Is there any difference in the fractional amplitude of low-frequency fluctuations between first episode major depressive disorder patients and subclinical depressive subjects?

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Research article

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Abstract

Background

To explore the differences in the fractional amplitude of low-frequency fluctuations (fALFF) at the whole-brain level between young adults with major depressive disorder (MDD) and those with Subclinical depression (SD).

Methods

Thirty-nine first-episode MDD patients, 30 SD subjects, and 37 healthy controls (HCs) were recruited. All participants underwent resting-state fMRI (Rs-fMRI) scans on a 3T MR scanner. We used the fALFF to explore spontaneous neuronal activity between groups.

Results

Significant differences in the fALFF were observed among the three groups. Compared with the HCs, an increased fALFF was found in the left cerebellum in MDD patients. When MDD patients were compared with SD subjects, we observed increased fALFF values in the bilateral fusiform gyrus and decreased fALFF values in the right inferior frontal gyrus, right superior frontal gyrus, right middle frontal gyrus, left cuneus and right precuneus. Compared with the HCs, the SD group demonstrated increased fALFF values in the precuneus. Additionally, a positive correlated was revealed between the fALFF values and Hamilton Anxiety Scale (HAMA)score in the right fusiform gyrus in MDD patients. Moreover, the fALFF value were negatively correlated with the Beck Depression Inventory (BDI) score in the right inferior frontal gyrus and with the age in the left fusiform gyrus in SD subjects.

Conclusions

Our findings suggest that alterations of cognitive and executive networks, default mode networks and visual recognition circuits may contribute to the different neural mechanisms between MDD and SD in young adult subjects.

1. Background

Major depressive disorder (MDD) is a common psychiatric illness with a high morbidity worldwide and has a larger far-reaching influence on total life [1]. Subclinical depression (SD) is considered a minor depressive condition with some depressive symptoms but does not meet the full criteria of clinical MDD depressive [2, 3] and has been identified as prodromal to MDD [4, 5]. It was found that the incidence of SD has been increasing among young adults, especially college students [6]. Recently, SD has attracted increasing attention from researchers as leading to a decrease in quality of life [7] and resulting in vast

economic costs [8]. It is sometimes difficult to differentiate SD and MDD due to their similar psychiatric symptoms. A number of studies have shown that psychological treatments are effective for SD [3]. However, MDD more often requires other treatment measures, such as antidepressant treatment, electroconvulsive therapy [9], or cognitive behavioral therapy (CBT) [10]. Therefore, understanding the differences in the neural bases between MDD and SD could be important in early diagnosis and the choice of the appropriate treatment. However, the exact relationship between the two conditions remains poorly understood.

In recent years, most studies have focused on examining the neural correlates between mental illnesses by using resting-state functional magnetic resonance imaging (Rs-fMRI), which can reflect correlations of activity between brain areas and provide new insights into the pathophysiology of depression [11, 12]. Several Rs-fMRI studies have reported that subclinical depression shows abnormal connections in the thalamus [6] and lateral habenula [6, 13], decreased degree centrality in subcortical regions [14], and a severity that is related to the distinct functional connectivity within the anterior cingulate cortex (ACC) [15].

Several approaches have been used to analyze Rs-fMRI data. Among them, functional connectivity (FC) analysis is the most popular strategy for measuring the temporal synchrony of LFOs among anatomically distributed brain regions and has been widely used in SD[16, 17] and MDD studies [18, 19]. Recently, a more straightforward approach, known as the amplitude of low-frequency fluctuations (ALFF), aims to measure the amplitude of low-frequency oscillations (LFOs) quantitatively and has attracted much interest in detecting local blood-oxygen level dependent (BOLD) signal variations due to regional spontaneous activity [20, 21]. Following the implementation of the ALFF approach, a modified method named fractional ALFF (fALFF), defined as the amplitudes of the fluctuations in the low-frequency (0.01–0.08 Hz) range divided by those in the entire frequency range, was implemented; the fALFF has higher sensitivity and specificity to spontaneous neural activities than ALFF because it can selectively suppress physiological noise and nonspecific signals [22, 23]. To date, a number of studies have used fALFF to explore alterations in spontaneous activity in MDD patients [24–26]. However, to the best of our knowledge, no study has attempted to explore the difference in spontaneous neuronal activity between SD and MDD using the fALFF strategy.

In our current study, we used the fALFF to determine whether there are any differences in spontaneous neuronal activity between MDD and SD, as well as to explore how those differences could contribute to the intrinsic neural mechanism of depression. Furthermore, we explored whether a neurological marker can be found to predict the possibility of SD progressing to MDD.

