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Altered frequency-specific/universal amplitude characteristics of spontaneous brain oscillations in patients with bipolar disorder

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ABSTRACT

The human brain is a dynamic system with intrinsic oscillations in spontaneous neural activity. Whether the dynamic characteristics of these spontaneous oscillations are differentially altered across different frequency bands in patients with bipolar disorder (BD) remains unclear. This study recruited 65 patients with BD and 85 healthy controls (HCs). The entire frequency range of resting-state fMRI data was decomposed into four frequency intervals. Two-way repeated-measures ANCOVA was employed to detect frequency-specific/universal alterations in the dynamic oscillation amplitude in BD. The patients were then divided into two subgroups according to their mood states to explore whether these alterations were independent of their mood states. Finally, other window sizes, step sizes, and window types were tested to replicate all analyses. Frequency-specific abnormality of the dynamic oscillation amplitude was detected within the posterior medial parietal cortex (centered at the precuneus extending to the posterior cingulate cortex). This specific profile indicates decreased amplitudes in the lower frequency bands (slow-5/4) and no amplitude changes in the higher frequency bands (slow-3/2) compared with HCs. Frequency-universal abnormalities of the dynamic oscillation amplitude were also detectable, indicating increased amplitudes in the thalamus and left cerebellum anterior lobe but decreased amplitudes in the medial superior frontal gyrus. These alterations were independent of the patients' mood states and replicable across multiple analytic and parametric settings. In short, frequency-specific/universal amplitude characteristics of spontaneous oscillations were observed in patients with BD. These abnormal characteristics have important implications for specific functional changes in BD from multiple frequency and dynamic perspectives.

1. Introduction

Bipolar disorder (BD) is a severe, chronic, and debilitating psychiatric disorder. It is characterized by recurrent depression, euthymia, and mania. Resting-state functional magnetic resonance imaging (fMRI) technology has provided a useful and noninvasive way to explore abnormal brain activity in patients with BD (Gong et al., 2020b; Huang et al., 2019). The oscillation amplitude of spontaneous brain activity has attracted increasing attention owing to these efforts. Physiologically, neural oscillations within specific classes generate brain rhythms (Gyorgy, 2006). Oscillation amplitude during rest may represent potentially meaningful and stable baseline brain function (Zuo et al., 2010). The amplitude of low-frequency fluctuations (ALFF) is recommended as an efficient index for quantifying the regional features of low-

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frequency oscillations of spontaneous brain activity, and has shown high test–retest reliability (Tomasi et al., 2013; Zhao et al., 2018). Static ALFF alterations have been frequently reported in patients with BD (Meda et al., 2015; Zhang et al., 2021c); however, most of these studies have focused on the routine frequency band (0.01–0.1 Hz), and inconsistent findings have been reported (Liu et al., 2012; Zhang et al., 2020; Zhong et al., 2019). Specifically, one study found that patients exhibited increased ALFF values in multiple brain regions, including the left insula, right caudate nucleus, temporal gyrus, bilateral inferior frontal gyrus, and cerebellum posterior lobe (Liu et al., 2012); however, one study only found increased ALFF values in the right inferior frontal gyrus (Zhang et al., 2020). Two studies found that patients exhibited decreased ALFF values in the left postcentral gyrus, left parahippocampal gyrus, cerebellum culmen, and cerebellum vermis (Liu et al., 2012); however, one study found that patients showed decreased ALFF values in the bilateral precuneus/PCC (PCu/PCC) (Zhong et al., 2019).

Other than the routine frequency band, convergent evidence suggests that the entire frequency band can be divided into distinct frequency intervals, and the most frequently reported frequency intervals are as follows: slow-5, 0.01–0.027 Hz; slow-4, 0.027–0.073 Hz; slow-3, 0.073–0.198 Hz; and slow-2, 0.198–0.25 Hz (Gong et al., 2021; Zuo et al., 2010). Several studies have found that the oscillation amplitude of blood oxygen level–dependent (BOLD) signals in different frequency bands has different neural manifestations and may represent specific physiological functions (Chai et al., 2020; Wang et al., 2016; Zuo et al., 2010). The neural oscillations of higher frequency bands (>0.1 Hz) may be correlated with more local information processing, and the neural oscillations of lower frequency bands (≤0.1 Hz) may be more useful for information exchange between distant brain regions (Gong et al., 2021). Thus, treating oscillations across different frequency bands may cause loss of information carried by different frequency bands (Gong et al., 2021). Frequency-specific ALFF alterations have been found in different neuropsychiatric disorders such as schizophrenia, major depressive disorder, and mild cognitive impairment (Li et al., 2017; Wang et al., 2016; Zuo et al., 2010). Few studies have been conducted in patients with BD. Zhong et al. (2019) found that patients with depressed BD had decreased ALFF values in the bilateral PCu/PCC at the slow-4 frequency, as well as decreased ALFF values in the right PCu and increased ALFF values in the right middle occipital gyrus at the slow-5 frequency. Chrobak et al. (2021) found that patients with euthymic BD have increased ALFF values in the left middle temporal pole at the slow-5 frequency and comparable ALFF values at the slow-4 frequency. Chang et al. (2019) did not distinguish patients' mood states and found that ALFF values were increased in the striatum, limbic, paralimbic, prefrontal cortex, and temporal gyrus and decreased in the visual cortex at the slow-5 and slow-4 frequencies. However, whether these abnormal ALFF manifestations are also present in higher frequency bands is unknown.

Notably, all the above findings relied on the assumption that brain activity remains static throughout the resting-state scanning process. However, the human brain is a complex dynamic signal system and dynamic alterations occur over the entire course of scanning (Faghiri et al., 2018). Exploring the dynamic characteristics of BOLD signals can deepen our understanding of intrinsic pathophysiological changes in mental disorders (Cui et al., 2020; Fu et al., 2018; Li et al., 2019). These explorations can be realized using a sliding-window approach. As a general rule, the temporal variability of the dynamic ALFF (dALFF) can be defined as the variance (such as the standard deviation) of ALFF maps across sliding windows (Liao et al., 2019). Studies on dALFF have rarely been conducted in patients with BD. Limited to the routine frequency band (0.01–0.1 Hz), two studies found that patients with depressed BD have decreased dALFF values in bilateral PCu/PCC (Gong et al., 2020a; Luo et al., 2021); two studies found that the patients with depressed BD have decreased dALFF values in the left and right temporal/fusiform gyrus (Sun et al., 2022; Tian et al., 2021); one study found that patients with manic BD have decreased dALFF values in the PCu/PCC (Liang et al., 2020); one study did not distinguish the patients' mood states and found that the patients have increased dALFF values in the right fusiform, right hippocampus, and right parahippocampus (Zhang et al., 2021a). These previous studies suggest that the dALFF in the PCu/PCC may be consistently decreased in patients with BD. However, due to the scarcity of related studies, more studies are needed to verify this speculation. Furthermore, no study has explored the dALFF alterations across different frequency bands in patients with BD.

