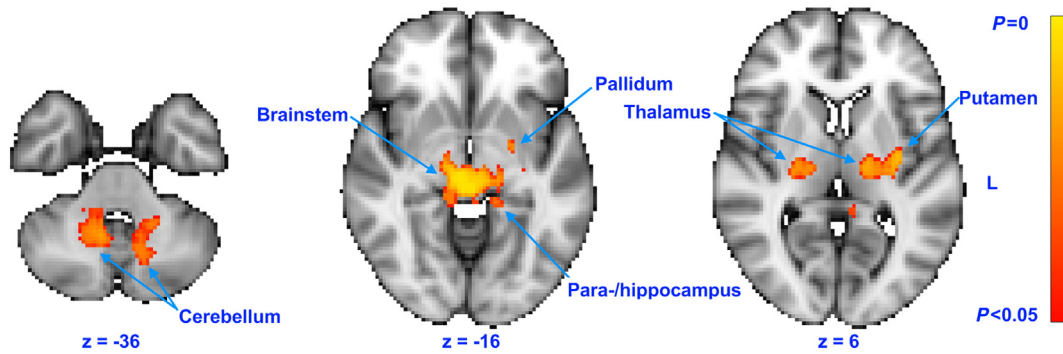


Fig. 2. Brain regions where patients with functional dyspepsia (FD) have increased resting-state functional connectivity (RSFC) with the right cerebellum than healthy controls (HC). The resulting images are overlaid on the MNI152 template. L, Left.

low-frequency range while fALFF is a normalized measure. Although ALFF has somewhat higher test–retest reliability, fALFF is less susceptible to physiological artifacts [23]. In the present study, patients with FD were found to have altered fALFF compared with healthy controls. However, no significant between-group difference in ALFF was observed. Distinct capacity of ALFF and fALFF in differentiating healthy controls from pathological conditions has also been noted by previous studies [35]. Thus, it would be of great importance to report the results of the two measures as suggested by Zuo et al. [23]. The findings in the present study likely suggest that fALFF might be more sensitive in detecting regional spontaneous brain activity changes in FD patients than that of ALFF, although further research is warranted.

Brain regions where patients with FD showed increased fALFF were involved in the "gastric sensation neuromatrix" which includes the anterior cingulate cortex, lateral orbitofrontal and prefrontal lobes, insula, thalamus, brainstem, cerebellum and primary and secondary somatosensory cortical regions [36]. The result of increased fALFF in the insula was consistent with findings in our previous study [10]. Patients with FD were found to have higher glycometabolism in the insula than healthy controls during the resting-state [10]. It should be noted that lower activation of the insula in patients with FD as compared with healthy controls has also been reported [18]. The discrepancy of the findings of these studies might be explained by the fact the pathophysiology of FD is likely to be heterogeneous [1]. The insula which is an important visceral sensorimotor area [14] is involved in the homeostatic afferent network [12]. More specifically, the right anterior insula plays a crucial role in the conscious perception of visceral sensations [12,37]. Thus, it was speculated that selective attention to the chronic or

recurrent uncomfortable sensations that rose from the stomach such as those suffered by patients with FD might contribute to the functional abnormalities in the insula. Furthermore, we found that the fALFF values of the right anterior insula were positively correlated with the severity of the disease (Fig. 3). Taken together, our findings of fALFF abnormalities in the insula might further support the notion of homeostatic dysregulation at the level of the CNS in patients with FD [10].

Increased fALFF was also observed in the brainstem and cerebellum. The brainstem sends modulator projections to cortical regions and plays an important role in the regulation of arousal [18,38]. The important role of the cerebellum in nociception and pain processing has also been confirmed in previous studies [39–41]. Our previous study has found that FD patients had higher levels of glycometabolism in the cerebellum than healthy controls [10]. Lukas et al. also found that gastric distension induced higher activation in the cerebellum in FD patients than that in healthy controls [18]. Furthermore, the present study revealed that the RSFC between the right cerebellum and multiple cortical and subcortical brain regions was increased in patients with FD (Fig. 2). Multiples of these connected regions were found to exhibit abnormal activity during the resting state or gastric distension. For example, FD patients showed increased levels of glycometabolism in the putamen, para-

Table 3

Brain regions where patients with functional dyspepsia have increased right cerebellum resting-state functional connectivity compared with healthy controls.

| Region | Cluster Size | Peak Coordinates (MNI) | | | p value | |
|-------------------|--------------|------------------------|-----|-----|---------|-------|
| | | x | y | z | | |
| Brainstem | L | 113 | -2 | -30 | -8 | 0.006 |
| | R | 327 | 4 | -30 | -6 | 0.006 |
| Cerebellum | L | 442 | -18 | -48 | -38 | 0.025 |
| | R | 431 | 10 | -54 | -34 | 0.019 |
| Para-/hippocampus | L | 15 | -14 | -36 | -6 | 0.028 |
| Hippocampus | L | 19 | -16 | -38 | 0 | 0.026 |
| Pallidum | L | 64 | -20 | -10 | 0 | 0.015 |
| Putamen | L | 123 | -30 | -16 | 2 | 0.013 |
| Thalamus | L | 219 | -2 | -16 | 0 | 0.016 |
| | R | 114 | 4 | -18 | -2 | 0.012 |

NOTE: L, Left; R, Right.

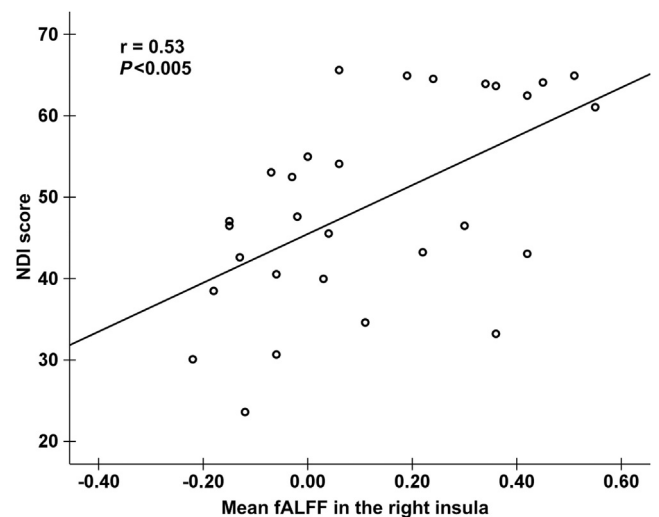


Fig. 3. Correlation between standardized fractional amplitude of low-frequency fluctuations (fALFF) (Z-score) in the right insula and Nepean Dyspepsia Index (NDI) score in the patient group. The age and gender were regressed out before correlation.

hippocampus and thalamus during resting state [10]. Vandenberghe and colleagues found that painful gastric distention failed to activate components of medial pain system including the thalamus [16]. The results of the present study were also consistent with those of another study of our group which revealed increased RSFC between the right cerebellum and contralateral homologous cerebellum [42]. These findings were likely to suggest that functional interactions across brain regions changes might be involved in the pathophysiology of the disease.

There are several limitations of the present study. Firstly, although the gender effect on the between-group difference was minimized by including it as a covariate, its exact role should be examined directly in future studies. Moreover, psychosocial factors such as anxiety and depression have been proven to bidirectionally interact with the onset of the symptoms of FGIDs [15]. Thus, the potential role of these factors in fALFF changes seen in our study should be examined in a future longitudinal study.

5. Conclusions

In conclusion, the results of the present study have provided further evidence of low-frequency spontaneous brain activity abnormalities in patients with FD. These findings might contribute to our better understanding of the pathogenesis of the symptoms of the disease.

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