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Shared and Distinct Fractional Amplitude of Low-Frequency Fluctuation Patterns in Major Depressive Disorders With and Without Gastrointestinal Symptoms

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Objective: Gastrointestinal (GI) symptoms are fairly common somatic symptoms in depressed patients. The purpose of this study was to explore the influence of concomitant GI symptoms on the fractional amplitude of low-frequency fluctuation (fALFF) patterns in patients with major depressive disorder (MDD) and investigate the connection between aberrant fALFF and clinical characteristics.

Methods: This study included 35 MDD patients with GI symptoms (GI-MDD patients), 17 MDD patients without GI symptoms (nGI-MDD patients), and 28 healthy controls (HCs). The fALFF method was used to analyze the resting-state functional magnetic resonance imaging data. Correlation analysis and pattern classification were employed to investigate the relationship of the fALFF patterns with the clinical characteristics of patients.

Results : GI-MDD patients exhibited higher scores in the HRSD-17 and suffered more severe insomnia, anxiety/somatization, and weight loss than nGI-MDD patients. GI-MDD patients showed higher fALFF in the right superior frontal gyrus (SFG)/middle frontal gyrus (MFG) and lower fALFF in the left superior medial prefrontal cortex (MPFC) compared with nGI-MDD patients. A combination of the fALFF values of these two clusters could be applied to discriminate GI-MDD patients from nGI-MDD patients, with accuracy, sensitivity, and specificity of 86.54, 94.29, and 70.59%, respectively.

Conclusion: GI-MDD patients showed more severe depressive symptoms. Increased fALFF in the right SFG/MFG and decreased fALFF in the left superior MPFC might be distinctive neurobiological features of MDD patients with GI symptoms.

Keywords: fractional amplitude low-frequency fluctuation, major depressive disorder, gastrointestinal symptoms, functional magnet resonance imaging (fMRI), somatic symptoms

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INTRODUCTION

As one of the most widespread mental illnesses across the world, major depressive disorder (MDD) is a serious public health problem and markedly impairs patient's quality of life. It is extremely common for patients with MDD to report somatic symptoms, such as constipation and stomachache. A multicenter study showed that half of MDD patients had multiple unexplained somatic symptoms (1). In elderly patients with MDD, the prevalence of somatic symptoms is even higher (2). Among these somatic symptoms, gastrointestinal (GI) symptom is prevalent in depressed patients and has a close connection to depression (3, 4). Over 70% of patients with depressive episodes reported concomitant GI symptoms (5). Patients with GI symptoms also have a greater probability of suffering from severe depression or anxiety (5, 6).

Early and accurate diagnosis of MDD is a matter of great importance to optimize patient outcomes. However, the existence of somatic symptoms in MDD patients makes it more difficult to recognize the psychological symptoms. According to the results of an international study across 15 centers in 14 countries, about 69% of patients with MDD only sought medical care for somatic symptoms, and 11% of patients denied depressed mood and feelings of guilt or worthlessness, which are the two most significant symptoms to the diagnosis of MDD (1). GI symptoms are common in primary care, but often, no pathological cause can be found. Functional gastrointestinal disorders (FGIDs) refer to chronic or recurrent GI symptoms without identified structural or biochemical abnormalities, such as irritable bowel syndrome (IBS) and functional dyspepsia (7). It is widely acknowledged that FGIDs are closely related to depression (8). Tricyclic antidepressants and serotonin noradrenergic reuptake inhibitors are recommended in the treatment of chronic GI pain and painful FGIDs (9). GI comorbidities might result in delays in accurate diagnosis and effective treatment for MDD. Moreover, patients with MDD often bounce from one specialist to another in search of a diagnosis of physical diseases because of the co-occurrence of GI symptoms, which also imposes great economic hardship on patients. A review reported that 6–38.5% of clinic patients with IBS have a diagnosis of depressive disorders (10). About 29% of patients with unexplained GI symptoms referred to upper endoscopy were detected as patients with MDD (11).

The close association between GI symptoms and depression indicates a connection between the pathological mechanisms of GI symptoms and depression. Numerous studies have suggested the significance of the gut–brain axis on human psychiatric health (12). The gut–brain axis, which refers to the bidirectional information transfer between the GI tract and the nervous system, is of great importance to normal healthy homeostasis (13). The gut microbial dysbiosis can participate in mental disorders through numerous pathways, such as the autonomic nerve system, neuroendocrine system, and the immune system (14). Therefore, GI symptoms might be the manifestations of gut microbiota dysfunction, which could show associations with functional changes in the brain. Studies on FGIDs exhibited evidence supporting this idea that functional GI symptoms are related to functional changes in the brain. Patients with functional dyspepsia manifested altered functional connectivity (FC) in the amygdala and insula (15, 16). Reduced FC between the hypothalamus and high-order cortical area was found in adolescent IBS patients (17). Compared to female healthy controls, female IBS patients showed altered FC of the dorsal anterior insular with the medial prefrontal cortex (MPFC) and precuneus (18). Nevertheless, only a few previous studies have focused on functional alterations related to comorbid GI symptoms in MDD patients (19, 20). Studies using regional homogeneity (ReHo) have found functional alterations of MDD patients with concomitant GI symptoms chiefly in the frontal lobe, precentral gyrus, and superior temporal gyrus, as well as the precuneus relative to MDD patients without GI symptoms (19, 20).

