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Altered spontaneous brain activity in MRI-negative refractory temporal lobe epilepsy patients with major depressive disorder: A resting-state fMRI study

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ABSTRACT

Objective: To investigate alterations in spontaneous brain activity in MRI-negative refractory temporal lobe epilepsy patients with major depressive disorder using resting-state functional magnetic resonance imaging (RS-fMRI).

Methods: Eighteen MRI-negative refractory temporal lobe epilepsy patients with major depressive disorder (PDD), 17 MRI-negative refractory temporal lobe epilepsy patients without major depressive disorder (nPDD), and 21 matched healthy controls (HC) were recruited from West China Hospital of SiChuan University from April 2016 to June 2017. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and 17-item Hamilton Depression Rating Scale were employed to confirm the diagnosis of major depressive disorder and assess the severity of depression. All participants underwent RS-fMRI scans using a 3.0 T MRI system. MRI data were compared and analyzed using the amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) to measure spontaneous brain activity. These two methods were both used to evaluate spontaneous cerebral activity.

Results: The PDD group showed significantly altered spontaneous brain activity in the bilateral mesial prefrontal cortex, precuneus, angular gyrus, right parahippocampal gyrus, and right temporal pole. Meanwhile, compared with HC, the nPDD group demonstrated altered spontaneous brain activity in the temporal neocortex but no changes in mesial temporal structures.

Conclusion: The PDD group showed regional brain activity alterations in the prefrontal-limbic system and dysfunction of the default mode network. The underlying pathophysiology of PDD may be provided for further studies.

1. Introduction

Depression is the most common psychiatric comorbidity in epilepsy, ranging from 24% to 50% in prevalence rates [1–3], and up to 50% to 60% in temporal lobe epilepsy [2,4]. Major depressive disorder was predicted to be the second leading global burden by 2020 [5]. Depression decreases quality of life and presents a higher risk of suicide in epilepsy patients [6–8].

Thirty percent of patients with refractory temporal lobe epilepsy (TLE) have normal structural MRI scans upon visual inspection (MRI-negative TLE) [9], in which there is no evidence of hippocampal sclerosis(HS). Compared to TLE patients with HS, MRI-negative TLE patients have special characteristics, including a later age at seizure onset, a higher frequency of secondary seizure generalization, and less impairment of memory function [10–14]. Seventy percent of TLE patients have a high risk of developing refractory epilepsy and are potential candidates for epilepsy surgery [15]. Notably, refractory MRI-negative TLE patients with major depressive disorder (PDD) need to receive epilepsy surgery to improve quality of life. However, previous studies demonstrated that the percentage of MRI-negative TLE patients who remained seizure-free post-surgery was only 51% compared with 75% of TLE with HS patients [16]. This cause may be difficult to identify the epileptogenic zone in MRI-negative TLE patients. However, with improved imaging techniques, these cases may be amenable to surgical resection. A recent RS-fMRI study suggested that MRI-negative TLE may involve different brain networks compared with TLE with HS [14]. Until now, there has been no research on PDD using RS-fMRI, which may help reveal the underlying mechanisms and assist

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preoperative localization in PDD to obtain better postsurgical outcomes.

RS-fMRI is a powerful tool for measuring intrinsic spontaneous neural activity without task design constraints [17,18] and is used widely to assess neuropsychiatric diseases such as Parkinson disease [19], schizophrenia [20,21], and depression [22]. In our previous studies focused on epilepsy, RS-fMRI findings provided interesting information to understand the mechanism of epileptic activity in the human brain [23–25]. ReHo and ALFF are two reliable algorithms used to quantify the neural activity in RS-fMRI [26]. ALFF represents the intensity of spontaneous neural activity in the resting state and represents energy metabolism [27]. Wang et al. found that altered ALFF in epilepsy might reflect the effects of epileptic activity [28]. ReHo evaluates the neural synchronization of a given voxel with its neighboring voxels [29]. High ReHo values in a given brain area represent oscillation of neurons in high synchronization [29]. Jiang et al. illustrated increased ReHo in thalami and motor-related regions in generalized epilepsy, suggesting that an abnormal thalamocortical circuit is related to generalized epileptic activity [30]. Another study showed that ALFF can be supplemented with ReHo to test global spontaneous activity and that ReHo was more powerful than ALFF in discovering regional abnormalities [31]. Hence, the combination of the two methods may offer more interesting information about spontaneous brain activity in patients with epilepsy than either method alone [31].