2. Methods

2.1 Participants

We recruited 39 MDD patients (10 males, 29 females, aged from 13 years to 33 years) from the First People's Hospital of Guangzhou, China. Thirty SD subjects (11 males, 19 females) and 37 healthy controls (HCs) (18 males, 19 females) were recruited from Guangzhou Medical University. Given that clinical and subclinical depression are different in terms of assessment, in this study, we used the Hamilton Depression Scale (HAMD) and Paper's Hamilton Anxiety Scale (HAMA) to assess the symptoms of the clinically depressive patients. For SD subjects, the Beck Depression Inventory II (BDI-II) scale was adopted to evaluate depression symptom severity. MDD patients were eligible if they met the following criteria: 1) the Statistical Manual of Mental Disorders IV (DSM-IV) criteria for MDD. 2) first episode of illness without any psychotropic medication treatment. 3) no history of neurological or systemic illness, head injury or any other relevant medical or additional psychiatric disease. Participants with a BDI-II score > 13 were placed into the SD group; none of them matched the diagnostic criterion of DSM-IV, and none had a history of psychiatric disorders. Healthy controls who had no psychiatric diagnoses were eligible (Table 1). Other inclusion criteria for all participants included age (range from 13 to 32 years), right-handedness, no organic lesions in the brain and no alcohol or drug dependence. All subjects completed informed consent forms, and the study was approved by the First People's Hospital of Guangzhou.

Table 1
Demographics of normal control, patients with sub-clinical depression and patients with major depression groups

Variables	control (n = 37)	Sub-clinical depression (n = 30)	Major depression (n = 39)	*p*
Gender (Male/Female)	18/19	11/19	11/28	0.172[a]
Age (Mean ± SD Years)	19.19 ± 0.149	19.69 ± 0.314	20.92 ± 0.996	0.552[b]

Note: SD, standard deviation. a p value obtained by using Chi-Square test among three groups. b p value for comparison between-groups differences obtained by using Kruskal-Wallis H test.

2.2 MR data acquisition

The fMRI measurements were obtained on a 3 T Siemens Verio scanner (Siemens, Erlangen, Germany) equipped with a 16-channel phased-array head coil. The Rs-fMRI parameters were as follows: repetition time (TR) = 2500 ms, echo time (TE) = 21 ms, flip angle (FA) = 90°, field of view (FOV) = 200 mm × 200 mm, matrix = 64 × 64, 42 axial slices, and voxel size = 3.5 mm × 3.1 mm × 3.1 mm. High-resolution T1-weighted structural images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 2530 ms, TE = 2.93 ms, FA = 7°, FOV = 256 mm × 256 mm, and a slice thickness of 1.0 mm with no gap. During the Rs-fMRI scanning, participants were asked to close their eyes but not to fall asleep. After MR scanning, they completed a simple questionnaire to confirm their wakefulness during the scanning.

2.3 MR data preprocessing

Rs-fMRI data preprocessing was carried out using the Data Processing Assistant for Rs-fMRI (DPARSF, http://www.rest.restfmri.ne) [27]. Most of the functions are based on Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Consistent with our previous work, for Rs-fMRI signal equilibrium and for the subjects to adapt to the scanning noise, the first 10 functional volume images of each subject were removed. Slice timing correction was conducted for the remaining 190 volume images. All subjects were allowed head motion only within 2 mm of movement or 2° rotation in any direction. Then, the 3D structural images were placed into the standard Montreal Neurological Institute (MNI) space provided by SPM8, which was used for spatial normalization with a resampling voxel size of 3 mm × 3 mm × 3 mm. The white matter, cerebral spinal fluid signal and the Friston 24 head-motion parameters were regressed out from the time series of every voxel. Then, a 4-mm full-width at half-maximum (FWHM) Gaussian kernel was used for spatial smoothing, the effects of low-frequency drift and high-frequency noise (e.g., respiratory and cardiac noise) were reduced by temporal bandpass filtering (0.01–0.08 Hz) of the functional data, and linear trending of the data was removed.

2.4 fALFF calculation

The fALFF analyses were calculated by using DPARSF software [23]. Following the above preprocessing, the resulting time series was transformed into the frequency domain by fast Fourier transform, and the power spectrum was obtained. The square root at each frequency of the power spectrum was calculated, and the averaged square root was obtained across the 0.01–0.08 Hz range at each voxel. The fALFF approach has been confirmed to be effective in wiping out confounding signals [23]. We used fALFF massage to characterize the magnitude of spontaneous brain activity. Gray matter (GM) analyses were performed on computation and subsequent statistical analysis.