Investigating the brain functional changes of depressed patients with GI symptoms is beneficial in order to obtain an understanding of the pathophysiology behind it. While ReHo reflects the regional property of spontaneous neural activity to some degree, it is based on the temporal similarity of spontaneous brain activity of spatially adjacent voxels. Knowledge of the amplitude of regional neural activity in MDD patients with GI symptoms is still limited. The amplitude of low-frequency fluctuation (ALFF), correlated with cerebral blood flow, is considered to reflect the strength of the low-frequency fluctuation of spontaneous neural activity (8, 9). To diminish the effect of physiological noise in ALFF analysis, Zou et al. (21) proposed fractional ALFF (fALFF) (10). ReHo and fALFF explore different aspects of spontaneous brain activity. Although similar trends of ReHo and fALFF have been shown in previous studies, opposite trends have also been reported (7). Therefore, it is significant to evaluate the effect of GI comorbidity on MDD from another aspect of spontaneous brain activity.

In this study, we explored the effect of concomitant GI symptoms on the clinical manifestations of MDD. Moreover, fALFF was employed to explore the shared and distinct patterns of functional changes in MDD patients with and without GI symptoms.

METHODS

Participants

This study involved 52 first-episode, treatment-naive patients with MDD and 28 age-, gender-, and education-matched healthy controls (HCs). MDD patients were divided into GI-MDD patients (patients with GI symptoms, $n = 35$) and nGI-MDD patients (patients without GI symptoms, $n = 17$) based on whether they had GI symptoms or not. These GI symptoms mainly incorporate medically unexplained nausea, vomiting, heartburn, flatulence, gastralgia, constipation, diarrhea, etc. The participants were all Han Chinese and right-handed. Detailed demographic characteristics of the three groups are presented in **Table 1**. The diagnosis of MDD was made by two psychiatrists independently according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). All patients had no psychotic symptoms and obtained a total score in the 17-item Hamilton Rating Scale for Depression (HRSD-17) of $\geq$17. Patients had no history of antidepressant use or electroconvulsive

TABLE 1 | Demographic and clinical characteristics of the participants.

	GI-MDD ($n = 35$)	nGI-MDD ($n = 17$)	HCs ($n = 28$)	F, t, or χ^2 value	*post-hoc t*-test or *p*-value
Age (years)	30.86 ± 6.84	30.29 ± 8.05	30.14 ± 5.00	0.102	0.903[a]
Sex (male/female)	13/22	6/11	14/14	1.377	0.502[b]
Handedness (right/left)	35/0	17/0	28/0		
Education (years)	14.51 ± 3.28	12.94 ± 3.46	14.61 ± 2.69	1.797	0.173[a]
Illness duration (months)	6.23 ± 4.63	6.94 ± 3.98		0.544	0.589[c]
HRSD-17 scores	22.69 ± 3.41	20.18 ± 2.67	0.89 ± 0.88	585.979	GI-MDD > nGI-MDD > HCs
Retardation symptoms	6.40 ± 1.42	6.76 ± 1.56	0.18 ± 0.39	253.030	GI-MDD, nGI-MDD > HCs
Cognitive disturbances	3.71 ± 1.78	3.41 ± 1.50	0	64.213	GI-MDD, nGI-MDD > HCs
Insomnia	4.46 ± 1.42	3.53 ± 1.28	0.32 ± 0.55	103.570	GI-MDD > nGI-MDD > HCs
Anxiety/somatization	7.31 ± 1.92	6.41 ± 1.66	0.39 ± 0.57	174.531	GI-MDD > nGI-MDD > HCs
Weight loss	0.80 ± 0.83	0.06 ± 0.24	0	18.741	GI-MDD > nGI-MDD, HCs

HRSD-17, 17-item Hamilton Rating Scale for Depression; GI-MDD, MDD with gastrointestinal (GI) symptoms; nGI-MDD, MDD without GI symptoms; HCs, healthy controls. [a]The p-value was obtained using analysis of variance. [b]The p-value was obtained using a chi-square test. [c]The p-value was obtained using a two-sample t-test.

therapy. HCs never had psychotic symptoms or a history or family history of psychiatric disorders. For all participants, the exclusion criteria included other psychiatric disorders following the DSM-5 diagnostic criteria, digestive diseases with structural or organic pathology, a history of substance abuse/neurological conditions/severe physical diseases, brain structural abnormalities, pregnancy, or inability to participate in brain MRI scan.

The severity of the GI symptoms was evaluated by the GI symptoms item in HRSD-17. The severity of the clinical symptoms of MDD patients was assessed by the scores of HRSD-17 and the following aspects in HRSD-17: retardation symptoms (items 1, 7, 8, and 14), cognitive disturbances (items 2, 3, and 9), insomnia (items 4, 5, and 6), anxiety/somatization (items 10–13, 15, and 17), and weight loss (item 16).

All participants provided written informed consent. This study conformed to the standards of the Declaration of Helsinki and was approved by the Medical Research Ethics Committee of the Second Xiangya Hospital of Central South University.

Image Acquisition

All participants underwent scanning on a Siemens 3.0-T scanner. Participants were requested to close their eyes and stay awake during the scan. Headphones and foam padding were used to restrict head motion and minimize scanner noise. Echo planar imaging (EPI) sequence was employed when obtaining resting-state functional magnetic resonance images (fMRI) data [repetition time (TR)/echo time (TE) = 2,000 ms/30 ms, flip angle = 90°, field of view = 240 × 240 mm, matrix = 64 × 64, 4-mm slice thickness, 0.4-mm gap, 30 slices, number of volumes = 250].