Our study investigated spontaneous brain activity in PDD using ReHo and ALFF. We hypothesized that significant differences in ALFF and ReHo data would be acquired within specific brain regions compared to MRI-negative temporal lobe epilepsy patients without major depressive disorder (nPDD) and matched controls. These altered regions will help better understand the underlying neurophysiology and assist in preoperative localization in PDD.

2. Methods

2.1. Participants

This study was approved by West China Hospital Ethics committee, and all participants signed informed consent forms. Thirty-five patients with TLE and 21 healthy controls (HC) were recruited from the outpatient department of West China Hospital from March 2016 to June 2017. Every patient was diagnosed separately by two senior neurologists. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and 17-item Hamilton Depression Rating Scale (17-HAMD) were employed to confirm the diagnosis of major depressive disorder and assess the severity of depression.

The inclusion criteria included the following: 1. Patients all met the diagnostic criteria of the International League Against Epilepsy [32,33] and refractory epilepsy was diagnosed according to the ILAE 2010 consensus [34]; 2. All patients underwent a 3T high-resolution MRI with oblique coronal thin sections specifically oriented perpendicular to the hippocampal long axis in order to confirm no potentially epileptogenic structural abnormalities; 3. All patients had at least three instances of ictal-interictal video EEG monitoring with the use of sphenoidal electrodes to confirm origin from the temporal lobe; 4. All patients with major depressive disorder met the DSM-IV criteria and a score of ≥ 17 on the 17-HAMD scale. The exclusion criteria included the following: 1. A history of mood disorders; 2. Use of anti-depressive drugs; 3. Independent left and right temporal lobe seizures. All 21 healthy controls were matched in terms of gender, age, and degree of education.

2.2. MRI data acquisition

All participants were scanned on a 3T scanner (GE Discovery MR750, Milwaukee, WI) at the MRI Research Center at the University of Electronic Science and Technology of China. During the scan, all participants were instructed to close their eyes without thinking of anything in particular. The scan parameters were as follows: 2000/30 ms repetition time/echo time (TR/TE), 90° flip angle; 64 × 64 matrix size; 24 × 24 cm^2 field of view; and 4/0.4 mm thickness/gap. A total of 205 volumes (32 slices per volumes) were obtained over a 410-second period. Axial anatomical T_1-weighted images were also obtained with a 3D fast-spoiled gradient echo sequence, and the parameters were as follows: 6.008/1.984 ms TR/TE; 90° flip angle; 256 × 256 matrix size; 25.6 × 25.6 cm^2 field of view; 1 mm slice thickness (no gap).

2.3. Data processing

Preprocessing of fMRI data was conducted using the SPM8 toolbox (statistical parametric mapping, http://www.fil.ion.ucl.ac.uk/spm) and included slice time correction, motion correction, and spatial normalization (3 × 3 × 3 mm^3) to the MNI template. The first 10 time points from each patient's data were discarded to ensure magnetic field stabilization. Subjects were excluded if their head motion exceeded 3.0 mm (translation) and 3.0° (rotation) during fMRI acquisition. In addition, we also assessed translation and rotation in both groups using the following formula: head motion/rotation $= \frac{1}{M-1}\sum_{i=2}^{M}\sqrt{|\Delta d_{x_i}|^2 + |\Delta d_{y_i}|^2 + |\Delta d_{z_i}|^2}$, where M is the length of the time course (M = 200 in this study); x_i, y_i and z_i are translations/rotations at the i^{th} time point in the x, y, and z directions, respectively, $\Delta d_{x_i} = x_i - x_{i-1}$, and similar for y_i and z_i. Then, the nuisance signals were regressed out, including white matter, cerebrospinal fluid and global signal, and six motion parameters. The resulting time course was detrended but no temporal filtering was performed in consideration of the following analyses in the full frequency band. Finally, these images were smoothed with a 6-mm full-width at half maximum (FWHM) of an isotropic Gaussian filter for the ALFF analysis. However, the smoothing step was performed for the ReHo map, which was computed in the unsmoothed images.