The current study aimed to explore the dALFF abnormalities across different frequency bands in patients with BD. We expected to understand the underlying characteristics of spontaneous oscillations in BD from the perspective of multiple frequencies and dynamic changes, which were lacking in previous studies. First, resting-state fMRI data were collected from 65 BD patients in a euthymic or depressed mood state and 85 matched healthy controls (HCs). The entire frequency band of the fMRI data was decomposed into four frequency intervals (slow-5, 0.013–0.029 Hz; slow-4, 0.029–0.081 Hz; slow-3, 0.081–0.223 Hz; and slow-2, 0.223–0.250 Hz). The dALFF maps of all subjects were acquired across the four frequency bands using the sliding window approach, and two-way repeated-measures ANCOVA was used to explore frequency-specific and frequency-universal dALFF alterations in patients with BD. Second, this study further explored whether frequency-specific and frequency-universal dALFF alterations were independent of patients' mood states. Patients with BD were divided into two subgroups (euthymic and depressed BD). Another two-way repeated-measures ANCOVA was used to explore frequency-specific and frequency-universal dALFF alterations among patients with euthymic BD, patients with depressed BD, and HCs. Third, an additional analysis was conducted to make the current study comparable to previous studies. That is, the dALFF differences between patients with BD and HCs were compared in the routine frequency band (0.01–0.1 Hz). Moreover, other window sizes, step sizes, and window types were used to replicate all analyses. Finally, the same analyses were used to explore frequency-specific and frequency-universal static ALFF in the whole sample of patients with BD and its subgroups (i.e., patients with euthymic BD and depressed BD). We hypothesized that patients with BD would show frequency-specific and frequency-universal dynamic or static ALFF alterations in some brain regions, such as the PCu/PCC, which has been the most frequently reported brain region in previous studies on ALFF. Considering that altered dynamic or static ALFF values of the PCu/PCC were found both in patients with depressed BD (Gong et al., 2020a; Luo et al., 2021; Zhong et al., 2019) and manic BD (Liang et al., 2020), we speculated that these alterations would be independent of the patients' mood states. This study would expand our knowledge of the pathological mechanisms underlying BD.

2. Materials and methods

2.1. Subjects

In this study, 65 patients with BD and 85 HCs were recruited. All the subjects participated in our previous study (Zhang et al., 2021c). All patients met the diagnostic criteria for BD according to the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID)-Patient Edition (First et al., 2002). Depressive and manic symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967) and Young Mania Rating Scale (YMRS) (Young et al., 1978) respectively. The YMRS scores of all patients were < 7. The patients were divided into two subgroups according to their HAMD scores (euthymic group ≤ 7, depressed group > 7), as in our previous study (Zhang et al., 2021c) and other studies (Frank et al., 1991; Munkholm et al., 2015). All HCs met the diagnostic criteria of the non-patient version of the SCID. As described in our previous study (Zhang et al., 2021c), 9 patients and 14 HCs were excluded due to large head motion. Ultimately, 56 patients and 71 HCs were included in the final data

analysis. Demographic and clinical data are presented in Tables 1 and S1.

This study was approved by the Institutional Review Boards of the Brain Image Center of Beijing Normal University and Beijing Anding Hospital of Capital Medical University. All subjects' written informed consent were acquired before the study.

2.2. Imaging data acquisition

All subjects were scanned using a Siemens TIM Trio 3 T System (Siemens, Erlangen, Germany) at the Brain Imaging Center of the Beijing Normal University. Resting-state fMRI images (240 volumes) and T1 images (128 volumes) were obtained. The instructions for the subjects were the same as those used in our previous study (Zhang et al., 2021c). The parameters for imaging acquisition were as follows: for the echo planar imaging sequence (for functional images): axially collected, slices = 33, interlaced scanning, repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle (FA) = 90°, field of view (FOV) = 200 mm × 200 mm, matrix size = 64 × 64, slice thickness = 3.5 mm, gaps = 0.7 mm, voxel size = 3.13 mm × 3.13 mm × 4.2 mm; for T1-weighted 3D magnetization-prepared rapid gradient echo sequence (for T1 images): sagittally collected, TR/TE = 2530/3.39 ms, FA = 7°, FOV = 256 mm × 192 mm, matrix size = 192 × 192, thickness = 1.33 mm, voxel size = 1.33 mm × 1 mm × 1 mm.

2.3. fMRI data preprocessing

Data processing and analysis for (resting-state) brain imaging (DPABI) v5.1 (http://rfmri.org/DPABI) (Yan et al., 2016) was used to preprocess the fMRI data. After the first five time points were discarded, the remaining 235 images were first corrected for slicing time, and then realigned to the first image to correct for head motion. The same method used in our previous study (Zhang et al., 2021c) was used to calculate the framewise displacement and mean framewise displacement values. Next, several covariates were used for the nuisance covariate regression. These covariates were the Friston-24 parameters for head motion, head motion scrubbing regressor, and white matter and cerebrospinal fluid signals. Individual T1 images and the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox were used for accurate normalization to the Montreal Neurological Institute (MNI) space (voxel size = 3 × 3 × 3 mm^3). Finally, the linear trend was removed to avoid the effects of drift and noise.

Table 1
Demographic and clinical factors of the whole sample of the patients with bipolar disorders and the healthy controls.

	Mean ± SD		T or χ^2	*P*
	BD	HC		
Age[a]	29.52 ± 10.95	30.61 ± 10.87	−0.56	0.578
Gender (male/female) [b]	35/21	34/37	2.69	0.101
Education[b,c]	7/22/12/15	6/15/18/32	7.08	0.069
mean FD[a]	0.14 ± 0.06	0.13 ± 0.04	1.35	0.180
HAMD[a]	8.45 ± 8.04	0.75 ± 1.52	7.69	<0.001***
Medicine use				
Medicine-free (N, %)	5 (8.92 %)	–	–	–
Mood stabilizers (N, %)	28(50 %)	–	–	–
Antidepressants (N, %)	19(33.93 %)	–	–	–
Antipsychotics (N, %)	27(48.21 %)	–	–	–
Anti-anxiety drugs (N, %)	2(3.57 %)	–	–	–
Diphenhydrin hydrochloride (N, %)	3(5.36 %)	–	–	–
Benzodiazepines (N, %)	5(8.93 %)	–	–	–
Traditional Chinese medicine (N, %)	1(1.79 %)	–	–	–

Note: BD: Patients with bipolar disorder; HC: Healthy controls; FD: Framewise displacement; HAMD: Hamilton depression scale;
[a] We used two-sample t tests to compare these variables;
[b] We used χ^2 tests to compare these variables;
[c] This variable was showed in the following sequence: Junior high school / Senior high school or special secondary school / Junior college / Bachelor degree or above.
*** $P < 0.001$.