Imaging Data Processing

Data preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF v5.2; http://rfmri.org/DPARSF) software package (22). The initial 10 volumes of each participant were deleted for the MRI signal to reach a steady state and for the participants to adapt to the scanning noise. After slice timing correction, head motion correction was conducted; participants with head motion exceeding 2 mm of the maximum displacement or 2° of the maximal rotation were excluded. Subsequently, these images were spatially normalized to the Montreal Neurological Institute (MNI) space and resampled to a resolution of $3 \times 3 \times 3$ mm^3. Spatial smoothing was conducted with a 4-mm Gaussian kernel of full width at half maximum (FWHM). The calculation of fALFF has been published in previous research (21). Fast Fourier transform was used to convert the time series into the frequency domain to generate the power spectrum. Then, the square root of the power spectrum was calculated and then averaged across the frequency of 0.01–0.08 Hz. The fALFF was the ratio of the sum of amplitude across 0.01–0.08 Hz to that across the entire frequency range. The fALFF of each voxel was divided by the global mean fALFF for standardization.

Statistical Analysis

We compared the demographic, clinical, and neuroimaging data across GI-MDD patients, nGI-MDD patients, and HCs. Student's *t*-tests or one-way analyses of variance (ANOVA) was used to compare continuous data. Categorical data were analyzed with a chi-square test. Analysis of covariance (ANCOVA) was adopted to analyze fALFF, and age, gender, years of education, and the mean framewise displacement (FD) were set as covariates. *Post-hoc t*-test was performed for multiple comparisons. Differences were considered significant at a false discovery rate (FDR)-corrected $p < 0.05$. The fALFF values of clusters with significant differences between groups were extracted for further correlation and classification analysis.

After assessing the normal distribution of the data, we analyzed the correlation between the extracted fALFF and the scores of HRSD-17 and its subscales. Benjamini–Hochberg correction was used in the correlation analysis.

To test the capability of extracted fALFF to discriminate between GI-MDD patients and nGI-MDD patients, the support vector machine (SVM) method was applied. SVM is a common supervised machine learning model that can be applied to

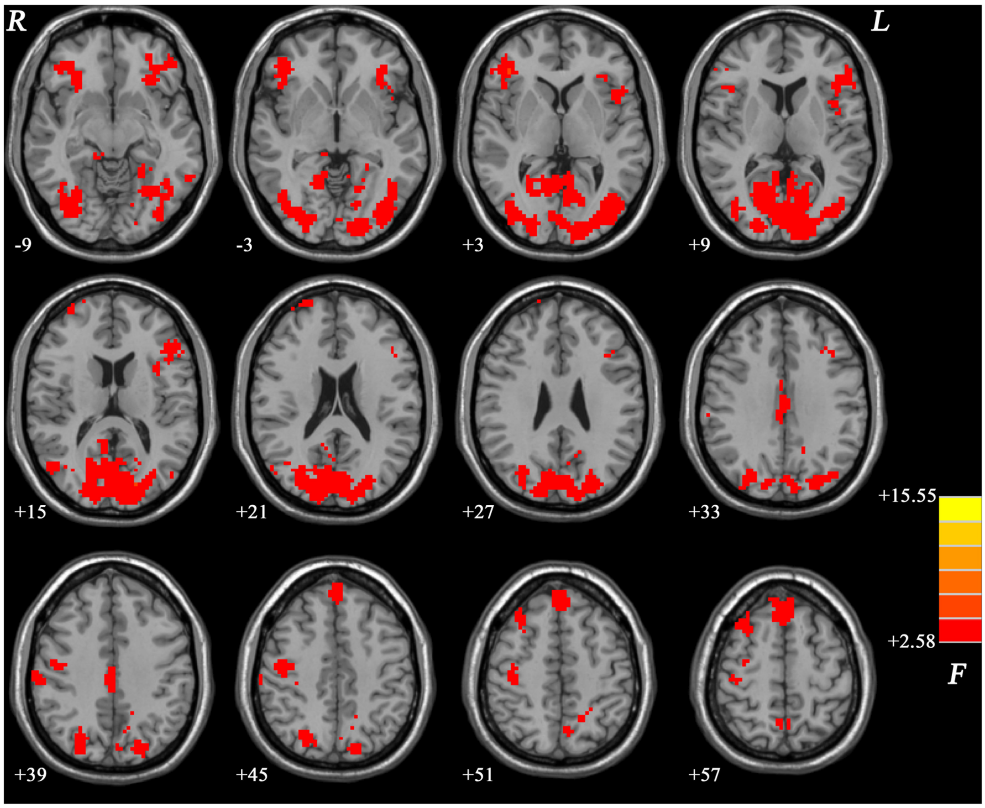

FIGURE 1 | Brain regions showing significantly different fALFF values across three groups at a false discovery rate (FDR)-corrected $p < 0.05$. The *color bar* indicates the *F* values based on ANCOVA. *fALFF*, fractional amplitude of low-frequency fluctuation; *ANCOVA*, analysis of covariance.

explore the best boundary between two categories to solve a binary classification problem. The analysis used a "leave-one-out" method and was conducted using the LIBSVM software package (23) in MATLAB.