2.4. ALFF analysis

The amplitude of low-frequency fluctuation maps were computed via REST software (http://www.restfmri.net/forum/REST). First, the time series of each voxel was transformed into a frequency domain via fast Fourier transform and the square root of the power spectrum was calculated. Next, the mean square root of the power across 0.01–0.08 Hz was obtained as the ALFF. Then, the ALFF of each voxel was divided by their own mean ALFF for each subject within the brain mask for standardization.

2.5. ReHo analysis

The values of ReHo (also named Kendall's coefficient of concordance) were computed using REST software. We measured the similarity of the ranked time series of a center voxel in a cluster composed of 26 nearest neighbor voxels. Then, for standardization purposes, the ReHo of each voxel was divided by its own global mean ReHo value within the brain mask. Next, the data were smoothed with an isotropic Gaussian kernel (6 mm full width at half maximum).

2.6. Statistical analysis

Statistical analysis of demographic and clinical data was performed using SPSS 19, an IBM company. A one-way ANOVA or *t*-test was used for continuous variables and a Chi-square test was used for categorical variables to assess the differences among the three groups (PDD, nPDD, HC). A Kruskal-Wallis test was used to compare ranked variables among different groups. The height threshold of statistical significance was set at $p < 0.05$.

Table 1
Demographic and clinical characteristics of participants.

Variables	PDD ± SD (N = 18)	nPDD ± SD (N = 17)	HC ± SD (N = 21)	P value
Age (year)	30.1 ± 7.6	29.0 ± 6.7	24.9 ± 3.9	0.119
Gender				
Male	5	8	8	0.499
Female	13	9	13	
Education years	11.7 ± 1.8	11.6 ± 2.5	11.8 ± 2.2	0.995
HAMD score	26.7 ± 6.4	5.1 ± 1.1		< 0.001
Epilepsy duration (year)	4.4 ± 1.3	4.3 ± 1.2		0.933
Lateralization				
Left	7	8		0.625
Right	11	9		

PDD: Patients with major depressive disorder; nPDD: Patients without major depressive disorder; HC: Healthy controls; SD: standard deviation; HAMD:17-item Hamilton Depression Rating Scale.

To assess the ReHo and ALFF differences among the three groups, a one-way analysis of variance (ANOVA) was performed in a voxel-wise manner in the whole brain ($p < 0.01$,) using SPM8. Then, by performing the results of ANOVA as a mask, post hoc *t*-tests were used between each group using a threshold at $p < 0.05$ with FDR correction to examine the spontaneous neuronal activity changes among the three groups.

2.7. Correlation analyses between ALFF/ReHo and HAMD scores

To investigate the underlying linear association, Pearson's correlations were used for ALFF/ReHo values and HAMD scores, controlling for the effects of age and gender.

3. Results

3.1. Demographics and clinical data

Detailed demographics and clinical data for the PDD, nPDD and HC groups are listed in Table 1. Age, sex, and years of education did not differ between the three groups. Likewise, the duration of epilepsy and localization of TLE did not differ between the PDD and nPDD groups. The 35 epileptic patients were divided into two groups based on their HAMD score. Patients who scored over 16 were included in the PDD group, while those who scored below 8 were included in the nPDD group. There were no significant differences between the two groups in head motion and rotation.