2.4. Frequency decomposition and dALFF calculation

The decoding rhythms of the brain system (DREAM) software (Gong et al., 2021), a reliable and valid tool for mapping human brain function from a multiple-frequency window into brain waves, was used to define different frequency intervals. The DREAM software was developed based on the natural logarithm linear law (N3L) (Buzsaki and Draguhn, 2004), which describes the relationship between the natural logarithm scale and different frequency intervals. It can be concluded that when plotted on a natural logarithm scale, the centers of each frequency interval fall on adjacent integer points. This law offers a theoretical framework for the parcellation of these brain oscillations into multiple frequency intervals. The DREAM software can decode brain oscillations using the sampling interval (TR) and the number of time points (N). The highest frequency $f_{max} = 1/(2 \times TR)$ can be detected in the neuronal signal, whereas the lowest frequency in the neuronal signals can be defined as $f_{min} = 1/(2 \times N \times TR)$. The range of different frequency bands of neural oscillations in the brain can be automatically divided using the DREAM software. In this study, the TR of the fMRI data was 2 s and N was 240. Thus, theoretically, in the logarithmic space, the highest frequency of our data should be $1/(2 \times 2) = 0.25$ Hz, and the lowest frequency should be $1/(2 \times 240 \times 2) = 0.001$ Hz. However, in our actual data, a frequency range of 0.001–0.013 Hz was not observed. Therefore, the actual lowest frequency of 0.013 observed in our data was taken as the lowest frequency. Thus, the whole frequency band of our subjects' resting-state fMRI data was decomposed into four frequency intervals: slow-5, 0.013–0.029 Hz, slow-4, 0.029–0.081 Hz, slow-3, 0.081–0.223 Hz, and slow-2, 0.223–0.250 Hz (Fig. S1). Although BOLD signals across higher frequency bands (e.g., slow-2 and slow-3 bands) are susceptible to physiological noise, previous studies have suggested physiological importance across higher frequency bands (Boubela et al., 2013; Salvador et al., 2005), and higher frequency bands may be more suitable for detecting individual differences in ALFF (Gong et al., 2021). Therefore, the following analyses were performed for all four frequency intervals.

The dALFF for each frequency interval was calculated using the sliding-window approach based on the temporal dynamic analysis (TDA) toolkit, which was merged in DPABI v5.1 (http://rfmri.org/DPABI) (Yan et al., 2016). Gonzalez-Castillo et al. (2015) suggested the use of a sliding window size between 10 s and 180 s to reasonably capture the dynamic fluctuations of whole-brain activities. Therefore, in the current study, a sliding window size of 48 TR was selected for the dALFF calculation with a step size of 2 TR. Hamming was selected as the window type for sliding the whole-brain BOLD time series. For each participant, 235 pre-processed time points were segmented into 102 sliding windows. In each sliding window, ALFF values were calculated voxel-wise. First, the time series of each voxel was converted into a frequency domain using a fast Fourier transform. Second, the square root of the power spectrum is calculated and averaged. The average square root is defined as the ALFF value. Third, each participant's ALFF maps was standardized into *z*-score maps using Fisher's *r*-to-*z* transformation. Across 102 sliding windows, the standard deviation of each *z*-score map was used to represent the dALFF of each subject. Then, *z*-standardization was applied to the dALFF maps to exclude the effects of global activity variability. Finally, all the dALFF maps were smoothed (full-width-at-half-maximum Gaussian kernel = 4 mm). The smoothed dALFF maps were entered into the second-level

analyses.

2.5. Additional dALFF calculation in the routine frequency band

The same method described in Section 2.4 was used to re-calculate each subject's dALFF values in the routine frequency band (0.01–0.1 Hz) using DPABI v5.1 software. The window size, step size, and window type were set to 48 TR, 2 TR, and Hamming, respectively.

2.6. Statistical analyses for dALFF

Differences in demographic and clinical factors between the whole sample of patients with BD and HCs were calculated using a two-sample *t*-test or the χ^2 test. Differences in the demographic and clinical factors among patients with euthymic BD, patients with depressed BD, and HCs were calculated using one-way ANCOVA or χ^2 test. All analyses were performed using SPSS 20.0 (SPSS, IL, USA).

A two-way repeated-measures ANCOVA was used in the second-level whole-brain analysis of dALFF in SPM12 (Wellcome Department of Cognitive Neurology, London, UK) to detect frequency-specific and frequency-universal dALFF alterations in the entire sample of patients with BD. In this analysis, group (patients with BD vs HCs) was a between-subject variable; frequency (slow-5 vs slow-4 vs slow-3 vs slow-2) was a within-subject variable; and age, gender, education level, and mean framewise displacement were nuisance covariates. The significance level was set at a cluster-level family-wise error–corrected *P* value ($P_{\text{FWE-corrected}}$) of < 0.05, and a voxel-level threshold of $P < 0.001$. Once a significant group * frequency interaction effect was found, dALFF values within the significant cluster would be extracted out for each voxel and averaged. The mean dALFF values of the significant cluster would be used in the following simple effect analysis to determine from which frequency interval differences between patients and controls came. And the significance level was set at Bonferroni-corrected *P* value of < 0.05.

The patients were further divided into euthymic BD and depressed BD groups to explore whether the findings were independent of the patients' mood states. Again, a two-way repeated-measures ANCOVA was used in the second-level whole-brain analysis of the dALFF. In this analysis, group (patients with euthymic BD vs patients with depressed BD vs HCs) was a between-subject variable; frequency (slow-5 vs slow-4 vs slow-3 vs slow-2) was a within-subject variable; and age, gender, education level, and mean framewise displacement were nuisance covariates. The significance level and post-hoc analyses were the same as those described above.

In our additional analysis, we focused on the routine frequency band (0.01–0.1 Hz). A second-level whole-brain analysis of the dALFF between patients with BD and HCs was performed using a two-sample *t*-test, and age, sex, education level, and mean framewise displacement were entered as nuisance covariates. The significance level was set at $P_{\text{FWE-corrected}} < 0.05$ and voxel-level threshold $P < 0.001$.

