

Altered Dynamic Amplitude of Low-frequency Fluctuations in Patients with Postpartum Depression

Fanghui Dong

School of Medical Imaging, Binzhou Medical University

Zhongsheng Zhang

Yantai Yuhuangding Hospital

Tongpeng Chu

Yantai Yuhuangding Hospital

Kaili Che

Yantai Yuhuangding Hospital

Yuna Li

Yantai Yuhuangding Hospital

Yinghong Shi

Yantai Yuhuangding Hospital

Heng Ma

Yantai Yuhuangding Hospital

Feng Zhao

School of compute Science and Technology, Shandong technology and Business University

Ning Mao

Yantai Yuhuangding Hospital

Haizhu Xie

xhz000417@sina.com

Yantai Yuhuangding Hospital <https://orcid.org/0000-0002-5962-3558>

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Abstract

Background

Postpartum depression (PPD) is a common mood disorder with increasing incidence year by year. However, the dynamic changes in local neural activity remain unclear. In this study, we utilized the dynamic amplitude of low-frequency (dALFF) to investigate the abnormal temporal variability of local neural activity.

Methods

Twenty-four patients with PPD and nineteen healthy postpartum women controls (HCs) matched for age, education level and body mass index were examined by resting-state functional magnetic resonance imaging (rs-fMRI). A sliding-window method was used to assess the dALFF, and a k-means clustering method was used to identify dALFF states. Two-sample t-test was used to compare the differences of dALFF variability and state metrics between PPD and HCs. Pearson correlation analysis was used to analyze the relationship between dALFF variability, states metrics and clinical severity.

Results

(1) Patients with PPD had lower variance of dALFF than HCs in the cognitive control network, cerebellar network, and sensorimotor network. (2) Four dALFF states were identified, and the number of transitions between the four dALFF states increased in the patients compared with that in HCs. (3) Multiple dALFF states were found to be correlated with the severity of depression. The variance of dALFF in the right middle frontal gyrus was negatively correlated with the Edinburgh postnatal depression scale score.

Conclusion

This study provides new insights into the brain dysfunction of PPD from the perspective of dynamic local brain activity, and highlights its important role in understanding the neurophysiological mechanisms of PPD.

1. Introduction

Postpartum depression (PPD) is a psychological disorder that often occurs in women before and after childbirth. It is a common type of puerperal psychiatric syndrome. Between 7.4% and 20% of women have this condition at different stages of pregnancy (A et al., 2004). The typical symptoms of PPD are insomnia, anxiety, irritability, exhaustion, and persistent low mood (Pawluski et al., 2017). Individuals with PPD often experience feelings and thoughts of sadness rarely feel pleasure. As the condition worsens, the parturient may even have thoughts of suicide or infanticide (Nguyen et al., 2019). This durable emotional

disturbance may represent a key aspect of the neuropathology of PPD, typified by a wide-ranging distribution of brain alterations involved in emotion processing (Hamann, 2012). Understanding or uncovering the brain mechanisms underlying this depressed emotional state is an important step towards improving treatment and has always been the focus and difficulty of PPD neuropathology (Susanne et al., 2019).

In recent years, many neuroimaging studies have greatly promoted the understanding of PPD. Functional magnetic resonance imaging (fMRI) has presented a tool for uncovering the underlying brain mechanisms for emotion processing, and previous studies found some emotion-related specific brain sites (Susanne et al., 2019). For example, the amygdala is implicated in fear (Nigel et al., 2021); the cingulate cortex (ACC) involves sadness (P et al., 2018); the inferior temporal gyrus and middle frontal gyrus respond to negative stimuli (Qiao et al., 2014). Although these results were not fully consistent in functional localization between different fMRI, the emotion processing is distributed in distinct brain regions (Simeng et al., 2019). So describing brain activity in these emotion-related areas was believed to be key to unraveling how emotion is represented in the brain. Over the past studies, resting-state functional MRI (rs-fMRI) has become a promising tool for the in vivo exploration of brain activity and connectivity, greatly enhancing our understanding of the pathophysiology of PPD (Deligiannidis et al., 2019; W et al., 2014). Rs-fMRI results showed that the voxel-mirrored homotopic connectivity (VMHC) of dorsal anterior cingulate cortex and orbitofrontal cortex were significantly decreased in patients with postpartum depression (Ning et al., 2020). Another study investigated the changes in information flow characteristics in different brain regions by comparing Pearson correlation coefficient, and the results showed that the information flow patterns in the amygdala, insula, and hippocampus were significantly changed in patients with PPD (Mao et al., 2020).