2.5 Statistical analysis

One-way ANOVA or the chi-squared test with post hoc analysis was used to determine group differences in demographic and clinical characteristics. $P < 0.05$ was considered to be statistically significant. For the fALFF metrics, nonparametric permutation tests were performed, and age and gender were included as covariates. The post hoc analyses were also implemented using nonparametric permutation tests to compare differences between each pair of groups within a mask including all the significant clusters in the ANOVA. All results were presented at the statistical threshold of $P < 0.01$ using the AFNI AlphaSim program correction, as determined by Monte Carlo simulations (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim. pdf), which was used to calculate the probability of false positive detection while accounting for both the individual voxel probability thresholding and cluster size (FWHM = 6 mm). Using this program, clusters of greater than 40 voxels were applied to the resulting statistical map at a corrected significance level of $P < 0.01$. We compared the fALFF values extracted from the brain areas with significant differences in the two groups. Then, we performed correlation analyses between the mean changes in symptom scores (including total HAMD scores, HAMA scores and BDI scores) and mean fALFF values in the brain areas. An uncorrected threshold of $p < 0.05$ was required for statistical significance.

3. Results

3.1 Demographic information and depressive assessment

As shown in Table 1, there were no significant differences in terms of gender, sex, or education level ($p>0.05$).

3.2 Differences in brain fALFF among the three groups

Mean fALFF maps of the MDD, SD, and HC groups were calculated (Figure 1a-c), and ANOVA showed significant fALFF differences among the three groups spread over 5 clusters (Figure 1d). The post hoc analyses were as follows.

3.2.1 MDD vs HC

Compared with HCs, MDD patients showed higher fALFF in the left cerebellum ($p<0.05$, corrected). Table 2 and Figure 2,

3.2.2 MDD vs SD

Compared with the SD subjects, the MDD subjects exhibited increased fALFF in the bilateral fusiform gyrus and decreased fALFF in the right inferior frontal gyrus, right middle frontal gyrus, right superior frontal gyrus, left cuneus and precuneus (Tables 2 and Figure 2).

3.2.3 HC vs SD

Compared with the SD subjects, the HCs showed decreased fALFF in the precuneus (Tables 2 and Figure 2).

3.3 Correlation of fALFF values with depressive assessment

A positive correlation between the mean fALFF values and HAMA scores was observed in the right fusiform in the MDD subjects ($r=0.354$, $p=0.027$). In addition, we found a positive correlation between the fALFF values and the PANNS score in the right middle frontal gyrus in the MDD subjects ($r=0.424$, $p=0.007$). For the SD subjects, we found a negative correlation between the fALFF values and the BDI scores in the right inferior frontal gyrus ($r=-0.394$, $p=0.034$) (Figure 3).

4. Discussion

We explored the differences in spontaneous activity between MDD and SD subjects and HCs using Rs-fMRI data and the fALFF analysis approach. Our findings indicated alterations in the fALFF in the right lateral prefrontal frontal lobes (PFC), the default mode networks (DMN) and the fusiform areas. In addition, there was a positive correlation between the fALFF value and the HAMA score in the right fusiform gyrus and a positive correlation between the fALFF value and the PANNS score in the right

middle frontal gyrus in MDD patients. Moreover, a negative correlation was revealed between fALFF values and the BDI score in the right inferior frontal gyrus in SD subjects. These data provide new insights into the neural mechanisms of SD and MDD.

We observed many prefrontal, occipital and parietal areas with fALFF alterations in MDD patients compared with those in SD patients, including the fusiform gyri, right prefrontal gyri, cuneus and precuneus. The fusiform gyrus, a common component of visual recognition circuits, is thought to be involved in facial processing [28]. Similar to previous studies [29, 30], increased fALFF was found in the bilateral fusiform gyri in first-episode, treatment-naive patients with MDD in our study. It is suggested that the recognition of facial expressions in MDD is altered as a result of this compensatory increase. In addition, previous studies reported a negative emotional bias related to the right fusiform gyrus in MDD [31–33] and conversely to the left fusiform gyrus in SD subjects [34]. There was a positive correlation between depressive symptom severity and fALFF in the right fusiform in the MDD subjects in our study. In line with these results, we suggest that the fALFF values of the fusiform might be a biomarker for distinguishing MDD from SD.

Of note, MDD subjects exhibited decreased fALFF in multiple areas of the right PFC in the present study. The PFC areas have been most consistently identified as being closely related to MDD [35, 36], and each distinct subregion of the PFC plays a different critical role in the cognitive bias of MDD [30]. The altered PFC regions in our study mainly consisted of the dorsal lateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and the premotor areas. The VLPFC, including the inferior frontal gyrus, is a critical region in cognitive processing, and the DLPFC is a component of the cinguloopercular network [37] and plays an important role in executive control [38]. In addition to individuals with MDD, SD subjects have shown reduced gray matter volume and white matter in the PFC [39, 40] and have displayed negative-word processing in the prefrontal lobe [41]. Moreover, in the correlation analysis, we found a positive correlation between the fALFF values of the right middle frontal gyrus and depressive symptom severity in the MDD group. This indicates that the right middle frontal gyrus may be vital to and plays a role in executive function, and its fALFF values can also be used as a biomarker for differentiating MDD and SD. Interestingly, our results showed a negative correlation between fALFF values in the inferior frontal cortex and BDI scores in SD subjects. The inferior frontal cortex has been linked to premotor cortical areas and related to executive function in depression [42]. Thus, we speculate that this area might be a target area for a treatment strategy for executive function recovery in preventing SD from developing into MDD.