2.7. Validation analyses for dALFF

Other window sizes (64 TR and 80 TR), step size (1 TR), and window type (rectwin sliding window) were used in the re-run of the dALFF analysis to validate our results. The significance level was the same as that described above.

All first- and second-level dALFF analyses were restricted to a gray matter mask, which was made using the same method described in our previous study (Zhang et al., 2021c).

2.8. Static ALFF calculation and statistical analyses

The static ALFF is calculated as the sum of amplitudes in a certain frequency band (Zang et al., 2007). Using preprocessed fMRI data, static ALFF for each frequency interval and for each subject was calculated in DPABI v5.1 software and then included in the second-level analysis.

A two-way repeated-measures ANCOVA was used in the second-level whole-brain analysis in SPM12 to explore static ALFF alterations in the entire sample of patients with BD. In this analysis, group (patients with BD vs HCs) was a between-subject variable; frequency (slow-5 vs slow-4 vs slow-3 vs slow-2) was a within-subject variable; and age, gender, education level, and mean framewise displacement were nuisance covariates. Furthermore, the patients with BD were divided into two subgroups (i.e., patients with euthymic BD and depressed BD), and another two-way repeated-measures ANCOVA was conducted to explore whether the findings found in the whole sample of patients with BD were independent of the patients' mood state. In this analysis, group (patients with euthymic BD vs patients with depressed BD vs HCs) was a between-subject variable; frequency (slow-5 vs slow-4 vs slow-3 vs slow-2) was a within-subject variable; and age, gender, education level, and mean framewise displacement were nuisance covariates. In these two analyses, the significance level and post-hoc analysis were the same as those in the dALFF analyses.

3. Results

3.1. Demographic and clinical factor analyses

No significant differences were found in any of the demographic factors (all $P > 0.05$). The entire sample of patients with BD showed higher HAMD scores than HCs ($P < 0.001$, Table 1). The HAMD scores among patients with euthymic BD, patients with depressed BD, and HCs were also significantly different from each other; the HCs showed the lowest HAMD scores, and the patients with depressed BD showed the highest HAMD scores (all $P < 0.001$, Table S1).

3.2. dALFF analyses between the whole sample of patients with BD and the HCs across the four frequency intervals

The dALFF maps for each group across the four frequency intervals are shown in Fig. S2.

Two-way repeated-measures ANCOVA revealed significant group main effects in five clusters: the thalamus (patients > controls), left cerebellum anterior lobe (patients > controls), medial superior frontal gyrus (patients < controls), right superior temporal gyrus (patients < controls), and right lingual gyrus (patients < controls, Fig. 1 and Table 2). These findings suggest the presence of frequency-universal alterations in the dynamic oscillation amplitude of spontaneous brain activity in BD patients.

A significant main effect of frequency was widely observed in the whole brain (Fig. 2 and Table 2). A significant group * frequency interaction effect was found at the PCu/PCC (Fig. 3 and Table 2). Further post-hoc analysis showed that compared with the HCs, the patients with BD showed significantly decreased dALFF in the slow-5 and slow-4 bands ($P < 0.001$), but comparable dALFF in the slow-3 and slow-2 bands ($P > 0.05$), which indicated the presence of frequency-specific alterations in the dynamic oscillation amplitude of spontaneous brain activity in patients with BD.

3.3. dALFF analyses among patients with euthymic BD, patients with depressed BD, and HCs across the four frequency intervals

Two-way repeated-measures ANCOVA revealed significant group main effects in six clusters: the thalamus, medial superior frontal gyrus, left and right cerebellum anterior lobe, and left and right cerebellum posterior lobe (Fig. 4 and Table 3). Post-hoc analysis showed that compared with HCs, patients with euthymic BD and depressed BD exhibited increased dALFF in the thalamus and left cerebellum anterior lobe and decreased dALFF in the medial superior frontal gyrus. Patients with depressed BD exhibited increased dALFF in the right anterior lobe of the cerebellum compared with HCs. Patients with euthymic BD