Among many indicators of rs-fMRI, the amplitude of low-frequency fluctuation (ALFF) has been used as a reliable neuroimaging marker in the exploration of resting-state regional brain activity in neuropsychiatric disorders (David et al., 2020; Wang et al., 2019; Ying et al., 2021; Zheng et al., 2019). It is a whole-brain analysis algorithm used to examine the total power of the local synchronization of spontaneous blood-oxygenation level-dependent signal fluctuations within a specific low-frequency range (typically 0.01-0.08 Hz) at the voxel level (Yu-Feng et al., 2007). However, ALFF is mostly used to study brain activity in the resting state, but ALFF is indeed time-varying because individuals are likely to engage in different mental processes which are associated with ALFF (Zening et al., 2018). In order to further explore the dynamics of brain activity, the intrinsic brain activity can be observed by quantifying its temporal variability (Enzo et al., 2014; Tomasi et al., 2017; Yan et al., 2017; Zening et al., 2018). During rs-fMRI scanning, the intrinsic brain activity is often assumed to be stable. If it is considered that the intrinsic brain activity changes over time in the study of whole brain activity, the dynamic evaluation index of the intrinsic brain activity dynamic low-frequency oscillation amplitude (dALFF) can be measured. dALFF is a further extension of ALFF, exploring ALFF on a time scale, which can promote the dynamic study of local brain activity.

In this study, dALFF method based on the sliding-window was used to study the local brain activity in PPD and HCs. And then the k-means clustering method was used to identify states that reoccur

throughout the entire rs-fMRI scan. Furthermore, the between-group differences in dALFF variability over time and state-wise dALFF were examined. In addition, the correlation between the dALFF clustering status in patients with PPD and the scores of different scales was studied, and the pathogenesis of PPD was further explained.

2. Materials And Methods

2.1 Participants

A total of 24 postpartum women were recruited from the psychological clinic of Yantai Yuhuangding Hospital in this study. In addition, 19 healthy postpartum women were recruited from the local community through advertisements as healthy controls (HCs), which matched the PPD group in terms of age, education level and body mass index (BMI). Details of the inclusion and exclusion criteria were provided in supplementary materials.

2.2 MRI acquisition

MRI was performed with a 3.0T MR (GE 750W, GE Healthcare, USA) with a standard eight-channel head coil. During the scan, all participants were instructed to close their eyes, stay awake, and try to stay still. Resting state functional scanning was acquired using a gradient echo sequence. The parameters were as follows: TR/TE = 2000 ms/30 ms, FA = 90°, FOV = 224 mm × 224 mm, slice number = 36, voxel size = 3.5 × 3.5 × 3.0 mm³, slice thickness = 3 mm and 175 volumes.

2.3 Data preprocessing

The rs-fMRI data preprocessing were carried out using data Processing and Analysis for Resting-State Brain imaging (DPARSF; <http://www.restfmri.net/forum/DPARSF>) (Chao-Gan et al., 2016). The preprocessing steps included slice timing, realignment, spatial normalization and smoothing (details in the Supplementary Materials).

2.4 Feature framework of dALFF

The flowchart is shown in Fig. S1.

2.5 dALFF calculation

The DPABI toolkit was used to calculate the dALFF value (Yan et al., 2017). A window with window width of 50 TRs (Li et al., 2019) and step length of 1 TR were selected in current study. The detailed calculate steps was shown in the Supplementary Materials.