Apart from the PFC, we observed decreased fALFF in the left cuneus in MDD subjects compared with that in SD subjects. The cuneus is a part of the visual recognition circuit [43], and its dysfunctional connectivity has been a target of antidepressant treatment effects [44]. MDD patients also exhibit decreased gray matter volume in the cuneus [45]. In contrast to a previous study that revealed increased fALFF in the left cuneus in MDD compared with that of control subjects [43], we observed decreased fALFF in the left cuneus in MDD subjects compared with that in SD subjects. We speculate that this may represent a compensatory increased function of visual recognition in SD subjects. As expected, we

observed decreased fALFF in the precuneus in MDD and SD subjects. The precuneus is a core node in the DMN [46], is involved in the processing of self-relevant information [47] and is associated with deficits in general autobiographical memory [48]. Previous studies have shown that the fALFF values in the right precuneus have a negative correlation with the number of depressive episodes [49]. Our findings support the role of the DMN in the neural mechanisms of both SD and MDD. Compared with that of MDD subjects and HCs, the precuneus of SD subjects presented consistent abnormal fALFF. This indicates the key role of the DMN in the neural basis of SD.

Consistent with a previous study [30], our findings demonstrated an increased fALFF in the left cerebellum in MDD patients compared with that of HCs. The cerebellum was reported to play a role in emotional and cognitive processes in recent depression studies [50–53] and to have connections with the limbic regions [54]. Moreover, frontocerebellar dysregulation has been found in adolescents with MDD [55]. Increased activation in the cerebellum at rest [55, 56] and during reduced activity were reported in the frontal regions in MDD patients [57]. Specifically, the anterior cerebellum may be related to the depression remitted process [51, 53, 58]. The neurological mechanism of cerebellar dysfunction is not completely understood, and future functional and structural connectivity analyses will be helpful in identifying the correlation between the cerebellum and other brain areas.

In addition to a relatively small sample size, other limitations should be noted. First, we only recruited young adults in the present study, and it is unclear whether the findings observed here will generalize to older or younger samples. Second, given that the clinical and subclinical conditions are different, we used different rating scales to assess their depressive severity within the groups. Therefore, the difference in the rating scales may influence the results. Third, as a cross-sectional study, we cannot ensure the clinical consistency of the MDD patients because the patients were all in the first episode of their illness, and some of them may develop bipolar disorder in subsequent years. Similarly, the relatively mild depressive symptoms of the SD subjects are not stable and might transform over time; thus, a longitudinal study is required to better address the results.

5. Conclusion

To the best of our knowledge, this is the first study using fALFF to explore spontaneous neural activity in young adults with MDD and SD. We presented novel results linking young adults with MDD and SD by using fALFF. Our findings indicated alterations of fALFF in the right lateral prefrontal frontal lobes, default mode networks (DMN) and fusiform areas. These data provide new insight into the neural mechanisms of SD and MDD.

Abbreviations

MDD, major depressive disorder; SD, subclinical depression; HCs, healthy controls; fALFF, fractional amplitude of low-frequency fluctuations; Rs-fMRI; resting-state functional magnetic resonance imaging; DMNs, default mode networks; CBT, cognitive behavioral therapy; ACC, anterior cingulate cortex; FC,

functional connectivity; LFOs, low-frequency oscillations; BOLD, blood-oxygen level dependent; HAMD, hamilton depression scale; HAMA, hamilton anxiety scale; BDI-II, beck depression inventory II scale; DSM-IV, statistical manual of mental disorders IV.

Declarations

Ethics approval and consent to participate

All subjects completed informed consent forms, and the study was approved by the First People's Hospital of Guangzhou. For the participation of the child, all legal guardians give written informed consent following comprehensive oral and written information about the study.

Consent for publish

All the authors listed have approved the manuscript to publish.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XW and LZ were responsible for the conception, study design FX and XR contributed to the Collection of data and were major contributor in writing the manuscript; GZ and LY performed the data analyses and modify the article. XC and LE helped to provide qualified patients. YD and XJ helped perform the analysis with constructive discussions.

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Availability of data and materials

The datasets during the current study available from the corresponding author on reasonable request.

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Tables

Table 1. Demographics of normal control, patients with sub-clinical depression andpatients with major depression groups

Variables	control (n=37)	Sub-clinical depression (n=30)	Major depression (n=39)	*p*
Gender (Male/Female)	18/19	11/19	11/28	0.172[a]
Age (Mean ± SD Years)	19.19±0.149	19.69±0.314	20.92±0.996	0.552[b]

Note: SD, standard deviation. a p value obtained by using Chi-Square test among three groups. b p value for comparison between-groups differences obtained by using Kruskal-Wallis H test.