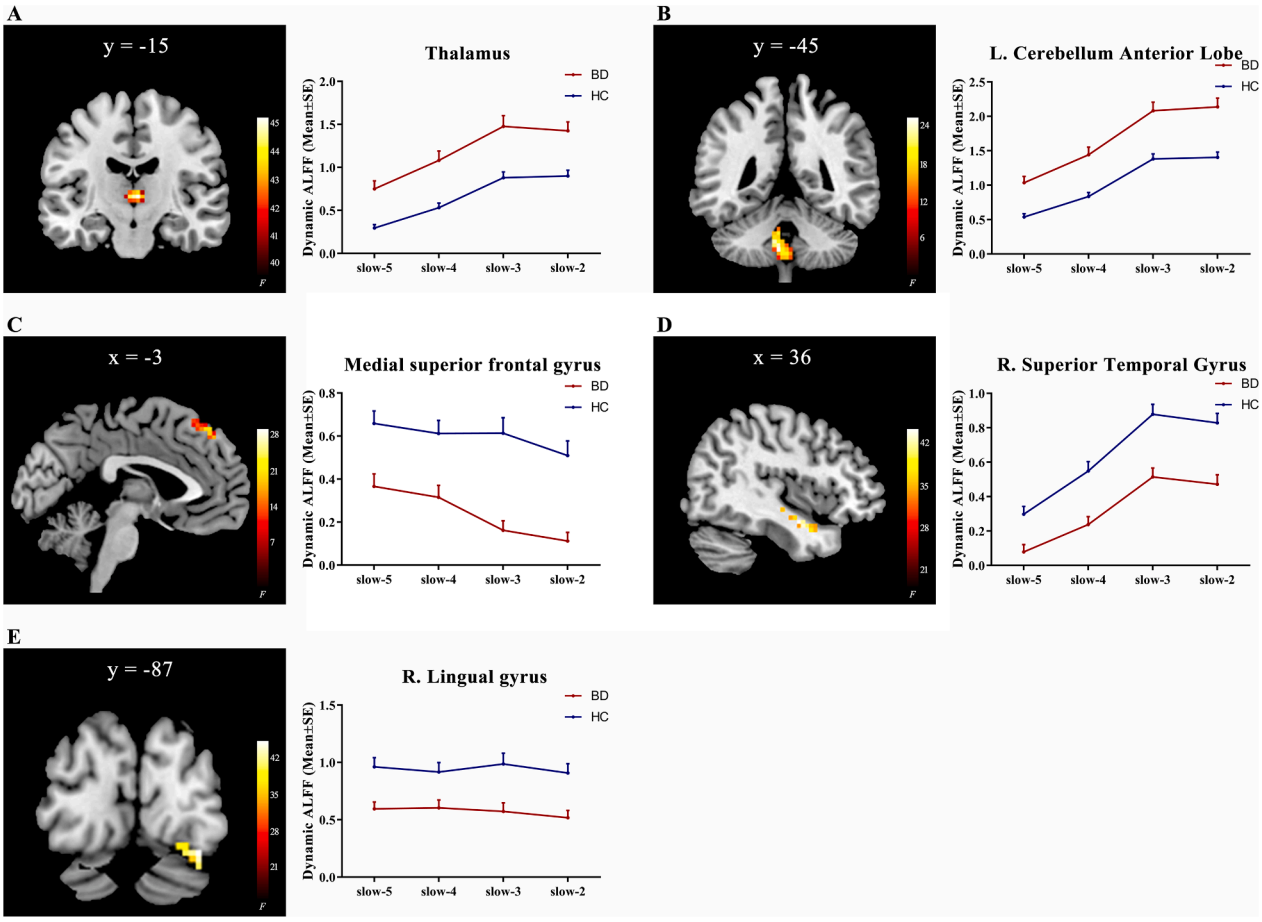

Fig. 1. Significant main effect of group on dALFF (window size, 48 TR; step size, 2 TR; window type, hamming). The left part is the significant brain regions, and the right part is the line charts of the averaged dALFF values within each frequency and within each group.

Table 2
Two-way repeated-measures ANCOVA analysis of dALFF in the whole sample of the patients with bipolar disorder and the healthy controls when the window size, step size and window type were set at 48TR, 2step and hamming.

Effects	Brain region	Hemisphere	Peak MNI coordinates	Peak F values	Cluster size	Cluster-level P_{FWE}	Post-hoc analyses (Bonferroni corrected)
Main effect of group	Thalamus	Left/Right	3, −15, 3	39.95	43	0.004**	–
	Medial superior frontal gyrus	Left/Right	0, 42, 48	29.32	42	0.005**	–
	Cerebellum anterior lobe	Left	−6, −45, −45	25.24	101	<0.001***	–
	Superior temporal gyrus	Right	42, −3, −18	18.13	34	0.016*	–
	Lingual gyrus	Right	30, −87, −18	16.41	33	0.019*	–
Main effect of frequency	Widespread in the brain	Left/Right	0, −60, 36	649.96	324,560	<0.001***	–
Group * frequency interaction	PCu/PCC	Left/Right	0, −54, 33	34.07	70	<0.001***	**slow-5: BD < HC, P < 0.001***** **slow-4: BD < HC, P < 0.001***** slow-3: BD = HC, P = 0.574 slow-2: BD = HC, P = 0.511

Note: BD: Patients with bipolar disorder; HC: Healthy controls; PCu/PCC: Precuneus/Posterior cingulate cortex; dALFF: Dynamic amplitude of low-frequency fluctuations.
*P < 0.05; ** P < 0.01; *** P < 0.001.

exhibited decreased dALFF in the left and right cerebellum posterior lobes compared to patients with depressed BD and HCs.

A significant main effect of frequency was found widely in the whole brain (Fig. 4 and Table 3). A significant group * frequency interaction effect was found at the PCu/PCC (Fig. 4 and Table 3). Post-hoc analysis showed that compared with HCs, patients with euthymic and depressed BD exhibited considerably decreased dALFF in the slow-5 and slow-4 bands, but comparable dALFF in the slow-3 and slow-2 bands.

3.4. Additional analyses of dALFF in the routine frequency band

In the routine frequency band (0.01–0.1 Hz), compared with the HCs, the whole sample of patients with BD showed a significantly decreased dALFF at the PCu/PCC (cluster size = 47, $P_{FWE\text{-corrected}}$ = 0.011, peak MNI coordinates: $x = -3$, $y = -51$, $z = 30$, $T = 5.64$, $P_{uncorrected} < 0.001$; Fig. 5). No remarkable increase in the dALFF was observed in the BD group.

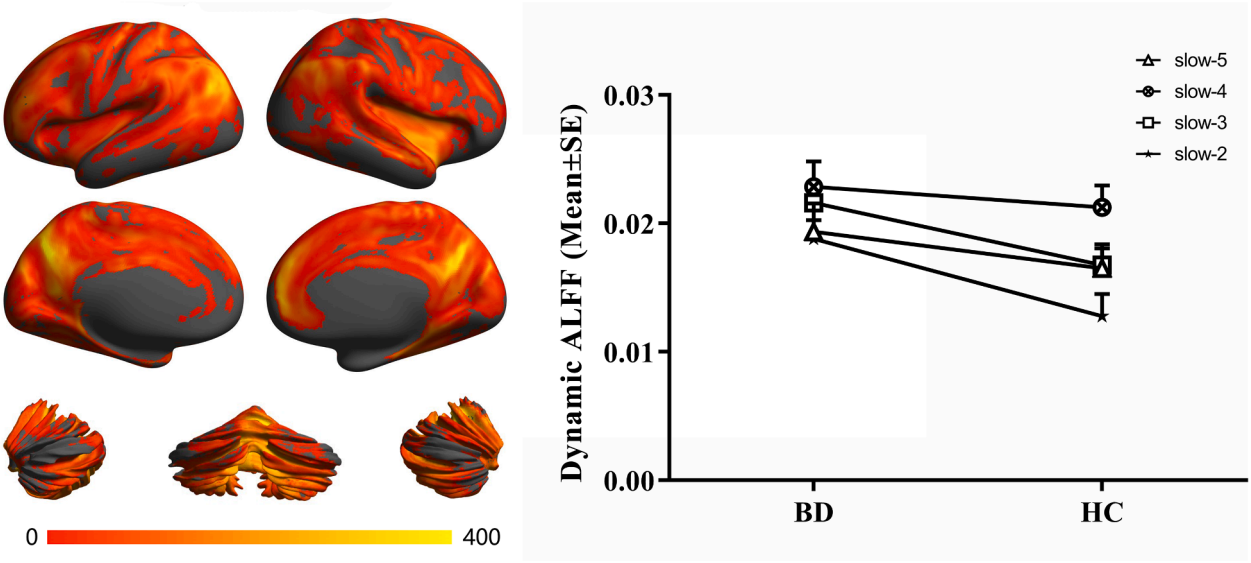

Fig. 2. Significant main effect of frequency on dALFF (window size, 48 TR; step size, 2 TR; window type, hamming). The left part is the significant brain regions, and the right part is the line charts of the averaged dALFF values within each frequency and within each group.