2.6 Clustering analysis

K-means algorithm was performed on the dALFF values of all participants in the two groups to evaluate the occurrence state of dALFF. The k-means algorithm aggregates information with similarities into “k”

groups. Group differences were assessed for the following properties: mean dwell time, fraction time and number of transitions (details in the Supplementary Materials).

2.7 Statistical analysis

Two-sample t-test were performed on SPSS 22.0 software to analyze the differences in the demographic data between the two groups ($p < 0.05$ was statistically significant). Two-sample t-test was performed to assess the group differences in dALFF variability between the PPD group and HCs, with age, BMI, and educational level as covariates. In order to reduce the occurrence of the error, the gaussian random-field (GRF) correction method was conducted with $p < 0.05$. This correction method is a relatively strict multi-comparison correction method used in many fMRI studies to reduce false positive rates in the results (Rong et al., 2018). And two-sample t-test was also performed to analysis the differences of state properties.

The mean dALFF variability values of ROI which have differences between PPD and HCs were extracted to calculate the Pearson's correlation coefficient with HAMD and EPDS scores to further investigate the potential associations of abnormal dALFF variability with the symptom severity of patients with PPD. Additionally, the correlation analysis was performed among properties of dALFF clustering state with HAMD and EPDS. In addition, $p < 0.05$ was considered statistically significant.

2.8 Validation analysis

Additional validation analyses were performed for different sliding window lengths (30 and 70 TRs) and step sizes (2 TRs).

3. Results

3.1 Demographic and clinical characteristics

Table 1 lists the clinical characteristics of all subjects. No significant differences were found in the age ($t = 0.086$, $p = 0.932$), BMI index ($t = -0.342$, $p = 0.734$) and educational level ($t = -1.299$, $p = 0.202$) between the HCs and PPD groups.

Table 1
Demographic and clinical characteristics of all subjects.

	PPD (n = 20)	HCs (n = 19)	<i>p</i> value
Age(year)	31.05 ± 2.96	30.95 ± 4.39	0.932
BMI	23.68 ± 3.62	24.08 ± 3.69	0.734
Education duration(year)	14.95 ± 2.87	16.05 ± 2.39	0.202
HAMD score	34.90 ± 9.26	5.06 ± 2.80	< 0.001*
EPDS score	17.35 ± 2.70	2.67 ± 0.19	< 0.001*

Data are presented as mean ± SD. PPD, postpartum depression; HCs, healthy postpartum women controls; HAMD, Hamilton Depression Rating Scale; EPDS, Edinburgh Postnatal Depression Scale; BMI, body mass index. **p* < 0.05 was considered significant.

3.2 Differences in dALFF variability

The dALFF variance of the left cerebellum_inferior (CereB_Inf_L), left cerebellum_superior (CereB_Sup_L), right middle frontal gyrus (MFG_R), right inferior frontal gyrus, orbital part (IFG_R), right precentral gyrus (PreCG_R), and right postcentral gyrus (PostCG_R) decreased in the PPD patients compared with that in HCs (Table 2 and Fig. 1).

Table 2 Regions showing significant differences in the variance of dALFF values between PPD and HCs group.

Brain regions	Peak MNI coordinates			t-values	Voxels
	X	Y	Z		
CereB_Inf_L	-3	-69	-21	-4.4392	84
CereB_Sup_L	-3	-69	-21	-4.4392	84
MFG_R	45	57	6	-4.3036	95
IFG_R	45	57	6	-4.3036	95
PreCG_R	54	-12	51	-4.6264	125
PostCG_R	54	-12	51	-4.6264	125

The threshold was set at a *p* < 0.05 (GRF corrected). PPD, postpartum depression; HCs, healthy postpartum women controls; MNI, Montreal Neurological Institute space; CereB_Inf_L, left cerebellum_inferior; CereB_Sup_L, left cerebellum_superior; MFG_R, right middle frontal gyrus; IFG_R, right inferior frontal gyrus, orbital part; PreCG_R, right precentral gyrus; PostCG_R, right postcentral gyrus.