Table 2. Differences in fragment amplitude of fALFF between normal control, subclinical depression and major depression groups.

Brain Region	BA	Cluster Size (voxels)	Peak MNI Coordinates (mm)			*T* Value
			X	Y	Z	
Major depression vs Healthy controls						
Cerebelum_6_L	37	8	-27	-57	-24	3.843
Major depression vs Subclinical depression						
Fusiform_R	36	8	24	0	-42	3.9851
Fusiform_L	37	8	-48	-54	-21	4.4279
Frontal_Inf_Oper_R	48	18	60	15	3	-4.2554
Frontal_Mid_R	45	12	42	39	9	-4.4235
Cuneus	18	12	0	-78	24	-3.8583
Precuneus	NA	33	12	-48	36	-4.271
Frontal_Mid_R	8	9	27	21	51	-4.1831
Frontal_Sup_R	6	8	21	0	60	-3.7469
Control vs subclinical depression						
Precuneus_R	NA	31	6	-48	42	-4.025

Note: BA, Brodmann's area; MNI, Montreal Neurological Institute; Frontal_Inf_Oper_R, Right inferior frontal gyrus, opercular part; Frontal_Mid_R, Right middle frontal gyrus; Frontal_Sup_R, Right superior frontal gyrus; L, Left; R, Right; N/A, not available.