3.2. Alterations of ALFF

To obtain the difference in ALFF among the three groups, a one-way ANOVA was performed ($p < 0.01$). Fig. 1 illustrates the cerebral regions with significant differences among groups, which included the bilateral prefrontal cortex (Brodmann's area, BA 9/10), left inferior temporal gyrus (BA37), angular gyrus (BA 39), right superior temporal gyrus (BA22), precuneus (BA7), and parahippocampal gyrus (BA37). Post-hoc *t*-tests between the three groups were performed to compare ALFF in these areas (Table 2). Compared with the nPDD group, an increased ALFF in the PDD group was observed in the bilateral prefrontal cortex, angular gyrus, inferior temporal gyrus, as well as a decreased ALFF in the right superior temporal gyrus, precuneus, and parahippocampal gyrus. Compared with the HC group, the nPDD group mainly showed decreased ALFF values in the inferior temporal gyrus and increased ALFF values in the superior temporal gyrus.

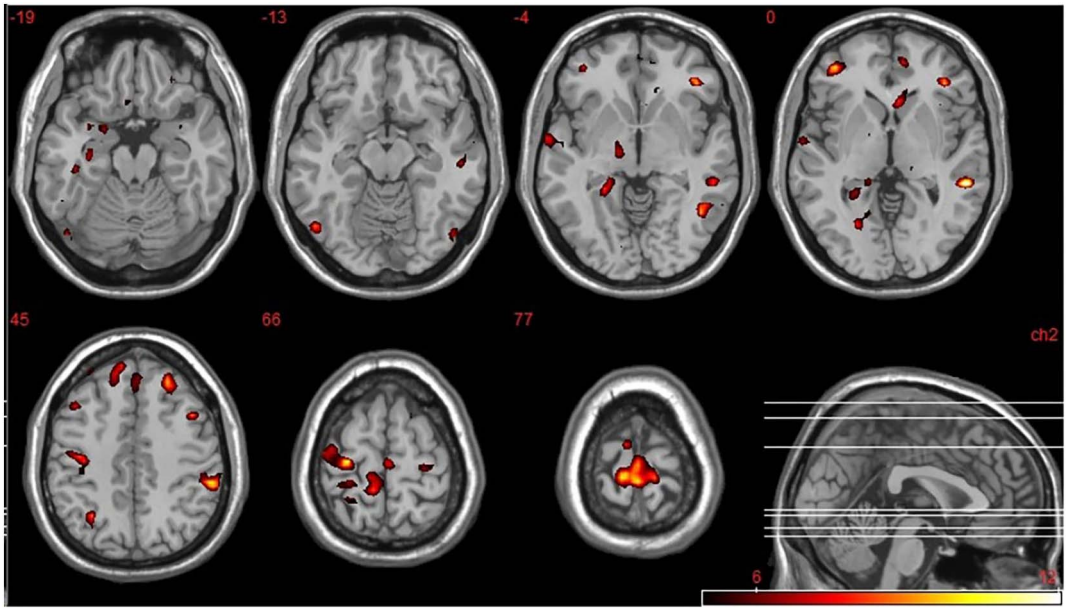

Fig. 1. The ANOVA maps of ALFF values showing significant differences among the PDD group, nPDD group, and healthy control group ($P < 0.01$). The significant differences included the bilateral prefrontal cortex (Brodmann's area, BA 9/10), left inferior temporal gyrus (BA37), angular gyrus (BA 39), right superior temporal gyrus (BA22), precuneus (BA7), and parahippocampal gyrus (BA37).

Table 2
The regions of ALFF value altered areas in whole brain analysis.

Location	BA	Peak MNI coordinate			Cluster size	Maximal T value	P
		x	y	z			
PDD > nPDD							
Left ITG	37	− 45	− 60	− 6	30	2.36	*
Left PFC	9	− 24	36	42	125	3.95	*
Right PFC	10	33	51	6	67	2.23	*
Right AG	39	30	− 60	45	42	2.87	*
PDD < nPDD							
Right PHG	37	24	− 42	− 6	84	− 3.67	*
Right PCU		27	− 48	12	84	− 3.25	*
Right STG	22	63	− 9	− 3	24	− 2.97	*
PDD > HC							
Right AG	39	30	− 60	45	42	4.17	*
nPDD > HC							
Right STG	22	63	− 9	− 3	24	3.78	*
Right PCU	7	27	− 48	12	84	3.49	*
Right PHG	37	24	− 42	− 6	84	3.38	*
PDD < HC							
Right PFC	9	33	18	36	26	− 3.26	*
nPDD < HC							
Left PFC	9	− 24	36	42	125	− 4.64	*
Left ITG	37	− 45	− 60	− 6	30	− 4.39	*
Right ACC	32	15	42	42	190	− 2.51	*