RESULTS

Demographic and Clinical Data

No participant was excluded because of excessive head motion. **Table 1** presents the demographic and clinical data of the three groups. There was no significant difference in age, gender, or years of education across the three groups. GI-MDD patients and nGI-MDD patients did not differ in the duration of illness. GI-MDD patients had higher HRSD-17 total scores and scored higher with respect to insomnia, anxiety/somatization, and weight loss than did nGI-MDD patients. Except for the weight loss subscale, both patient groups exhibited higher scores in the HRSD-17 scale and four other subscales relative to HCs.

Group Differences in fALFF

We compared individual whole-brain fALFF across GI-MDD patients, nGI-MDD patients, and HCs. Significant differences in fALFF were displayed mainly in the frontal and occipital regions (**Figure 1**).

fALFF Differences Between GI-MDD Patients and nGI-MDD Patients

Compared with nGI-MDD patients, GI-MDD patients exhibited increased fALFF in the right superior frontal gyrus (SFG)/middle frontal gyrus (MFG) and decreased fALFF in the left superior MPFC (**Figure 2**, **Table 2**). There was no other significant difference in the fALFF between the two patient groups. Considering the potential effect that the severity of depression might be a confounding factor in the comparison, we further added the total score of HRSD-17 as a covariate in the between-group comparison and obtained similar results, suggesting that the severity of depression had limited effects on the results (**Figure S1, Table S1**).

fALFF Differences Between GI-MDD Patients and HCs

In GI-MDD patients, increased fALFF was found in the right MFG/inferior frontal gyrus (IFG) compared to HCs. Also, decreased fALFF was present in the right fusiform and left cuneus in GI-MDD patients (**Figure 3**, **Table 2**).

fALFF Differences Between nGI-MDD Patients and HCs

Compared with HCs, nGI-MDD patients showed higher fALFF values in the bilateral superior MPFC. Moreover, decreased

fALFF was shown in nGI-MDD patients in the bilateral middle occipital gyrus (MOG)/inferior occipital gyrus (IOG), as well as in the bilateral cuneus (**Figure 4**, **Table 2**).

Correlation Analysis

After assessment of normality, correlation analysis was conducted between the fALFF values and the scores of the HRSD-17, the scores of five subscales, and the severity of GI symptoms.

For all MDD patients, the fALFF values of the left superior MPFC showed an inverse correlation with the score of weight loss ($r = -0.404$, $p = 0.003$, corrected $p = 0.021$) (**Figure 5A**). In addition, the results showed that the severity of GI symptoms were positively correlated with fALFF in the right SFG/MFG ($r = 0.380$, $p = 0.005$, corrected $p = 0.023$) (**Figure 5B**) and negatively correlated with fALFF in the left superior MPFC ($r = -0.438$, $p = 0.001$, corrected $p = 0.014$) (**Figure 5C**).

For GI-MDD patients, the fALFF in the left superior MPFC was positively correlated with the total scores of HRSD-17 ($r = 0.356$, $p = 0.036$) and the scores in the anxiety/somatization aspect ($r = 0.377$, $p = 0.025$), but these correlations did not survive after correction.

No correlation was discerned in nGI-MDD patients between the fALFF values and the scores of the HRSD-17 or its subscales.

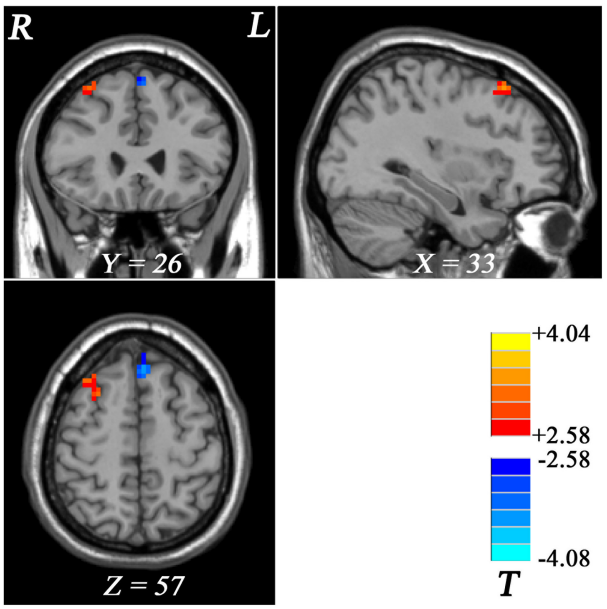

FIGURE 2 | Regional fALFF differences between GI-MDD patients and nGI-MDD patients. The *color bar* indicates the *t* values from *post-hoc t*-tests. *Red* and *blue colors* denote increased and decreased fALFF, respectively. *fALFF*, fractional amplitude of low-frequency fluctuation; *GI-MDD*, major depressive disorder with gastrointestinal symptoms; *nGI-MDD*, major depressive disorder without gastrointestinal symptoms.