Figures

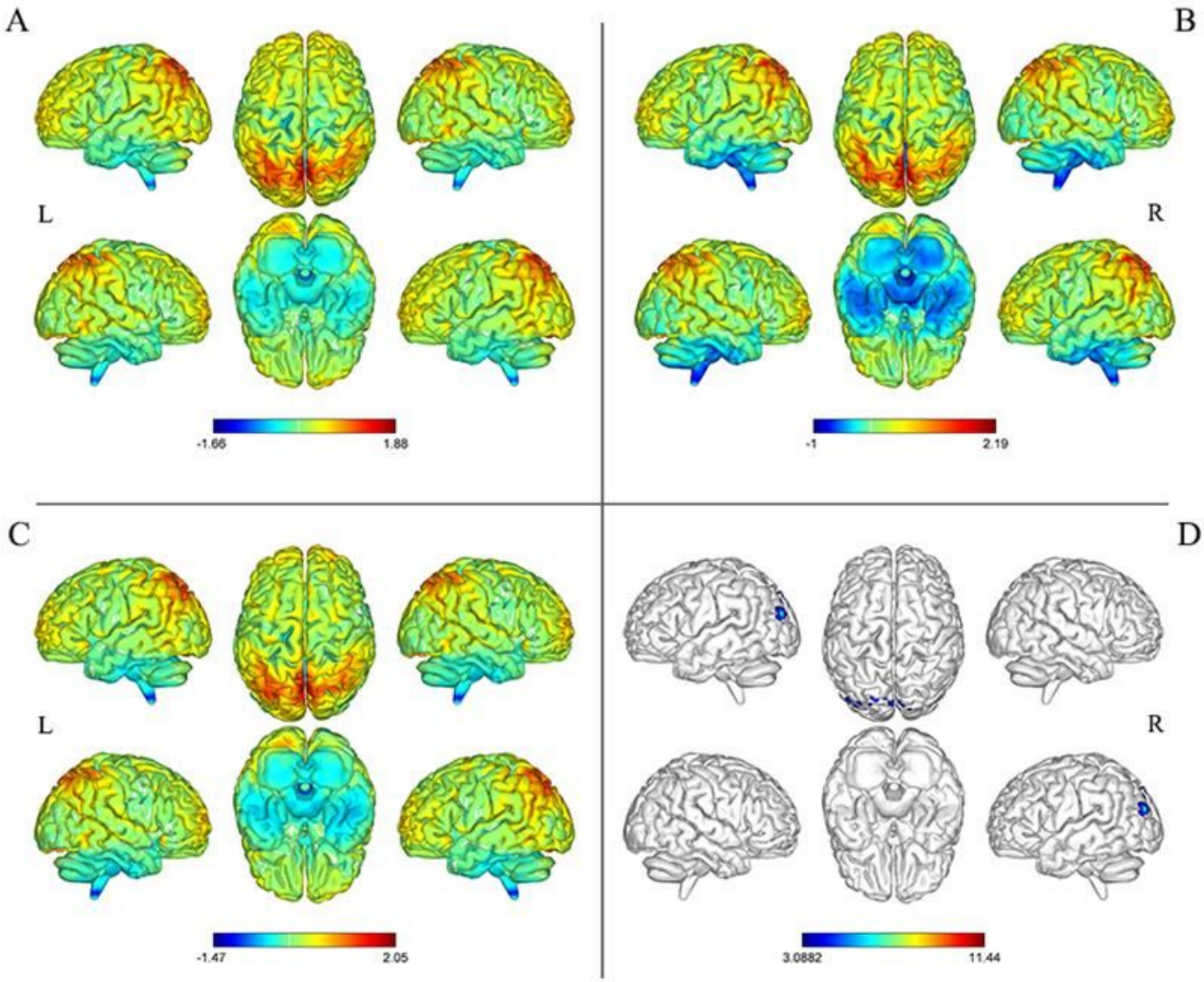

Figure 1

Within-group mean fALFF differences among the MDD, SD and HC groups. (A-C) Mean fALFF maps of the MDD, SD, and HC groups; (D) ANOVA results showing fALFF differences across the three groups. fALFF, fractional amplitude of low-frequency fluctuations; MDD, major depression; SD, subclinical depression; HC, healthy controls; L, left; R, right. These rendered brain surface images were visualized using BrainNet Viewer (http://www.nitrc.org/projects/bnv/)

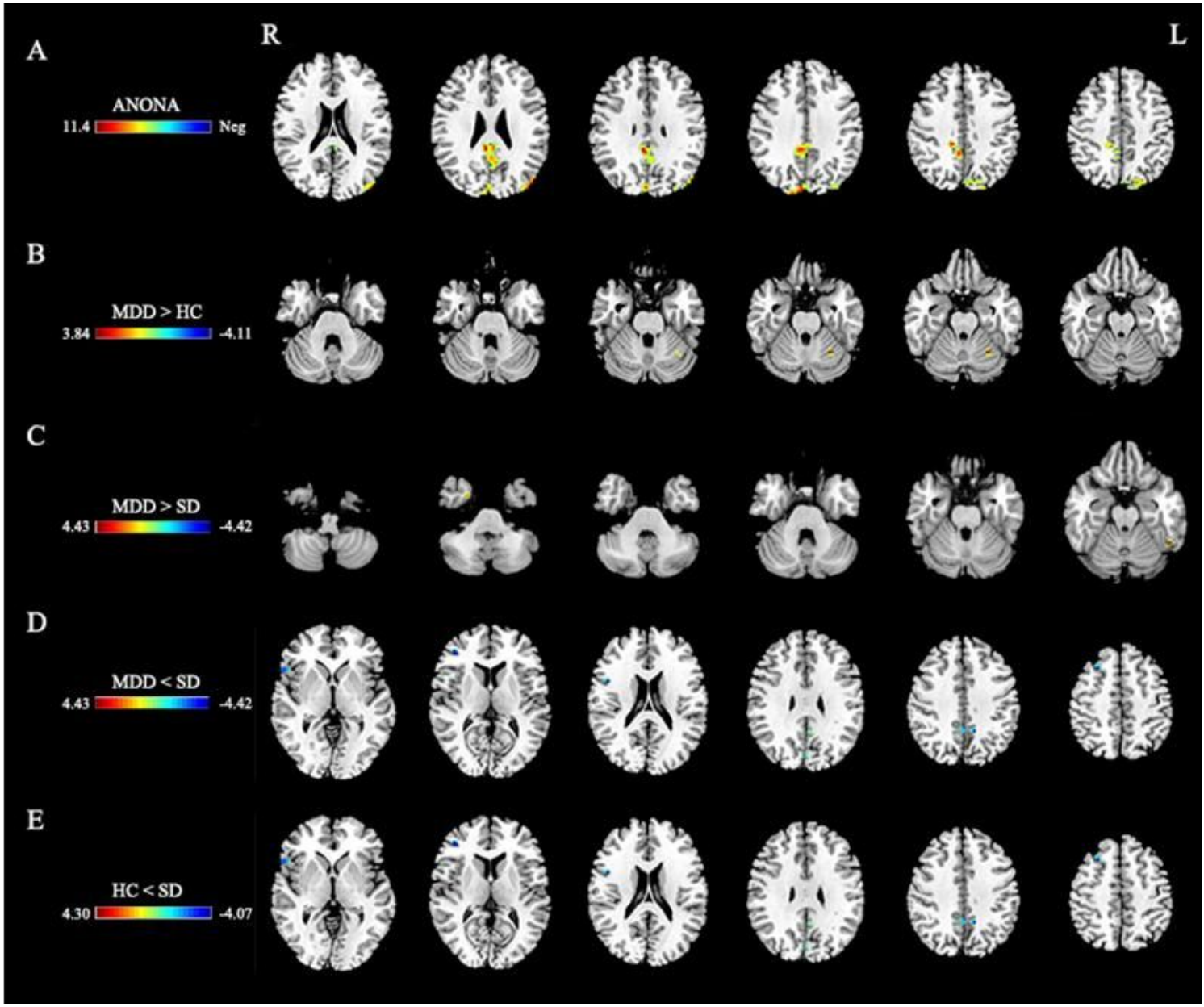

Figure 2

Statistical parametric map showing the significant differences in the fALFF values among the MDD, SD and HC groups. (A) ANOVA of fALFF across the three groups. (B) Differences between the MDD and HC groups; (C) Regions with increased fALFF between the MDD and SD groups; (D) Regions with decreased fALFF between the MDD and SD groups; (D) Differences between the SD and HC groups. Additional details regarding these regions are described in Table 2. fALFF, fractional amplitude of low-frequency fluctuations; MDD, major depression; SD, subclinical depression; HC, healthy controls; L, left; R, right.