PDD: Patients with major depressive disorder; nPDD: Patients without major depressive disorder; HC: healthy control; BA, Brodmann area;ITG, inferior temporal gyrus; PFC, prefrontal cortex; AG, angular gyrus; PHG, parahippocampal gyrus; PCU, precuneus; STG, superior temporal gyrus; ACC, anterior cingulate cortex.
* $p < 0.05$, with FDR correction.

Table 3
The regions of Reho value altered areas in whole brain analysis.

Location	BA	Peak MNI coordinate			Cluster size	Maximal T value	P
		x	y	z			
PDD > nPDD							
Left PFC	9	− 36	24	51	74	5.45	*
Right AG	39	51	− 48	36	29	3.67	*
Right cerebellum		9	− 42	− 42	31	3.20	*
PDD < nPDD							
Left ITG	37	− 36	− 39	− 12	36	− 3.48	*
Right PCU	7	9	− 39	57	69	− 3.48	*
PDD > HC							
Right PCG	6	36	− 12	60	115	3.96	*
Left MFG	9	− 36	24	51	74	2.94	*
Right putamen		30	− 18	54	115	3.33	
nPDD > HC							
Left ITG	37	− 36	− 39	12	36	3.82	*
Right TP		57	3	− 15	53	3.99	*
Right PCU	37	9	− 39	57	69	2.66	*
PDD < HC							
Left PFC	9	− 36	24	51	74	− 2.18	*
nPDD < HC							
Right AG	7	33	− 66	51	34	− 3.88	*

PDD: Patients with major depressive disorder; nPDD: Patients without major depressive disorder; HC: healthy control; BA, Brodmann's area; PFC, prefrontal cortex; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; AG, angular gyrus; PCU, precuneus; PCG, precentral gyrus; TP, temporal pole.
* $p < 0.05$, with FDR correction.

3.3. Alterations of ReHo

Similar to the ALFF, a one-way ANOVA was performed among the three groups to assess differences in ReHo value. Fig. 2 demonstrates the cerebral regions with significantly different ReHo values among groups, which included the prefrontal cortex (Brodmann's area, BA9), left inferior temporal gyrus (BA37), angular gyrus (BA 39), right temporal pole, precuneus (BA7), and right cerebellum. Post hoc *t*-tests between the three groups were performed to compare ReHo values in these areas (Table 3). Compared with the nPDD group, increased ReHo values in the PDD group were observed in the left prefrontal cortex, angular gyrus, and right cerebellum, and decreased ReHo values were observed in the left inferior temporal gyrus and precuneus. Compared with the HC group, the nPDD group mainly showed decreased ReHo values in the angular gyrus and increased ReHo values in the precuneus.

3.4. Correlation analyses between ALFF/ReHo and HAMD scores

There was no significant correlation between altered ALFF/ReHo values and HAMD scores in the PDD group ($P > 0.05$).