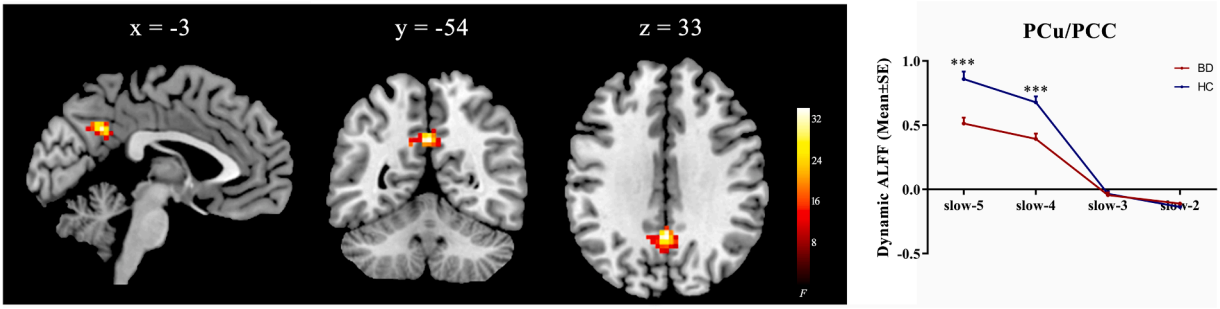

Fig. 3. Significant group * frequency interaction effect on dALFF (window size, 48 TR; step size, 2 TR; window type, hamming). The left part is the significant brain regions, and the right part is the line charts of the averaged dALFF values within each frequency and within each group.

3.5. Validation analyses for dALFF

The results for other window sizes (64 TR, 80 TR), step size (1 TR), and window type (rectwin) supported the main findings described above (Supplementary Materials).

3.6. Static ALFF analyses across the four frequency intervals

For the whole sample of patients with BD, two-way repeated-measures ANCOVA revealed significant group main effects in five clusters: the thalamus (patients > controls), left cerebellum anterior lobe (patients > controls), medial superior frontal gyrus (patients < controls), right superior temporal gyrus (patients < controls), and right lingual gyrus (patients < controls). A significant main effect of frequency was widely observed in the whole brain. A significant group * frequency interaction effect was found in the PCu/PCC and superior frontal gyrus. For the PCu/PCC, post-hoc analysis showed that compared with the HCs, the patients with BD showed significantly decreased static ALFF in the slow-5 and slow-4 bands ($P < 0.001$) but comparable static ALFF in the slow-3 and slow-2 bands ($P > 0.05$). For the superior frontal gyrus, post-hoc analysis showed that compared with the HCs, patients with BD showed significantly decreased static ALFF in the slow-5 and slow-4 bands ($P < 0.001$) and comparable static ALFF in the slow-3 band ($P > 0.05$), but increased static ALFF in the slow-2 band ($P = 0.010$) (Fig. 6 and Table 4).

For patients with euthymic BD and depressed BD, two-way repeated-measures ANCOVA revealed significant group main effects in six clusters: the thalamus, medial superior frontal gyrus, left and right cerebellum anterior lobes, and left and right cerebellum posterior lobes. Post-hoc analysis showed that compared with HCs, patients with euthymic BD and depressed BD exhibited increased static ALFF in the thalamus and left and right cerebellum anterior lobes and decreased static ALFF in the medial superior frontal gyrus. In addition, patients with euthymic BD exhibited decreased static ALFF in the left and right cerebellum posterior lobes compared to patients with depressed BD and HCs. A significant main effect of frequency was widely found in the whole brain. A significant group * frequency interaction effect was found in the PCu/PCC and superior frontal gyrus. For PCu/PCC, post-hoc analysis showed that compared with the HCs, patients with euthymic BD and depressed BD exhibited considerably decreased static ALFF in the slow-5 and slow-4 bands, but comparable static ALFF in the slow-3 and slow-2 bands. For the superior frontal gyrus, post-hoc analysis showed that, compared with the HCs, patients with euthymic BD exhibited considerably decreased static ALFF in the slow-5 and slow-4 bands; patients with depressed BD exhibited considerably decreased static ALFF in slow-5 frequency band, but increased static ALFF in the slow-4 band (Fig. S7 and Table S5).

4. Discussion

In the current study, dynamic spontaneous brain activity was assessed using the dALFF across four frequency intervals (slow-5,