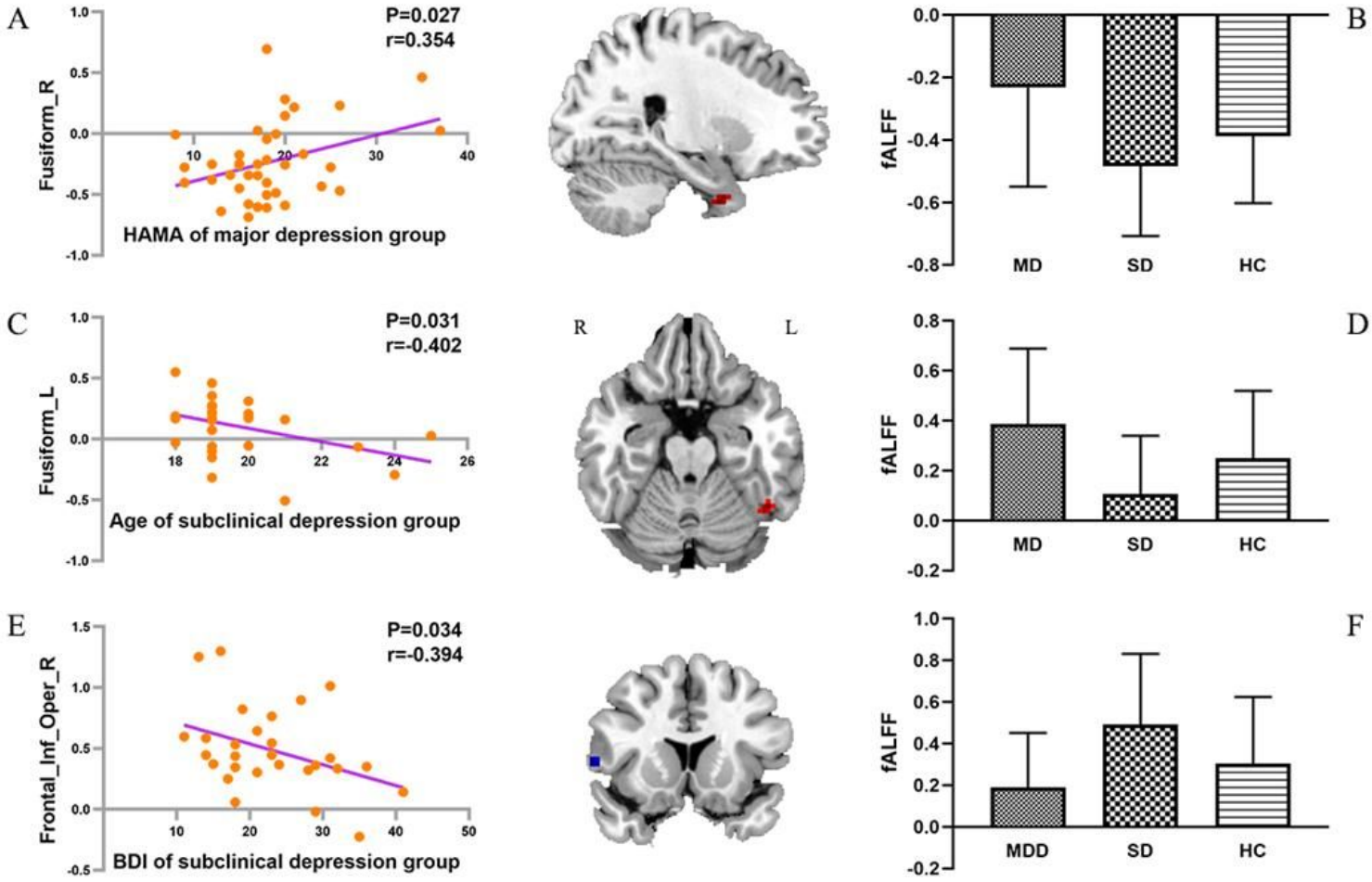

Figure 3

Plots showing the relationship between altered fALFF values and clinical variables among MDD, SD and HC groups; (A) A positive correlation was observed between HAMA score and the fALFF values of the right fusiform in the MDD group; (C) A negative correlations was observed between age and the fALFF values of the left fusiform in the SD group; (E) A negative correlation was observed between the BDI scores and the fALFF values of the right inferior frontal gyrus (opercular part) in the SD group; (B/D/F) fALFF values in the right fusiform, left fusiform and right inferior frontal gyrus (opercular part), respectively, among the three groups. fALFF, fractional amplitude of low-frequency fluctuations; HAMA, Hamilton Anxiety Scale; BDI, Beck Depression Inventory; MDD, major depression; SD, subclinical depression; HC, healthy controls.