SVM Results

We used SVM classifiers to explore features that could distinguish between GI-MDD patients and nGI-MDD patients. The clusters exhibiting significantly different fALFF values (right SFG/MFG and left superior MPFC), separately or together, were used as features. The results showed that classification based on the combination of the fALFF values in the right SFG/MFG and the left superior MPFC reached a higher accuracy (86.54%) than did those based on fALFF of the right SFG/MFG (76.92%) or the left superior MPFC (84.62%) alone. When using the fALFF values of the right SFG/MFG as the feature, the sensitivity and specificity were 94.29 and 41.18%, respectively. The sensitivity and specificity were 100 and 58.82%, respectively, when using the fALFF values of the left superior MPFC to discriminate between GI-MDD patients and nGI-MDD patients. The combination of the fALFF values of these two

TABLE 2 | Significant fractional amplitude of low-frequency fluctuation (fALFF) differences across three groups.

Cluster location	Peak (MNI)			No. of voxels	*t* value
	x	y	z		
GI-MDD vs. nGI-MDD					
Right superior frontal gyrus/middle frontal gyrus	33	24	54	35	3.3962
Left superior MPFC	−3	30	57	28	−3.5590
GI-MDD vs. HCs					
Right middle frontal gyrus/inferior frontal gyrus	39	36	0	55	5.1164
Right fusiform	36	−63	−15	47	−4.4455
Left cuneus	−18	−84	15	132	−4.6258
nGI-MDD vs. HCs					
Bilateral superior MPFC	0	39	57	178	5.1691
Right middle occipital gyrus/inferior occipital gyrus	36	−81	−9	50	−4.0813
Left middle occipital gyrus/inferior occipital gyrus	−36	−84	−3	106	−4.5530
Bilateral cuneus	0	−87	21	157	−4.6956

MNI, Montreal Neurological Institute; MPFC, medial prefrontal cortex; GI-MDD, MDD with gastrointestinal (GI) symptoms; nGI-MDD, MDD without GI symptoms; HCs, healthy controls.

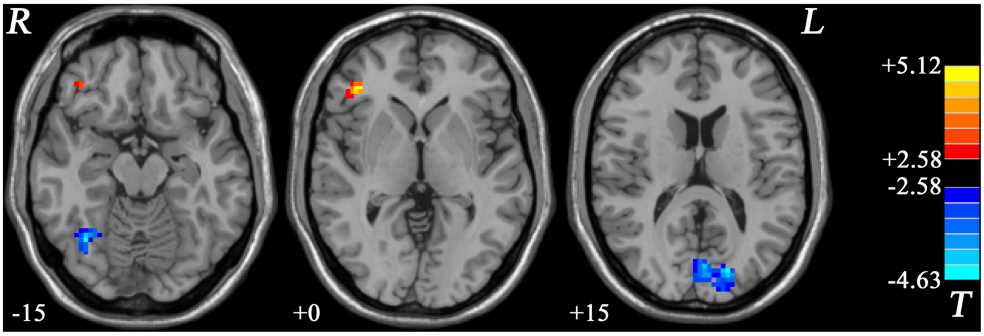

FIGURE 3 | Statistical maps showing the fALFF differences between GI-MDD patients and HCs. The *color bar* indicates *t* values from *post-hoc t*-tests. *Red* and *blue colors* denote increased and decreased fALFF, respectively. *fALFF*, fractional amplitude of low-frequency fluctuation; *GI-MDD*, major depressive disorder with gastrointestinal symptoms; *HCs*, healthy controls.

