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Fractional amplitude of low frequency fluctuation in drug-naïve first-episode patients with anorexia nervosa

A resting-state fMRI study

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Abstract

To characterize the fractional amplitude of low-frequency fluctuation (fALFF) in drug-naïve first-episode female patients with anorexia nervosa (AN) using resting-state functional magnetic resonance imaging (rs-fMRI).

Whole brain rs-fMRI data were collected from 7 drug-naïve first-episode female patients with *DSM-5* AN and 14 age-matched healthy female controls. fALFF values were calculated and compared between the two groups using a two-sample *t* test. Correlation analysis between the fALFF values in the entire brain and body mass index (BMI) was performed.

Compared with the healthy controls, increased fALFF values were observed in the AN patients in their right hippocampus and left superior frontal gyrus, while decreased fALFF values were observed in their left rectus and left middle occipital gyrus. Moreover, low BMI was significantly associated with decreased fALFF in the left inferior frontal gyrus but increased fALFF in the left calcarine. In particular, the z-standardized fALFF (zfALFF) value of the left rectus was positive associated with BMI.

Our findings suggest that spontaneous brain activity in the frontal region, hippocampus and rectus, characterized by fALFF values, was altered in drug-naïve, first-episode female patients with AN.

Abbreviations: AN = anorexia nervosa, BMI = body mass index, BOLD = blood oxygen level-dependent, DMN = default mode network, fALFF = fractional amplitude of low-frequency fluctuation, fMRI = functional magnetic resonance imaging, FWHM = full width at half maximum, ICA = independent component analysis, OFC = orbitofrontal cortex, PFC = prefrontal cortex, rs-fMRI = resting-state fMRI, SMN = sensorimotor network, VN = visual network, zfALFF = z-standardized fALFF.

Keywords: anorexia nervosa, fractional low-frequency fluctuation, resting-state functional MRI

1. Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder marked by restriction of food intake, intense fear of weight gain and distortion of body image, associated with clinically significant low body weight.[1] According to *DSM-5*, AN can generally be classified into 2 types, the binge-purge type and the restricting type.[2] AN affects predominantly adolescent girls and young women, and is an important cause of psychiatric morbidity and even death.[3]

To date, the etiology of AN remains unclear. Nevertheless, increasing evidences from recent neuroimaging studies have indicated abnormal alterations in neurocircuitry in AN patients,

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which are possibly relevant to the pathophysiology of AN.[4–6] Using task-based functional MRI (fMRI), these studies mainly explored the neural responses to different experimental paradigms and stimuli, including food, taste, body image, reward, emotion, pain and neuropsychological tests.[4] Although results from these studies were different, overlapping findings indicated that the fronto-striato and limbic circuits played an important role.[5] Moreover, an integrated model of the imbalanced prefrontal cortex (PFC)-mesolimbic convergence on the insular cortex was previously proposed to explain the maladaptive behaviors and emotion regulation in AN patients, manifesting as hypo-activation in the bottom-up mesolimbic regions (e.g., striatum, hippocampus, amygdala, hypothalamus and cerebellum) and top-down PFC regions (e.g., dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex).[6]

In contrast to task-based fMRI, stimulus-free technique was less frequently used in identifying resting-state brain activities in AN patients. Among the brain networks that received investigations, the default mode network (DMN), as well as the sensorimotor network (SMN) and the visual network (VN), were the most intensively studied.[7,8] Based on independent component analysis (ICA), increased temporal coherence was discovered between the right precuneus, the frontal region (the dorsolateral prefrontal cortex/inferior frontal gyrus) and the DMN in a sample of recovered AN patients.[7] Using a seed-driven approach, another study reported no difference in the functional connectivity in DMN between patients with current AN and healthy controls; however, decreased functional connectivity was found in the SMN and the VN.[8] Employing a graph-theoretical measure, investigators identified in patients with current AN an abnormal global brain architecture, along with decreased local network efficiency in the posterior insula and in the thalamus.[9] Moreover, a reduced temporal correlation between the executive control network and the anterior cingulate cortex was found in those with early-stage of AN.[10] Having checked all the different analytic approaches systematically, a recent review categorized pertinent studies into four types: seed-based analysis, graph analysis, whole brain-based ICA and network-based ICA.[11] Despite the methodological inconsistency, these studies consistently identified alterations of resting-state functional connectivity in the cortico-limbic circuitry, which was implicated in self-referential processing, cognitive control and visuospatial processing.[7–11]