3.3 Clustered dALFF states

Four dALFF states were identified using the k-means clustering method. Fig. 2 shows the group differences in metrics of the dALFF states. In states 2 and 4, the mean dwell time and fraction time of the

PPD group were lower than those of HCs. However, in states 1 and 3, the mean dwell time and fraction time of PPD group were higher than HCs group. Among them, state 2 accounted for the largest proportion of all states by more than 50%. In addition, the number of transitions of four states in PPD group was also higher than that in HCs group.

3.4 Correlational analysis

As shown in Fig. 3, the z score of mean dwell time in state 1 was positively correlated with HAMD ($r = 0.486$, $p = 0.015$; Fig. 4a) and EPDS ($r = 0.419$, $p = 0.033$; Fig. 3c) scores. However, the z score of fraction time in state 2 was negatively correlated with HAMD score ($r = -0.379$, $p = 0.05$; Fig. 3b). In addition, a significant negative correlation between dALFF variance value and EPDS score in the MFG_R of patients with PPD ($r = -0.384$, $p = 0.047$; Fig. 3d).

4. Discussion

A dALFF method was used in this study to investigate the temporal variability of local brain activity in PPD. Patients with PPD showed reduced dALFF variability in cerebellar circuits, MFG_R, IFG_R, PreCG_R and PostCG_R. It also found that the clustered dALFF status was correlated with the severity of the disease. These findings indicated the importance of considering dynamic local brain activity in PPD.

4.1 Differences in dALFF variability

Compared to the HCs, the results showed that dALFF was decreased in the cognitive control network (CNN) in patients with PPD. The MFG and IFG plays an important role in CNN (Stange et al., 2017). The MFG is interconnected with frontal cortex and motor system, playing an essential role in cognitive regulation and emotional processing (Alexander and Roland, 2008). Aberrant local activity in the MFG may disturb the balance of the CNN network, resulting in abnormal emotional regulation. Through the fALFF and ReHo method, Che et al. (Kaili et al., 2020) and Wang et al. (Xiao-juan et al., 2011) also found that MFG activation was reduced in patients with PPD. Furthermore, IFG is mainly involved in response inhibition. When we are performed inhibitory tasks, the IFG activity was reduced (F et al., 2019). We thus suggest that decreased dALFF activity in the MFG and IFG may underlie the phenomenon of abnormal executive function and emotional processing in PPD.

We also found decreased the dynamic ALFF in sensorimotor network including PreCG_R and PostCG_R. The PreCG is mainly involved in motor function (Zhang et al., 2019). Changes in emotional state may affect the preparation of behavioral responses before exercise. By lowering or increasing the threshold of stimulation, the different psychological activities of patients are affected (Shao et al., 2019). Hence dALFF abnormalities in PreCG may be related to the reduction in behavioral activity, and the changes of dALFF in sensorimotor network (SMN) may be a direct response to somatic diseases in patients with PPD.

We found another decreased dALFF in the left cerebellar network. Many frontal and limbic regions are connected by the cerebellum (Schmahmann and Sherman, 1998). These areas are important for emotional and cognitive (Dutta et al., 2014; Schmahmann and Caplan, 2006). And Fitzgerald et al. (Fitzgerald et al., 2006) identified that the cerebellum is relevant to depression. In addition, the cerebellar network often shows weak activation in the face of negative emotions. Previous studies (Guo et al., 2011; Liang et al., 2020; Zhifen et al., 2010) have found that cerebellar ALFF is lower in MDD patients with cerebellar dysfunction. It has also been speculated that the anterior cerebellum may be involved in the pathophysiological processes of depression (Xiaoyue et al., 2019). In a word, these results suggested that changes in cerebellar network activity may affect the internal activity of PPD.