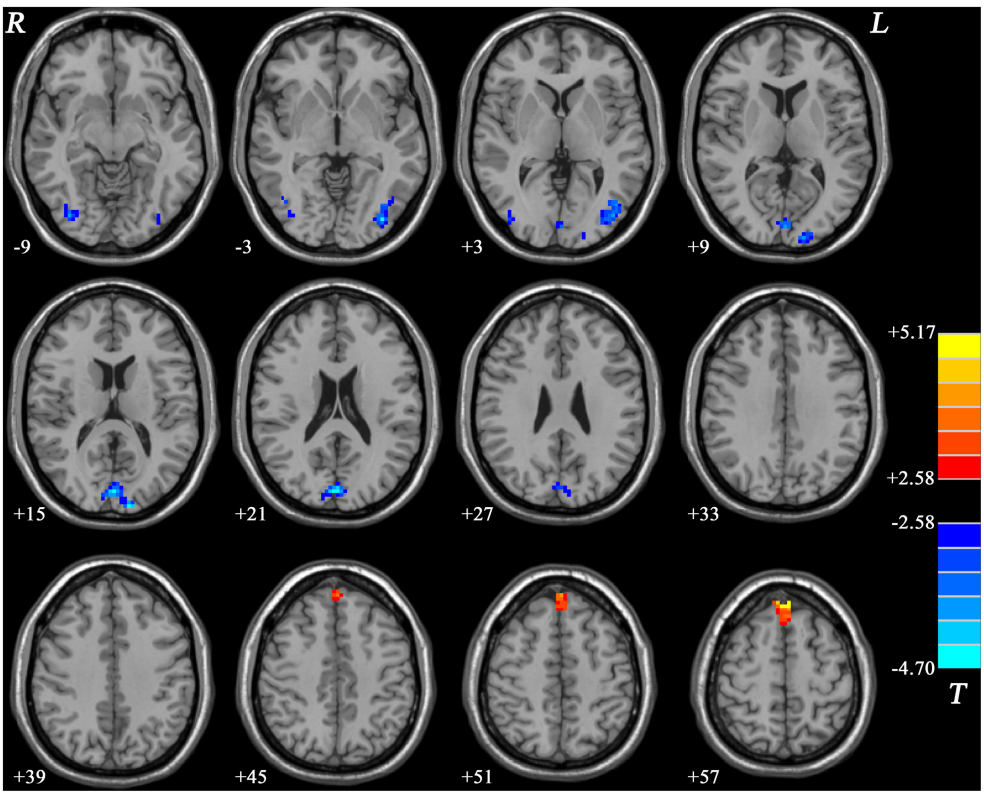

FIGURE 4 | Statistical maps showing the fALFF differences between nGI-MDD patients and HCs. The *color bar* indicates *t* values from *post-hoc t*-tests. *Red* and *blue colors* denote increased and decreased fALFF, respectively. *fALFF*, fractional amplitude of low-frequency fluctuation; *nGI-MDD*, major depressive disorder without gastrointestinal symptoms; *HCs*, healthy controls.

regions exhibited sensitivity and specificity of 94.29 and 70.59%, respectively (**Figure 6**).

DISCUSSION

This research showed that GI-MDD patients suffered a higher level of depression than nGI-MDD patients, especially in terms of insomnia, anxiety/somatization, and weight loss, which reinforced the negative effect of concomitant GI symptoms on MDD patients. More importantly, the fMRI results revealed that GI-MDD patients exhibited increased fALFF in the right SFG/MFG and decreased fALFF in the left superior MPFC compared to nGI-MDD patients. The SVM analysis exhibited that a combination of the fALFF values of these two regions could

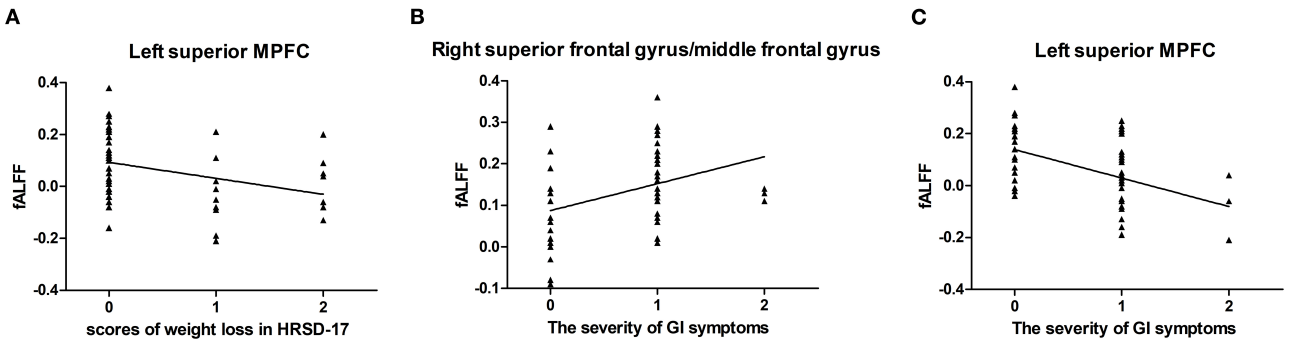

FIGURE 5 | Correlations between abnormal fALFF and clinical variables. For all MDD patients, a negative correlation was found between the scores of weight loss in HRSD-17 and the fALFF of the left superior MPFC **(A)**. The severity of GI symptoms was found positively correlated with the fALFF values of the right superior frontal gyrus/middle frontal gyrus **(B)** and negatively correlated with the fALFF values of the left superior MPFC **(C)**. *fALFF*, fractional amplitude of low-frequency fluctuation; *MDD*, major depressive disorder; *HRSD-17*, 17-item Hamilton Rating Scale for Depression; *MPFC*, medial prefrontal cortex.