Unlike functional connectivity, the fractional amplitude of low-frequency fluctuation (fALFF) is an index similar to ALFF that reflects spontaneous neuronal activities.[12] Based on blood oxygen level-dependent (BOLD) fMRI signals, fALFF reflects the relative ratio of low-frequency range (e.g., 0.01–0.08 Hz) to the whole measurable frequency range.[12] This measurement has been applied in studies on various neuropsychiatric diseases, for example, major depressive disorder,[13–15] schizophrenia,[16–18] panic disorder,[19–20] mild cognitive impairment and others.[21] To the best of our knowledge, fALFF has not been used to characterize the spontaneous brain activities of patients with current AN.

The aim of present study was to study the neuromechanism of AN in young females. In particular, we aimed to

(1) quantify the fALFF index in patients with current AN,
(2) conduct a whole-brain correlation analysis between the fALFF and the BMI values, and
(3) correlate the mean values of fALFF with BMI, in brain regions that were significantly different from the other regions.

We hypothesized that altered fALFF would be observed in specific brain regions in the drug-naïve first-episode patients with current AN.

2. Methods

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. The data was collected between July 2014 and June 2016, and all procedures were in accordance with the *Helsinki Declaration*.

2.1. Participants

Seven inpatients diagnosed with AN, the restricting subtype, according to the criteria of *DSM-5*, were recruited from the First Affiliated Hospital, Zhejiang University School of Medicine. All patients were in their first episode and psychotropic drug-naïve except for Chinese herbs. The AN patients were from 15 to 25 years old, and their BMIs were lower than 17.5 kg/m^2. Meanwhile, 14 healthy volunteers from local high schools and universities were enrolled, matched for age ($P = .256$), sex ($P = 1.0$), height ($P = .739$), handedness ($P = 1.0$) and education level ($P = 310$). Careful physical examinations and routine laboratory tests were conducted on all the participants to exclude any significant physical abnormality or neurological condition. Other exclusion criteria included other psychiatric comorbidities, intracranial implants, substance abuse, past suicide attempts, brain injuries, current pregnancy, breastfeeding and any other contraindication to MRI scanning. Demographic data and clinical assessment are listed in Table 1. All participants provided informed consent before commencement of the study.

2.2. MRI scanning

The acquisition of MRI data was from a 3.0-Tesla General Electric (GE) Signa Scanner (Milwauee, WI). Axial T1- and T2-weighted images were obtained before functional scans to check for any silent anatomical abnormalities. Resting-state fMRI scans were conducted using an echo-planar imaging sequence according to the following parameters: repetition time, 2 seconds; echo time, 3 ms; flip angle, 90°; matrix, 64×64; field of view, 24×24

Table 1

Demographic and clinical data of AN patients and healthy controls in this study.

	AN Patients (mean±SD)	Healthy controls (mean±SD)	P value*
Age/year-old	17.54±2.37	19.14±3.11	.256
Illness course/month	10.29±6.68	/	/
Height/centimetre	161.79±3.11	161.21±3.89	.739
Handedness (right/left)	7/0	14/0	1.0
Education/year	11.57±2.37	12.79±2.58	.310
Premorbid weight/kilograms	47.14±3.76	/	/
On-admission weight/kilograms	37.07±3.50	52.18±3.91	< .001
Body mass index/kg*m^{-2}	13.71±1.38	19.57±1.83	< .001

* Independent sample t test, $P < .05$ is statistically significant.
AN = anorexia nervosa, SD = standard deviation.

cm^2; slice thickness/gap, 3.0 mm/0.8 mm; number of axial slices, 32. During the scanning, the participants were required to close their eyes, keep relax, awake and motionless, and avoid any active thinking if possible. In total 180 rs-fMRI volumes were acquired for each participant.