The results of this study showed that the brain section of the decreased dALFF variability in the PPD group was mainly in the right hemisphere compared with HCs. This discovery is opposite of that in MDD (Guo et al., 2013; Liang et al., 2020). Li et al. (Li et al., 2018) found that the right hemisphere has a leading role in depression. Compared with normal people, the spontaneous neuropathy of the whole brain in the resting state in MDD, the right hemisphere was increased, but in this study it is decreased. This finding indicated that PPD also has a hemispherical biasing of the regulation of emotions and is inconsistent with MDD. However, whether this conjecture is correct needs further research.

4.2 Difference in metrics of dALFF states

In this study, we found that the HCs group and the PPD group had similar dALFF clustering states in the resting state, but the proportion of the states was different. In the four states, state 2 accounted for more than 50% of the whole cluster state, indicating that state 2 might represent a major common brain activity pattern in the whole rs-fMRI scan. Windows occurrence proportion and mean dwell time are commonly used as measures in temporal dynamic pattern analysis to characterize state properties, reflecting the state configuration across time windows (Allen et al., 2014). These properties represent mental activity during the rs-fMRI scan and may be reconfigured in some conditions suffering from mental illness (A et al., 2017; Marusak et al., 2018; Zening et al., 2018). In the present study, compared to HCs group, the windows occurrence proportion and mean dwell time were changed in PPD group and were related to depressive symptoms, suggesting that the state configuration in the emotion network might relate to emotional disturbance of PPD. The results also found that the number of transitions of dALFF states increased. The number of transitions between different states enables multiple brain regions to change flexibly without being locked into a fixed coactivity pattern. However, the increased number of transitions is clinically manifested as insufficient attention when performing a certain task, indicating that the efficiency of information flow in the functional brain network of PPD patients may be lower (Lei et al., 2021). This finding also suggested that the whole brain integration of PPD brain network may be abnormal.

4.3 Correlation results

Figure 4 shows that the longer the mean dwell time in state 1 is, the more severe the clinical depression. The longer the fraction of time spent in state 2, the milder the clinical symptoms. Therefore, the

characteristics of these two clustering states were completely different. In addition, with the aggravation of depression, the number of transitions between the four states actually decreased in the PPD group. An increase or decrease in the number of state transitions causes the brain's emotional networks to reset (Junchao et al., 2017). The reduction in the number of transitions between the four states in the PPD group suggests that inflexible state reconfiguration may be a potential factor leading to persistent feelings and thoughts of sadness. As a result, patients with PPD often show the phenomenon of deep thought (David et al., 2020). When the dALFF variance value of MFG_R in PPD decreased, the symptoms aggravated. Some studies reported that MFG plays a mediating role in cognitive stress and depression (Michalski et al., 2017). Therefore, changes in functional activation of MFG may be used as an objective indicator to measure the degree of depression in patients with PPD. So our results provide a more complete understanding of emotional dysfunction in PPD patients from the perspective of time-varying internal brain activity in emotional networks.

4.4 Limitations and future directions

This research has several limitations. First, the two sets of samples were relatively small, which may affect the stability of the experimental results. More patients should be included in the future to obtain more reliable data sets, and more imaging techniques and algorithms should be combined to deepen the understanding of PPD neural mechanisms. Second, the selection of the sliding window remains a controversial topic. However, in this study, the window lengths of 30 TR and 70 TR were selected for verification analysis. The result was basically consistent with that under 50 TR window length. Therefore, the results of this study are relatively reliable. Finally, this study is a cross-sectional study, and longitudinal research is needed to further explore the changes in brain activities of patients with PPD.

5. Conclusion

In summary, the temporal variability of dALFF in multiple brain regions in patients with PPD changed. This change was correlated with the clinical symptoms of PPD to a certain extent. The study provides new insights into the brain dysfunction in PPD from a dynamic perspective. Further understanding of the neuropathological mechanism of PPD is of great significance.

Declarations

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Conflicts of Interest

None of the authors have a conflict of interest to declare.

Ethics approval

This study was approved by the Ethics Committee of Yuhuangding Hospital.