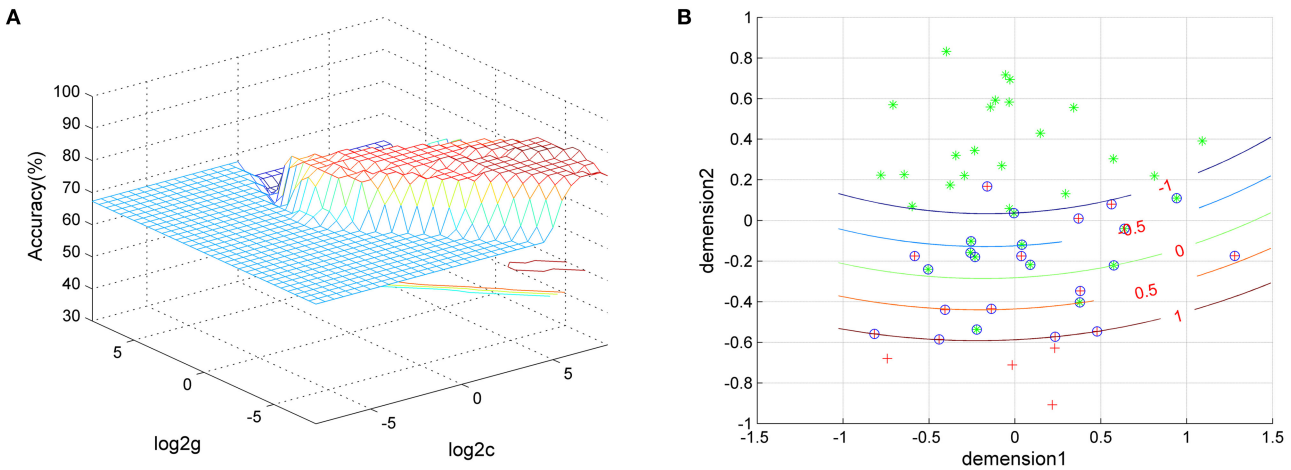

FIGURE 6 | Visualization of the classification using the combination of fALFF values of the left superior MPFC and the right superior frontal gyrus/middle frontal gyrus through SVM. **(A)** SVM parameter results with 3D view. **(B)** Classified map of the results. *Green crosses* represent GI-MDD patients and *red crosses* represent GI-MDD patients. *fALFF*, fractional amplitude of low-frequency fluctuation; *MPFC*, medial prefrontal cortex; *SVM*, support vector machine; *GI-MDD*, major depressive disorder with gastrointestinal symptoms; *nGI-MDD*, major depressive disorder without gastrointestinal symptoms.

discriminate between GI-MDD patients and nGI-MDD patients with accuracy, sensitivity, and specificity of 86.54, 94.29, and 70.59%, respectively.

Our results found that GI-MDD patients obtained higher scores in the HRSD-17 and its subscales on insomnia, anxiety/somatization, and weight loss, which suggested that GI symptoms were related to a higher level of depression. Other research papers have reported similar results (5, 6, 24). A multicenter study found that GI symptoms made patients almost five times more likely to be subject to severe depression and nearly four times more likely to undergo severe anxiety (6). Another research studying 3,256 MDD patients in China reported that increased frequency of GI symptoms showed a correlation with higher possibilities of anxiety, depression, and insomnia (5). In patients with FGIDs, as the number of FGIDs and the severity and frequency of the GI symptoms increased, the risk of depression and anxiety increased in a stepwise manner (24). These studies indicated that concomitant GI symptoms would negatively influence the course of MDD. The gut–brain axis concept provides a possible Mechanism by which gut microbiota could play a crucial role in the development of diseases, including depression. The two-way communication between the GI tract and the brain has been widely recognized. For instance, the gut microbiota can regulate the function of the hypothalamic–pituitary–adrenal (HPA) axis and directly influence the function of the central neural system through the activation of neurons in the stress circuits (12). Some experiments and clinical trials have found that probiotic treatment is helpful in reducing depressive behavior (25–27). Therefore, the management of GI symptoms is of great clinical significance in the treatment and prognosis of MDD.

The fALFF, related to cerebral blood flow, reflects the spontaneous neuronal activity. In this study, GI-MDD patients displayed increased fALFF in the right SFG/MFG compared with nGI-MDD patients. For all MDD patients, the fALFF values of the right SFG/MFG positively correlated with the severity of GI symptoms. The results also showed that fALFF was higher in the right MFG/IFG in GI-MDD patients compared to HCs. These findings suggested that the frontal lobe, especially the MFG, might have a close connection to GI symptoms in MDD. The study of Geng et al. showed altered ReHo in the right MFG in MDD patients with somatic symptoms (28). In GI-MDD patients, decreased gray matter volume (GMV) and ReHo in the right SFG and MFG were also found (19). It is considered that the MFG is critical for bottom-up sensory-driven exogenous attention. Reorienting to unpredicted stimuli can activate the right MFG (29). Some researchers have proposed that the MFG serves as the gatekeeper between the dorsal attention network and the ventral attention network, and it could interact with both networks and interrupt processes of goal-directed attention to reorient to stimulus-driven attention (30). It is speculated that patients with FGIDs selectively attend to GI sensations, and this selective attention or hypervigilance may lead to hyperalgesia (31). Patients with IBS relative to HCs exhibited greater brain response in the MFG when they were in contextual threat of abdominal electrical stimulation, suggesting inappropriate allocation of attentional resources (32). Therefore, abnormal fALFF in the right MFG might be associated with hypervigilance and attentional bias toward visceral interoceptive sensations.

Numerous studies have supported the connection between depression and the default-mode network (DMN), which includes the MPFC, posterior cingulate cortex, and the inferior parietal lobe (33, 34). Among these regions, MPFC is closely related to chronic stress and self-focus, both of which are risk factors of depression (35–37). We found decreased fALFF in the left superior MPFC in GI-MDD patients compared to nGI-MDD patients. The fALFF values of the left superior MPFC showed inverse correlations with the scores of weight loss and the severity of GI symptoms. Also, a higher fALFF was exhibited in the bilateral superior MPFC in nGI-MDD patients compared to HCs. These results implied that MPFC was not only related to MDD but also involved in the GI symptoms of MDD. MPFC has gained consensus for having an involvement in MDD (38). Our previous research reported that the left superior MPFC showed an increased DMN homogeneity in first-episode, drug-naive MDD patients, and this finding was replicated in two other separate but similar samples (39, 40). Thus, an altered functional activity in the left superior MPFC might reflect the core neuropathological mechanism in MDD. It is widely considered that self-focus features prominently in patients with MDD, accompanied by increased rumination thinking and negative affectivity (41, 42). MPFC is of great importance in processing emotion and self-related information (43, 44). A meta-analysis exploring the neural substrates of rumination found that rumination-related hyperactivation included the core and the dorsal MPFC subsystems of the DMN (45). Moreover, impaired function of the MPFC, together with the dorsolateral prefrontal cortices, was associated with deficiencies in executive function and effortful regulation of behavior and emotional state, which might lead to depressed mood and anhedonia (46). These findings indicated that abnormal functional activity of the left superior MPFC might be a possible biomarker for MDD.