2.3. Data preprocessing

The functional images were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net). The first 10 volumes were discarded to reduce the initial interferential effects from scanner and participants. The remaining 170 volumes were then slice-time corrected, spatially realigned and normalized to the Montreal Neurological Institute template, resampled to a $3 \times 3 \times 3\,mm^3$ resolution, and smoothed with a Gaussian kernel of 4-mm full width at half maximum (FWHM). The head movements of all subjects were no more than 2.0 mm in any direction, and no more than 2° in any angular dimension. Removal of lineal trend was performed.

2.4. fALFF computation

Computation of fALFF was performed in accordance to previous method.[12] The sum of the absolute amplitudes of low-frequency (across from 0.01 Hz to 0.08 Hz) was extracted from the time series of each voxel, which was defined as ALFF.[22] Extended from ALFF, fALFF was introduced to overcome the limits of ALFF, such as the signal fluctuations that are elicited by physiological noise.[17] fALFF represents the fractional sum of the amplitudes of low-frequency, divided by that of the entire frequency range (across from 0 to 0.25 Hz). zfALFF (z-standardized fALFF) are the values after z-standardization.

2.5. Statistical analysis

When appropriate, demographic and clinical profiles were compared between the two groups using Chi-square test or two-sample t test. The group difference of fALFF was calculated with a voxel-wise, two-tailed *t* test. The significance threshold for multiple comparisons was set at $P < .05$ using Gaussian Random Field (GRF) theory (min $z > 1.96$, cluster significance: $P < .05$, corrected). Linear correlation analysis was conducted between BMI and the fALFF values in the entire brain and at voxels showing a statistical difference of fALFF value ($P < .05$ was set as significance level).

3. Results

3.1. Demographic and clinical characteristics

Thedemographic and clinical profiles of all participants are presented in Table 1. The average age of the healthy controls was 19.1 ± 3.1 years and the average height was 161.2 ± 3.9 cm, both of which did not significantly differ from the AN group.

3.2. Group differences of fALFF

Compared with the healthy controls, increased fALFF values were observed in the AN patients in the right hippocampus and left superior frontal gyrus, while decreased fALFF values were observed in the left rectus and left middle occipital gyrus (Fig. 1 and Table 2).

3.3. Correlation analysis of whole brain fALFF and BMI

Within the AN group, BMI was positively associated with fALFF in the left inferior frontal gyrus, but negatively associated with fALFF in the left calcarine. (Fig. 2 and Table 3).