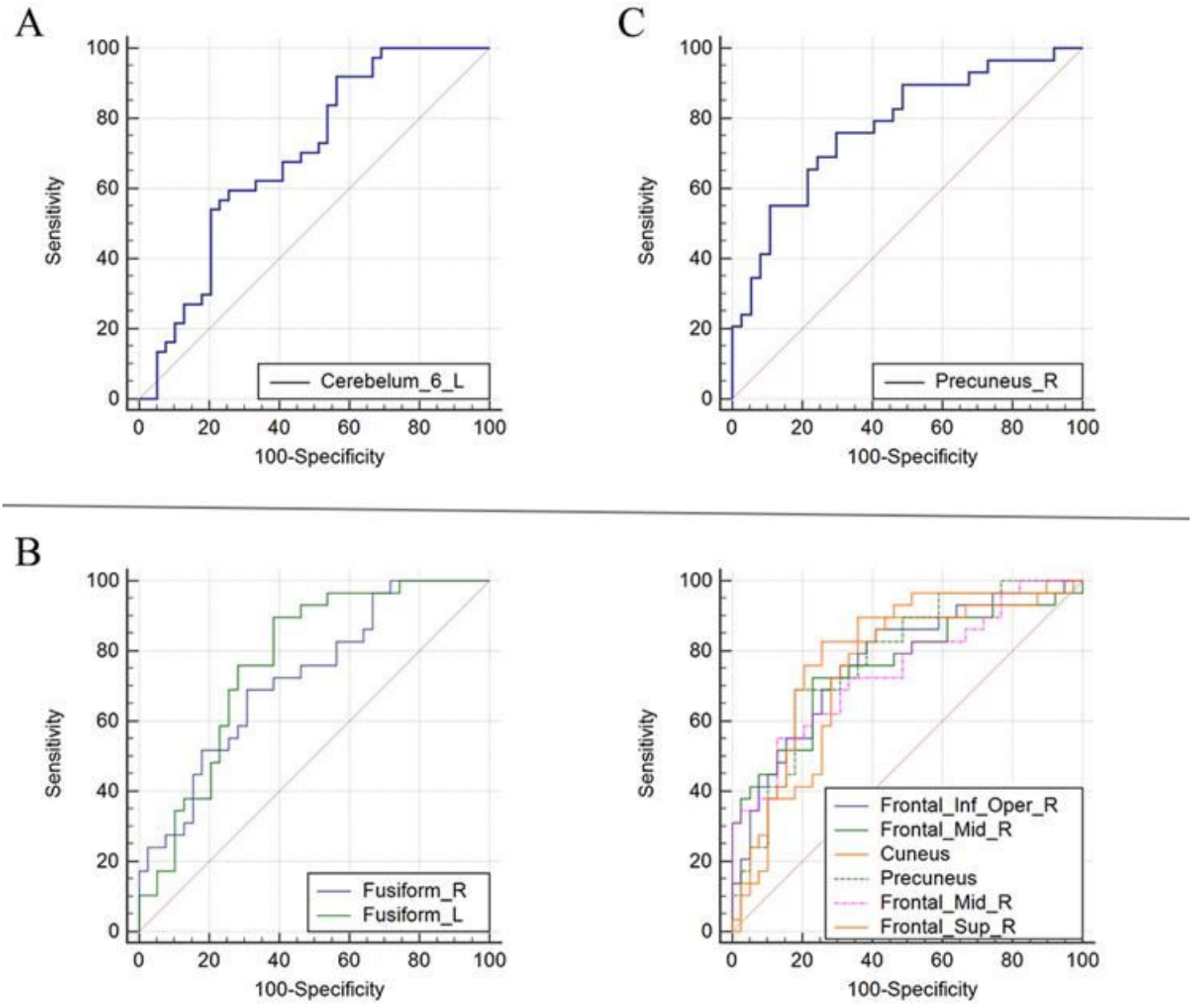

Figure 4

The receiver operating characteristic (ROC) curves for the discriminations among MDD, SD and HC groups. (A) showed the ability of altered fALFF value in left cerebellum to discriminate MDD from HC group; (B) showed the ability of altered fALFF value in bilateral fusiform gyrus, right inferior frontal gyrus (opercular part), cuneus, precuneus, right middle frontal gyrus and right superior frontal gyrus to discriminate MDD from SD group; (C) showed the ability of altered fALFF value in right precuneus to discriminate SD from HC group. fALFF, fractional amplitude of low-frequency fluctuation; MDD, major depression disorder; SD, subclinical depression; HC, health controls.

Supplementary Files

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- STROBEchecklistcrosssectional.doc