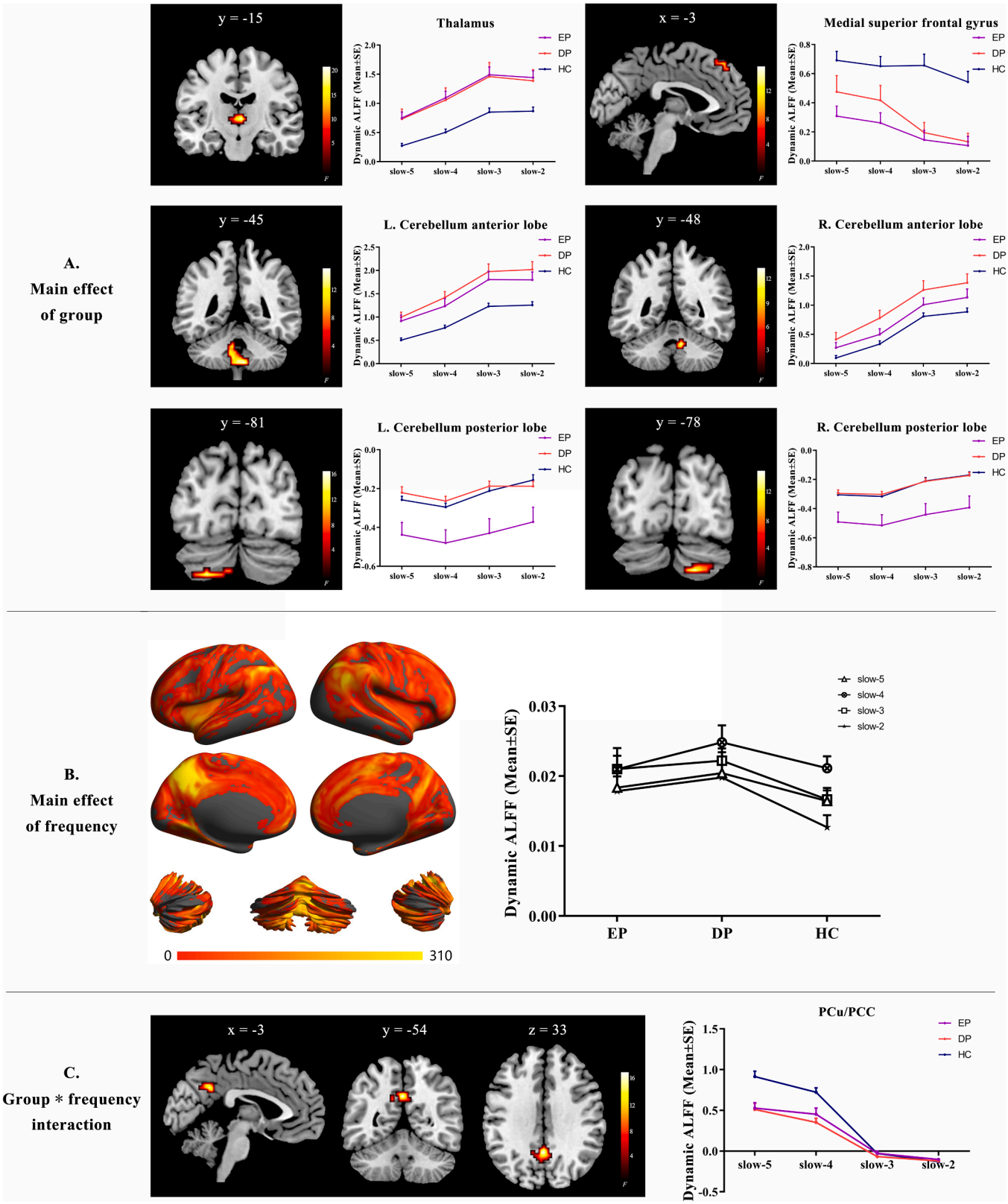

Fig. 4. Two-way repeated-measures ANCOVA of dALFF among patients with euthymic BD, patients with depressed BD, and HCs (window size, 48 TR; step size, 2 TR; window type, hamming). The left part is the significant brain regions, and the right part is the line charts of the averaged dALFF values within each frequency and within each group.

Table 3
Two-way repeated-measures ANCOVA analysis of dALFF among the patients with euthymic BD, the patients with depressed BD and the healthy controls when the window size, step size and window type were set at 48TR, 2step and hamming.

Effects	Brain region	Hemisphere	Peak MNI coordinates	Peak F values	Cluster size	Cluster-level P_{FWE}	Post-hoc analyses (Bonferroni corrected)
Main effect of group	Thalamus	Left/Right	3, −15, 3	20.46	37	0.005**	**EP > HC, *P* < 0.001***** **DP > HC, *P* = 0.001**** EP = DP, *P* = 1.000
	Medial superior frontal gyrus	Left/Right	0, 42, 48	15.02	33	0.010*	**EP < HC, *P* < 0.001***** **DP < HC, *P* = 0.009**** EP = DP, *P* = 1.000
	Cerebellum anterior lobe	Left	−6, −45, −45	14.38	94	<0.001***	**EP > HC, *P* = 0.001**** **DP > HC, *P* < 0.001***** EP = DP, *P* = 0.986
	Cerebellum anterior lobe	Right	9, −48, −30	13.95	30	0.016*	EP = HC, *P* = 0.272 **DP > HC, *P* = 0.002**** EP = DP, *P* = 0.317
	Cerebellum posterior lobe	Left	−24, −78, −45	15.24	34	0.008**	**EP < HC, *P* < 0.001***** DP = HC, *P* = 1.000 **EP < DP, *P* = 0.003****
	Cerebellum posterior lobe	Right	18, −81, −42	16.34	88	<0.001***	**EP < HC, *P* < 0.001***** DP = HC, *P* = 1.000 **EP < DP, *P* = 0.002****
Main effect of frequency	Widespread in the brain	Left/Right	0, −60, 36	655.04	324,620	<0.001***	–
Group * frequency interaction	PCu/PCC	Left/Right	0, −54, 33	17.28	47	0.001**	**Slow-5** **EP < HC, *P* = 0.001**** **DP < HC, *P* = 0.002**** EP = DP, *P* = 1.000 **Slow-4** **EP < HC, *P* = 0.010***** **DP < HC, *P* < 0.001***** EP = DP, *P* = 1.000 Slow-3 EP = HC, *P* = 1.000 DP = HC, *P* = 0.953 EP = DP, *P* = 1.000 Slow-2 EP = HC, *P* = 1.000 DP = HC, *P* = 1.000 EP = DP, *P* = 1.000

Note: BD: Patients with bipolar disorder; EP: Patients with euthymic BD; DP: Patients with depressed BD; HC: Healthy controls; PCu/PCC: Precuneus/Posterior cingulate cortex; dALFF: Dynamic amplitude of low-frequency fluctuations.
*$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

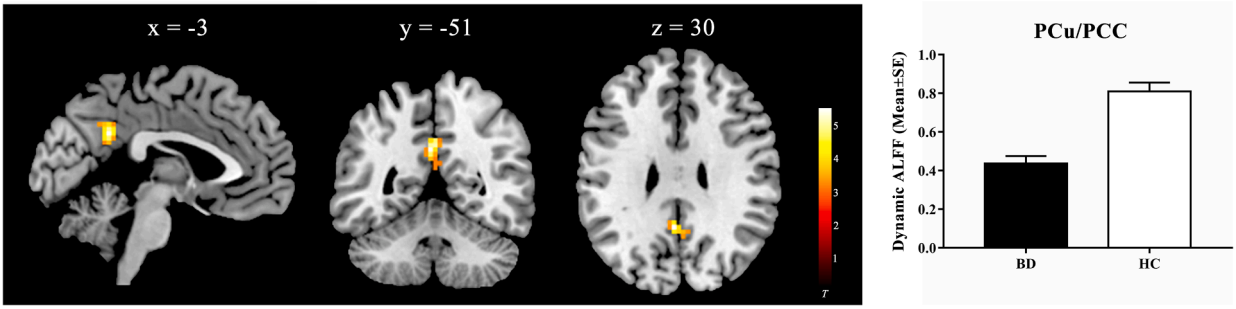

Fig. 5. Significant differences in dALFF between the whole sample of patients with BD and the HCs in the routine frequency band of 0.01–0.1 Hz (window size, 48 TR; step size, 2 TR; window type, hamming). The left part is the significant brain region, and the right part is the averaged dALFF values within each group.