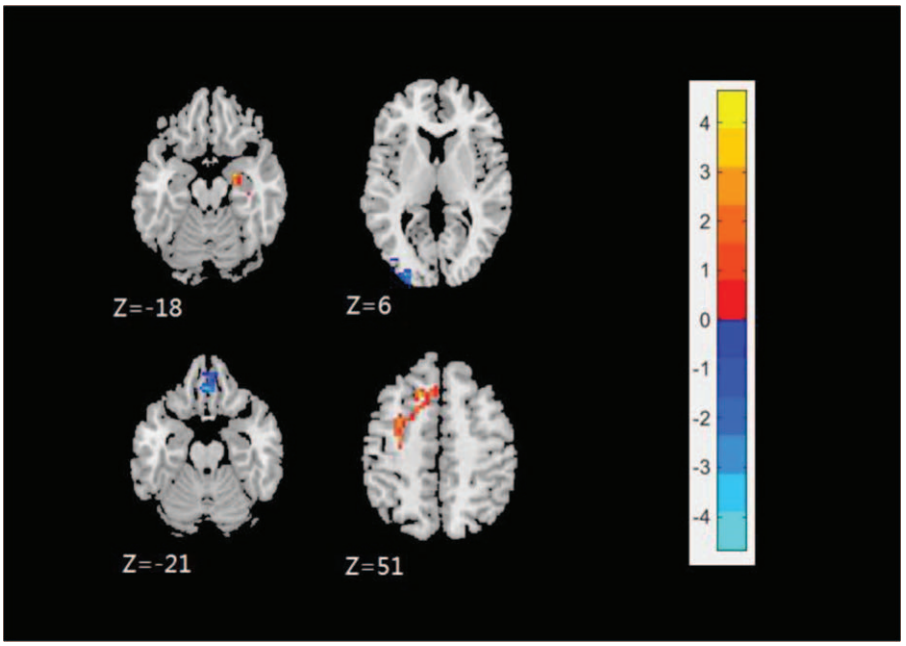

Figure 1. Brain regions showing abnormal fALFF in the AN group relative to healthy controls. The color bars indicate the student's *t* test value and the statistical significance at $P < .05$ (GRF theory). The red and yellow regions represent the fALFF value of the AN patients is greater than the control group, and the blue and green region represent the fALFF value of the AN patients is smaller than the control group. AN = anorexia nervosa, fALFF = fractional amplitude of low frequency fluctuation, GRF = Gaussian Random Field.

Table 2

Brain regions with abnormal fALFF.

Brain regions	MNI coordinates			Number of voxel	T value
	x	y	z		
Right hippocampus	24	–6	–18	89	4.6669
Left rectus	0	36	–21	96	–4.3772
Left middle occipital gyrus	–30	–93	6	97	–4.5469
Left supper frontal gyrus	–15	21	51	110	4.347

fALFF = fractional amplitude of low frequency fluctuation, MNI = Montreal Neurological Institute.

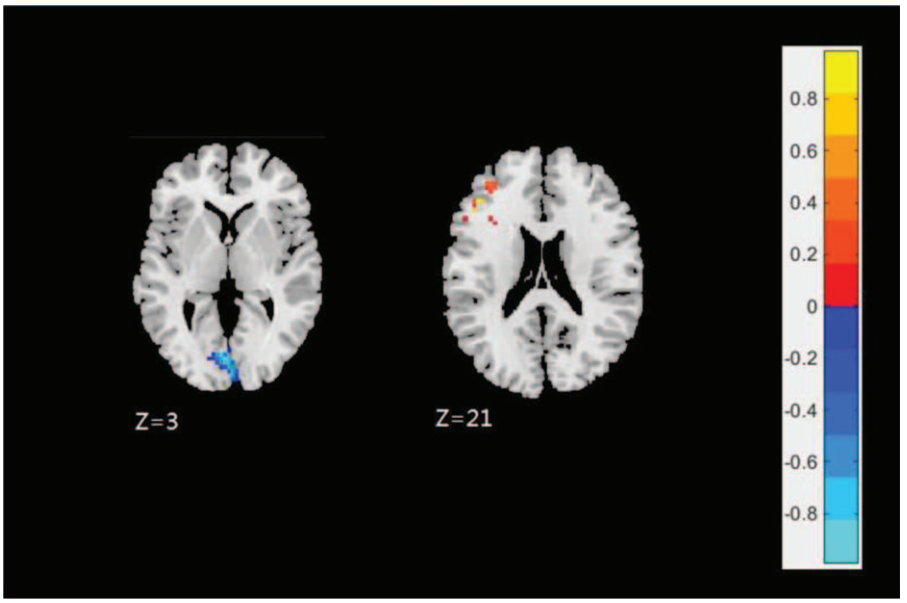

Figure 2. Correlation analysis of whole brain fALFF and BMI in AN patients. The color bars indicate the strength of the correlation between the brain region and BMI. The red and yellow regions represent a positive correlation, while the blue and green regions represent a negative correlation. Statistical significance was set at $P < .05$ (GRF theory). AN = anorexia nervosa, BMI = body mass index, fALFF = fractional amplitude of low frequency fluctuation.

3.4. Correlation analysis of fALFF value of abnormal brain regions and BMI

Within the brain areas where fALFF was abnormal, including right hippocampus, left rectus, left middle occipital gyrus and left supper frontal gyrus, BMI was positively associated with zfALFF in the left rectus (Fig. 3 and Table 4).