Consent to participate

All participants provided written informed consent before undergoing MR imaging.

Consent for publication

I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript. The manuscript is approved by all authors for publication.

Data availability

Imaging data could be provided upon request.

Code availability

Not applicable.

Author Contributions

DFH, CTP: Investigation, Data curation, Formal analysis, Writing - original draft. CKL, LYN: Investigation, Conceptualization, Data curation. SYH, MH, ZF: Data curation. MN, XHZ: Methodology, Investigation, Writing - review and editing.

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Figures

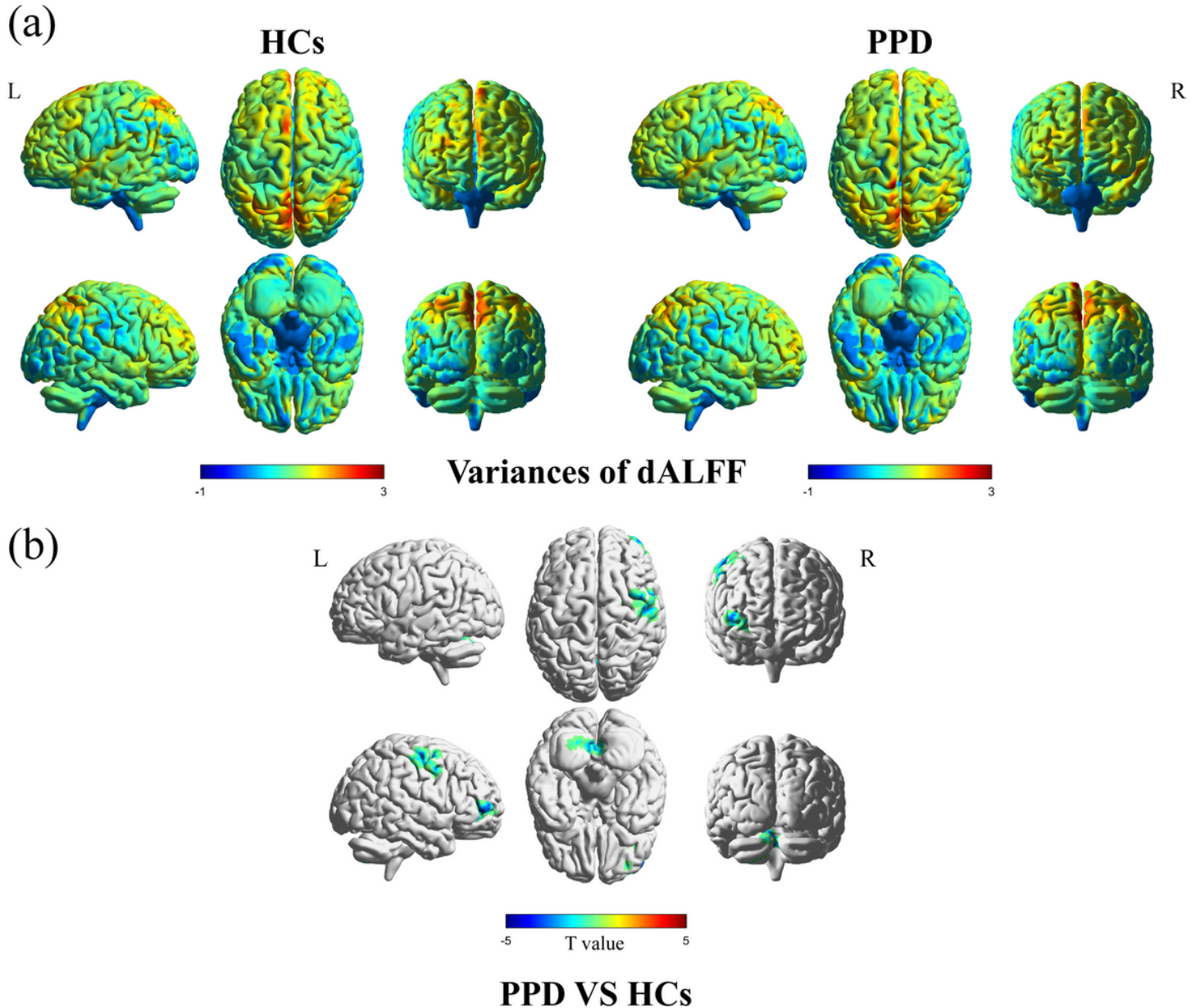


Figure 1