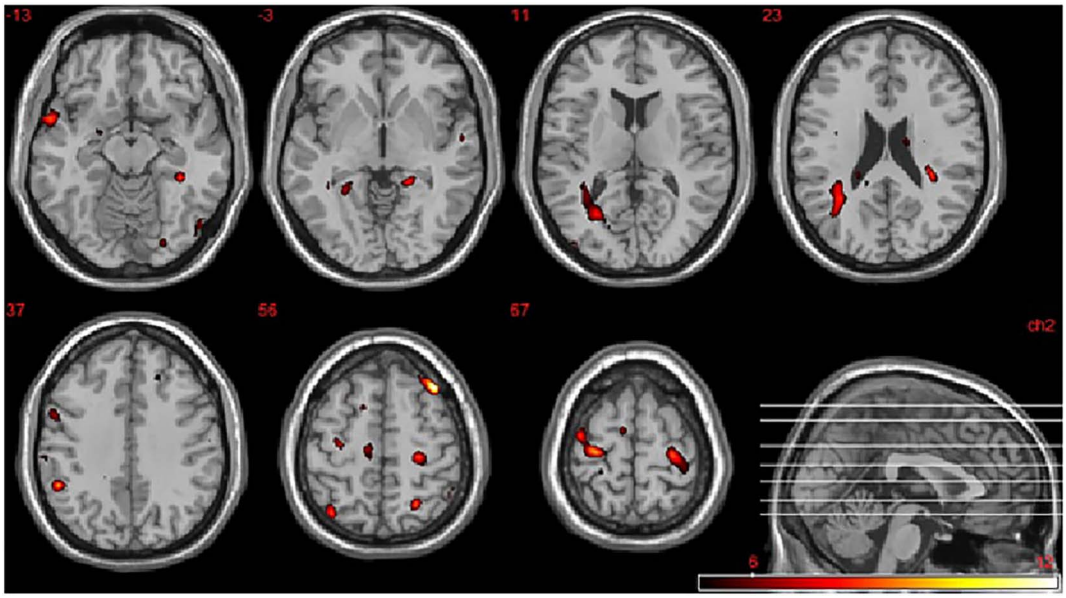

Fig. 2. The ANOVA maps of ReHo values showing significant differences among the PDD group, nPDD group, and healthy control group ($P < 0.01$). The significant differences included the prefrontal cortex (Brodmann's area, BA9), left inferior temporal gyrus (BA37), angular gyrus (BA 39), right temporal pole, precuneus (BA7), and right cerebellum.

4. Discussion

The resting-state fMRI characteristics of MRI-negative temporal lobe epilepsy patients with major depressive disorder are unclear. This is the first study to investigate resting-state fMRI in PDD patients. In our study, patients with major depressive disorders showed altered ALFF and ReHo values in several brain regions when compared with nPDD. These regions included prefrontal cortex (PFC), inferior temporal gyrus, precuneus, and angular gyrus. Compared with HC, the nPDD group demonstrated altered spontaneous brain activity in the temporal neocortex, but no changes in mesial temporal structures.

The regional cerebral blood flow (RCBF) and the regional metabolic rate for glucose (RMRFG) are related to the functional activities of neurons [35]. Many studies have found that in most brain regions, RCBF/RMRFG and ReHo/ALFF values show a significantly positive correlation. Therefore, high regional ReHo/ALFF values represent high RCBF/RMRFG, and conversely, low regional ReHo/ALFF values represent low RCBF/RMRFG [36–38].

4.1. Functional impairment in the prefrontal-limbic system

Whole-brain voxel-based analysis of ALFF and ReHo showed that increased ALFF values in the PDD group were located mainly in the bilateral mesial prefrontal cortex, compared with the nPDD group. Moreover, we also found a decreased ALFF value in right parahippocampal gyrus and a decreased ReHo value in right temporal pole. Much evidence supports the notion of a common biological foundation of depression and temporal lobe epilepsy as a comorbidity [39–41]. One brain pathway is the prefrontal-limbic system, which contains the prefrontal cortex, amygdala, parahippocampal gyrus, hippocampal formation and regions of the neocortex, including the temporal pole [42,43]. This pathway regulates emotion and the epileptic pathogenic pathways. The medial prefrontal cortex may regulate the limbic system, especially the amygdala [44]. Functional connectivity between the medial temporal lobe structures and the prefrontal cortex was a strong predictive factor of depressive symptoms in patients with TLE [45]. Another study found altered ALFF value in the medial prefrontal cortex (mPFC) in temporal lobe epilepsy patients with depressive symptoms [42]. A recent study uncovered a significant negative correlation between Beck Depression Inventory scores and the cortical thickness of the temporal pole in patients with a mood disorder [46]. The parahippocampal gyrus was considered an important epileptogenesis area in temporal epilepsy. Some studies have reported consistent changes in reduced ALFF, the fractional amplitude of low frequency fluctuations value (fALFF), and ReHo in the parahippocampal gyrus in major depressive disorder [47–49]. Abnormal fMRI signals have previously been shown in the mood network between the amygdala, temporal poles, and parahippocampal gyrus in major depressive disorder [50,51]. Therefore, our results demonstrated regional brain activity alterations in the prefrontal-limbic system and disruption of the mood regulation network.