4. Discussion

To the best of our knowledge, this is the first study using fALFF to evaluate brain activity in drug-naïve and first-episode patients with current AN. The results showed widespread alterations of fALFF values in brain regions related to AN compared with healthy controls, associated with frontal lobe, limbic system and rectus dysfunction. Furthermore, low BMI was significantly associated with decreased fALFF in the left inferior frontal gyrus but increased fALFF in the left calcarine. Particularly, we found reduction of fALFF values in the rectus, which were positively associated with BMI.

Table 3

Brain regions of significant fALFF correlated with BMI.

Brain regions	Brodmann areas	MNI coordinates			r value
		x	y	z	
Left inf-tri-frontal gyrus	18	–45	33	21	0. 98736
Left calcarine	46	–3	81	3	–0.99295

BMI = body mass index, fALFF = fractional amplitude of low frequency fluctuation, MNI = Montreal Neurological Institute.

The frontal lobe, especially the prefrontal lobe, is linked to emotion and motivation regulation.[23] Structural MRI studies have demonstrated that a decrease in grey matter volume in the frontal regions, including superior frontal gyrus and inferior frontal gyrus, is associated with body dissatisfaction in AN patients.[24,25] Decreased grey matter volumes in these regions may be linked to the impaired visuospatial perception, executive functioning and inhibitory control, which could be involved in the pathogenesis of AN onset.[24,25] Using visual stimuli (e.g., images of food and body form), many fMRI studies have reported functional abnormalities within the emotion circuits in AN patients, including the prefrontal cortex, insula and amygdala.[26,27] The dysfunction in frontostriatal circuitry is associated with emotional and behavioral control abnormalities, which may mediate the neurobiology of this disorder.[28,29] Notably, an rs-fMRI study revealed that the inferior frontal gyrus is possibly a specific region of functional importance within the whole-brain network, and decreased functional connectivity in this region

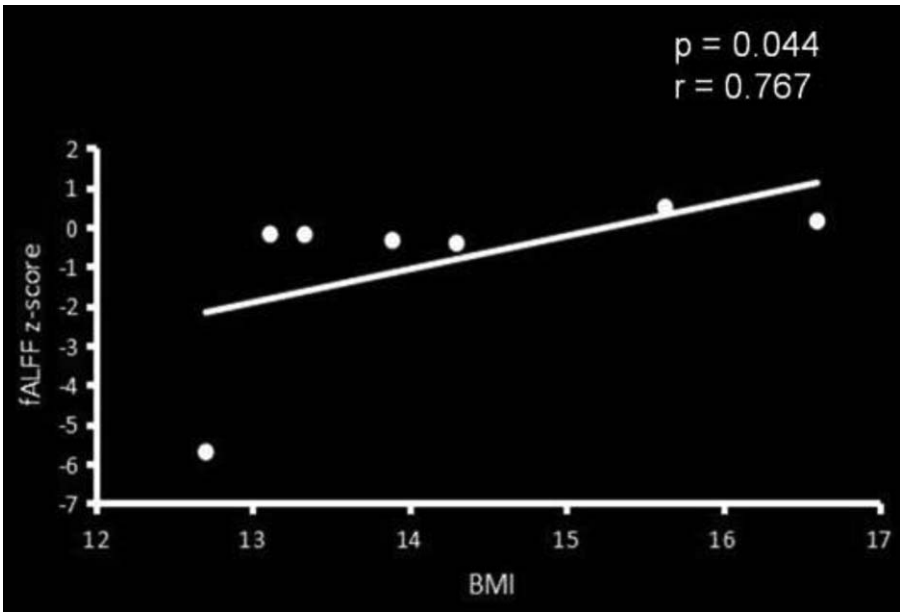

Figure 3. Correlation analysis of the mean value of fALFF in ROI and BMI. Pearson correlation was used in the abnormal regions and BMI; zfALFF of left rectus is positive associated with BMI (r, 0.767; *P*, 0.044). BMI = body mass index, fALFF = fractional amplitude of low frequency fluctuation, ROI = region of interest.

may impair its role in behavioral control and contribute to hyperactivity of patients with current AN.[30] Consistent with previous studies, we found that AN patients exhibited significantly decreased fALFF values in the region of left frontal gyrus, which was positively correlated with BMI. These findings may indicate that the altered fALFF values in the frontal gyrus are associated with dysfunctional emotion and motivation control in AN patients.