(a) Variances of dALFF value in different brains between HCs and PPD group; (b) Regions showing differences in the variances of dALFF between PPD and HCs ($p < 0.05$ corrected by GRF). The warm colors represented the significance of higher variances of dALFF values and the cool colors represented the significance of lower variances of dALFF values for the group comparisons. PPD, postpartum depression; HCs, healthy postpartum women controls.

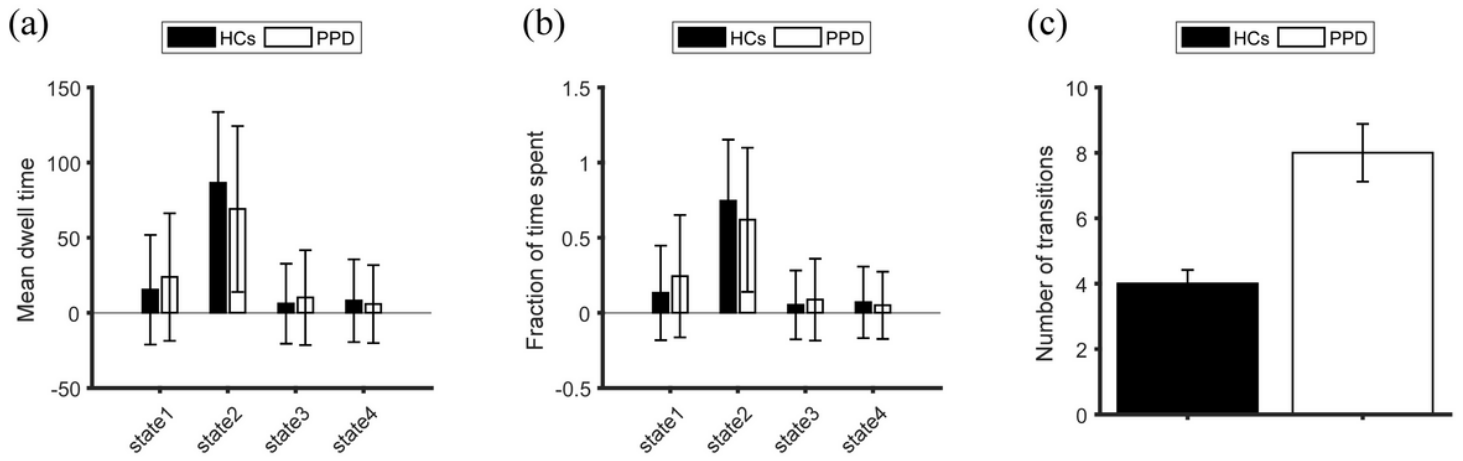


Figure 2

Group differences in metrics of dALFF states. (a) Group difference in the mean dwell time of four states. (b) Group difference in the fraction of time for four states. (c) Group difference in the number of transitions between HCs and PPD group. PPD, postpartum depression; HCs, healthy postpartum women controls.