The MPFC was reported to have portions of cortical neurons that control the parasympathetic output of the stomach (47). In addition, the MPFC was found to be related to the development of stress-induced gastric mucosal lesion (SGML) (48). This might be the reason for the abnormal functional activity of MPFC having been observed in mental illness with somatic symptoms, including GI symptoms. Increased connectivity between the left superior MPFC and the lobule IX was found in patients with somatization disorder (49). Patients with somatization disorder had increased fALFF in the bilateral superior MPFC compared to HCs (50). A study investigating the functional activity of the brain in hyperalgesia reported increased activity in the MPFC in central sensitization, which is a state of high reactivity of the nervous system resulting in hypersensitivity to pain, and this hyperactivity could be suppressed with antihyperalgesic treatment (51). It seems to be in line with our results as some studies have proposed that FGIDs are often comorbid with hyperalgesia (38). In a paper on the abnormalities of regional brain activity in IBS, decreased ALFF in the MPFC and altered functional connectivity of the MPFC were found in IBS patients, and the aberrant ALFF was not eliminated when anxiety and depression were set as covariates (52). Therefore, a decreased ALFF in the left superior MPFC might have a connection with hyperalgesia, which could be induced by chronic psychological stress and serve as an important pathophysiological component underlying FGIDs (53–56).

Decreased fALFF was shown in nGI-MDD patients in the bilateral cuneus and the bilateral MOG/IOG compared to HCs. Decreased fALFF has also been found in the left cuneus in GI-MDD patients compared to HCs, which suggested that the hypoactivity of these regions was important in the pathogenesis of MDD. Structural and functional changes of the occipital lobe are not rare in MDD patients. Reductions in the volume of the bilateral MOG and the right IOG have been described in MDD (57). A study interested in occipital bending, a type of structural asymmetry of the brain where one occipital lobe wraps across the midline, found that the prevalence of occipital bending was three times higher in MDD patients than in controls (58). As for the functional abnormality of the occipital lobes, it was reported that both unipolar depression and bipolar depression shared ReHo changes in the cuneus (59). Decreased fALFF in the occipital cortex was also found in our previous study on MDD patients (60). In addition, a graph-based analysis study revealed that MDD patients showed abnormal nodal degree in the occipital cortex, suggesting altered regional connectivity of the occipital cortex (61). It has been reported that the γ-aminobutyric acid (GABA) levels in the occipital cortex decreased in MDD patients and that selective serotonin reuptake inhibitors (SSRIs) could reverse this reduction (62, 63). Moreover, the occipital lobe contributes to visual-induced emotional information processing and the perception of facial emotion (44, 64). Depressive adolescents exhibited distorted processing of emotion- and self-related visual information (65).

Chechko et al. found that the bilateral MOG and IOG showed greater activation in an emotional conflict task (66). However, unmedicated patients with MDD showed poor accuracy and lower functional activity in the MOG and IOG in an emotional conflict task (64). Therefore, our findings, in line with these studies, suggested that aberrant activity in the occipital cortex was possibly related to the disrupted visual-induced emotional information processing in MDD patients.

The right fusiform gyrus only exhibited decreased fALFF in GI-MDD patients compared to HCs. The fusiform gyrus is an important structure in processing high-order visual information such as face perception (67). The study of Liu et al. has reported increased ReHo in the right fusiform gyrus in GI-MDD patients (19). But the findings on the right fusiform gyrus in patients comorbid with MDD and GI symptoms were not consistent (20). A study on brain structural alterations reported that patients without GI symptoms displayed increased regional GMV and gray matter density (GMD) in the right fusiform gyrus compared to HCs (68). Thus, the association between GI symptoms in MDD and the fusiform is still vague. But several studies found structural or functional deficits of the fusiform gyrus in MDD patients (69–72). An imaging meta-analysis also reported decreased ALFF in the right fusiform gyrus in MDD patients (73).

We should note some limitations. Firstly, we did not further categorize patients according to their GI symptoms to discover the distinction of the brain functional changes between patients with different GI symptoms because of the small sample size. Secondly, only one item in the HRSD-17 was used to assess the severity of GI symptoms. Although some previous works have also used this evaluation approach (1, 2), it would be better to use a more specific scale to evaluate GI symptoms. Thirdly, this is a cross-sectional study, so it is a theme worth discussing that the abnormality of fALFF is the driver of GI symptoms in MDD or a consequence. Longitudinal research is needed to deepen the awareness of the pathophysiological features of MDD co-occurring with GI symptoms.

CONCLUSION

This study reinforced the negative effect of concomitant GI symptoms on MDD patients. Our findings exhibited the shared and distinct patterns of functional changes in MDD patients with and without GI symptoms. The fALFF values in the right SFG/MFG and the left superior MPFC were distinct between MDD patients with and without GI symptoms, which suggested a possible association of the functional activity in these regions with MDD-related GI dysfunction.

DATA AVAILABILITY STATEMENT

The data in this study are available upon request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Research Ethics Committee of the Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XF wrote the manuscript. HL conducted the study. MY, JC, FL, and JZ contributed to managing and analyzing the imaging data. WG designed the study and analyzed the data. All authors contributed to and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.744898/full#supplementary-material

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