Hippocampus is an important component of the marginal system, which participates in regulating instinctual and emotional behavior. Structural and functional alterations in the hippocampus have been reported in patients with eating disorders.[31–33] A recent structural MRI study revealed that the regional grey matter of the right hippocampus, the left middle and right inferior frontal gyrus was reduced in patients with acute AN.[31] However, these alterations were not shown in recovered AN patients, which indicated that the changes were largely reversible.[31] Based on rs-fMRI and graph theory analysis, female patients with bulimia nervosa showed lower nodal strength and hypoconnectivity in the marginal system (e.g., hippocampus) and paralimbic regions (e.g., parahippocampal gyrus), which was correlated with the severity of disease and BMI.[32] The hippocampus plays a central role in various aspects of human cognition, and its impairment could possibly cause dysregulation in food intake and health-related consequences.[33] The hippocampus-dependent regulation of food intake may function via different pathways, such as interoception, craving and imagery for food, declarative memory processes and inhibitory processes.[33] In animal models, the appetite control circuits originating from the ventral hippocampus to its projections in the lateral septum was shown to be a potential target for regulating feeding behavior.[34] Therefore, decreased fALFF values of the marginal system, especially hippocampus in AN patients as shown in the current study, may have suggested inhibitory neuronal activity of this area, which may be related to the emotional and behavioral abnormalities in AN patients.

Interestingly, our study is the first to report decreased fALFF values in the left rectus gyrus, and it was positively correlated with BMI. The rectus locates at the most medial and lower side of the frontal lobe and is considered as part of the orbitofrontal cortex (OFC). The OFC participants in terminating food intake and its dysfunction could contribute to self-starvation.[35] Larger

Table 4

The zfALFF values of the ROI in each AN patient.

Patient number	Right hippocampus (ROI1)	Left rectus (ROI2)	Left middle occipital gyrus (ROI3)	Left supper frontal gyrus (ROI4)
No.1	–0.03	–0.57	–0.15	0.22
No.2	–0.08	0.15	–0.16	0.30
No.3	–0.22	–0.18	0.21	0.40
No.4	0.03	–0.19	0.22	0.31
No.5	0.02	–0.41	0.24	0.37
No.6	-–0.13	0.5.	0.3.	0.16
No.7	–0.16	–0.34	0.36	0.06

BMI = body mass index, fALFF = fractional amplitude of low frequency fluctuation, ROI = region of interest.

volume of left rectus was found in female patients with current AN, or recovered AN, or bulimia nervosa, and this enlargement can predict the taste pleasantness experiences in those individuals.[36] In recovered AN patients, greater white matter connectivity was shown between insula and ventral striatum or middle OFC or the gyrus rectus, which was considered to be the taste-reward processing regions.[37] The findings in our study may indicate that reduced neural activities in the gyrus rectus was associated with eating behaviors in AN patients.

The present study bears several limitations. First, the sample size in the current study was small, which hindered further subgroup analysis of the differences between the two types of AN, that is, the binge-purge type and the restricting type. Second, we calculated in the patients only the BMI, but did not evaluate other clinical symptoms of this disorder, such as body image distortion or accompanying affective instability. Therefore, whether or not an association may possibly exist between the variables and the findings in our study remained unclear. Third, since this study was cross-sectional but not longitudinal, we were unable to determine whether the altered fALFF values in specific brain regions are trait- or state-related characteristics. Lastly, the initial threshold $z > 1.96$ is too liberal to identify group differences of fALFF, and this is also a limitation of our study.

5. Conclusions

Our study suggests that AN patients may have a significant alteration of fALFFs in several brain areas involved in emotion and behavior regulation. Further studies with larger size of samples are needed to verify these findings.

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