4.2. Disruption of default mode network

Moreover, in the present study, changes in ALFF and ReHo values occurred in precuneus, mPFC, angular gyrus and cerebellum that involved the default mode network (DMN). The DMN includes the posterior cingulate cortex (PCC)/precuneus, mPFC, lateral and inferior parietal cortex (including angular gyrus and supramarginal gyrus) and cerebellum [52]. The two most consistently delineated regions of the DMN are the precuneus/PCC and the mPFC, according to their functional roles. The precuneus/PCC is responsible for monitoring internal and external environments [53], while the mPFC helps to observe internal psychological states, as well as those of others. The epileptic deactivation of the default-mode regions, including the precuneus and mPFC, has been reported in a few fMRI studies [54–56]. In humans, the cerebellum may also be involved in regulating fear and pleasure responses. Both functional and structural abnormalities of the cerebellum have been demonstrated in emotional disorders, including depression and schizophrenia [57]. The cerebellum and its relevant neural connections to prefrontal areas are integrated into pathological models of depression [58]. Consistent with our expectations, the angular gyrus is recognized as the core region of the DMN. Located at the junction of the temporal, parietal, and occipital lobules, the angular gyrus is considered to be a major hub that links different subsystems [59]. Another study demonstrated that patients with late-life depression showed significantly decreased ReHo values in the right anterior cingulate gyrus, right angular gyrus, bilateral prefrontal cortex, and right precuneus, and a significantly increased ReHo value in the left cerebellum posterior lobe compared to healthy controls [60]. Taken together, the abnormal local activities of these areas in the PDD group implicates disruption of default mode network.

4.3. Other findings

In our study, we found that the PDD group showed a decreased ALFF value in the inferior temporal gyrus and an increased ALFF value in the superior temporal gyrus, which are all related to the temporal neocortex. Interestingly, the abnormal area did not involve any mesial temporal structures, such as the amygdala and hippocampus. In a recent study, patients with TLE with mesial temporal sclerosis (MTS) showed decreased fALFF in the ipsilateral amygdala and hippocampus; however, the TLE-without MTS group showed minimally decreased fALFF value in the ipsilateral amygdala, but not the hippocampus [14]. Therefore, we speculate that MRI-negative TLE may implicate distinct pathologic mechanisms other than TLE with MTS.

4.4. Limitations of this study

Several limitations were involved in the present study. First, the main limitation was the relatively small number of participants in each group. This study is preliminary, and we will continue to enlarge the database to solve this problem. Second, this was a cross-sectional study, which cannot provide dynamic and evolving fMRI information regarding the recovery of spontaneous brain activity caused by antidepressants or other treatments. A longitudinal study design may answer these questions in the future.

4.5. Conclusion

The PDD group showed regional brain activity alterations in the prefrontal-limbic system and dysfunction of the default mode network. The ReHo and ALFF methods provided different perspectives on pathophysiological mechanisms, and they were complementary in describing regional spontaneous neural activity. Taken together, these two fMRI methods can help researchers better understand the underlying neurophysiology and compensatory mechanisms behind MRI-negative TLE and assist with preoperative localization. Furthermore, our explorative study of PDD may facilitate the development of future longitudinal studies.

Conflicts of interest

None.

Acknowledgements

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