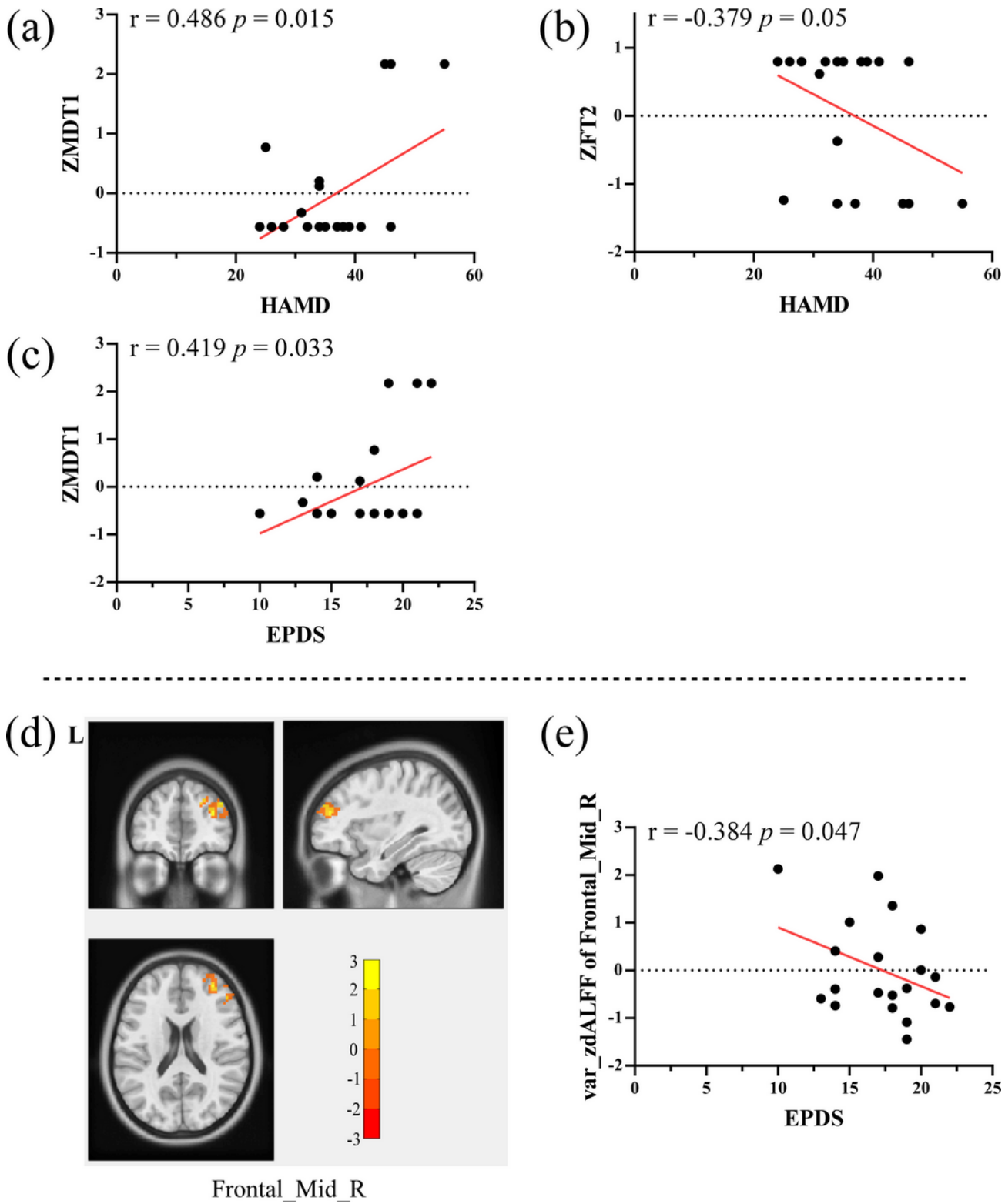


Figure 3

(a-c) Scatter plot showing the relationship between the metrics of dALFF states and HAMD, EPDS scores. (d) Specific brain region related to EPDS score. (e) Correlations between the var_zdALFF of Frontal_Mid_R and EPDS score ($r = -0.384$, $p = 0.047$). The warm colors represented the significance of higher variances of dALFF values. ZMDT1, the z score of the mean dwell time of state 1; ZFT2, the z score of the time fraction of state 2; var_zdALFF, the z score of variance of dALFF; Frontal_Mid_R, right middle frontal gyrus

Supplementary Files

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