0.013–0.029 Hz; slow-4, 0.029–0.081 Hz; slow-3, 0.081–0.223 Hz; and slow-2, 0.223–0.250 Hz) in patients with BD. Frequency-specific and frequency-universal dynamic characteristics of the oscillation amplitudes were found in these patients. In particular, frequency-universal dynamic characteristics of oscillation amplitude were found in the thalamus, left cerebellum anterior lobe, medial superior frontal gyrus, right superior temporal gyrus, and right lingual gyrus, and frequency-specific dynamic characteristics of oscillation amplitude were found in the PCu/PCC of patients with BD. Furthermore, most of the frequency-specific and frequency-universal dynamic characteristics of oscillation amplitude were independent of patients' mood states (i.e., euthymic and depressed mood states). In addition, analysis of the routine frequency band (0.01–0.1 Hz) validated the presence of a decreased dALFF in the PCu/PCC of patients with BD. The results were further validated using different window sizes, step sizes, and window types. In addition, all brain regions found in the dALFF analyses showed static ALFF alterations across the four frequency intervals in patients with BD, and most of these alterations were independent of the patients' mood states.

This study found that PCu/PCC showed frequency-specific alterations in patients with BD, as indicated by decreased dALFF (i.e., less dynamic segregation) in the slow-5 and slow-4 frequencies, and comparable dALFF in the slow-3 and slow-2 frequencies compared to the HCs. Previously, all studies relating to dALFF focused on the routine frequency band (0.01–0.1 Hz), and the most consistent finding was the

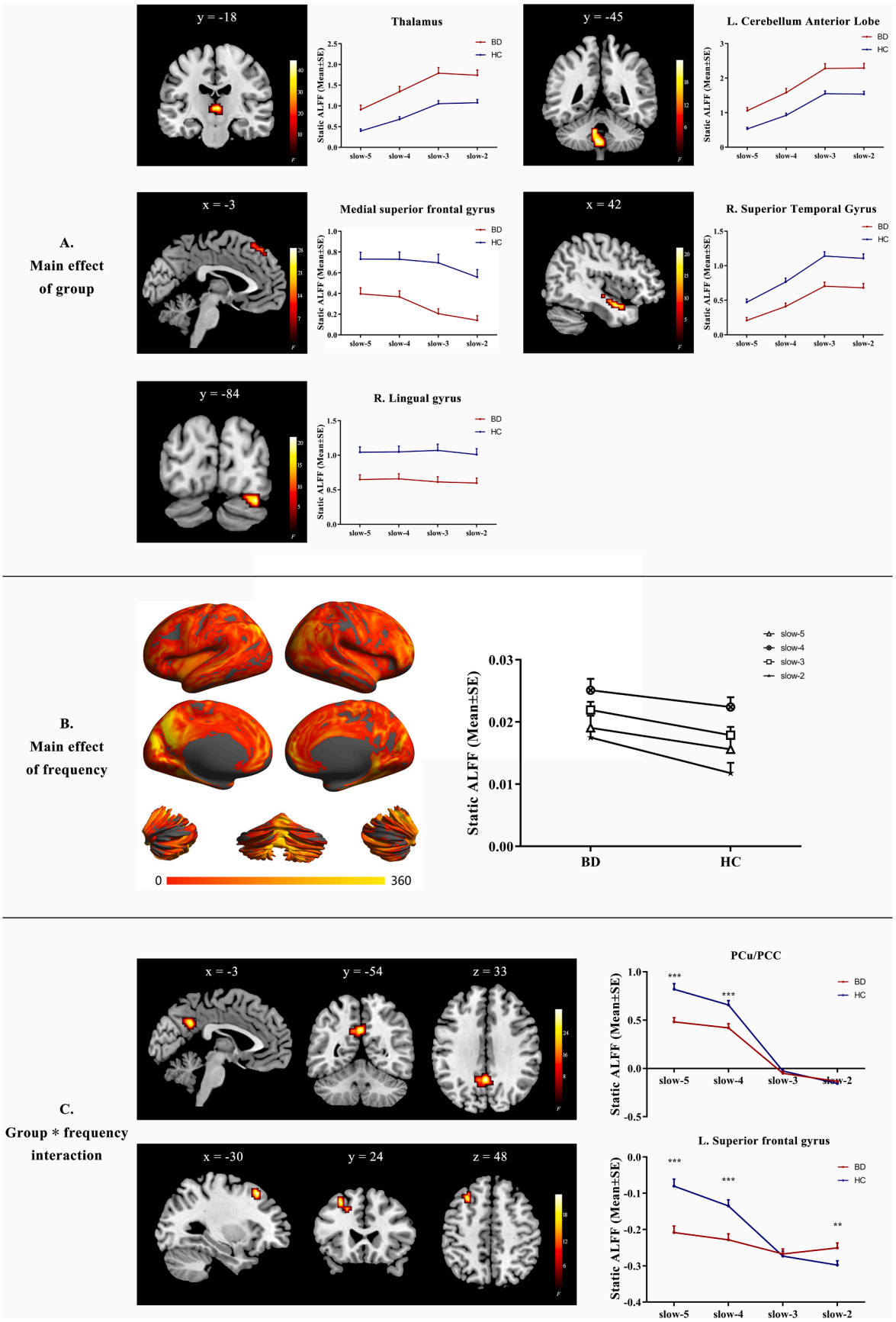

Fig. 6. Two-way repeated-measures ANCOVA of static ALFF in the whole sample of patients with BD and the HCs. The left part is the significant brain regions, and the right part is the line charts of the averaged static ALFF values within each frequency and within each group.

Table 4
Two-way repeated-measures ANCOVA analysis of static ALFF in the whole sample of the patients with bipolar disorder and the healthy controls.

Effects	Brain region	Hemisphere	Peak MNI coordinates	Peak F values	Cluster size	Cluster-level P_{FWE}	Post-hoc analyses (Bonferroni corrected)
Main effect of group	Thalamus	Left/Right	3, −18, 3	44.88	40	0.016*	–
	Medial superior frontal gyrus	Left/Right	0, 39, 51	29.14	36	0.027*	–
	Cerebellum anterior lobe	Left	−6, −45, −45	22.45	108	<0.001***	–
	Superior temporal gyrus	Right	42, 0, −21	21.65	42	0.012*	–
	Lingual gyrus	Right	33, −84, −21	21.82	42	0.012*	–
Main effect of frequency	Widespread in the brain	Left/Right	3, −63, 36	732.31	338,210	<0.001***	–
Group * frequency interaction	PCu/PCC	Left/Right	0, −54, 33	31.64	66	0.001**	**slow-5: BD < HC, *P* < 0.001*** slow-4: BD < HC, *P* < 0.001*** slow-3: BD = HC, *P* = 0.417 slow-2: BD = HC, *P* = 0.400**
	Superior frontal gyrus	Left	−30, 24, 48	23.38	78	<0.001***	**slow-5: BD < HC, *P* < 0.001*** slow-4: BD < HC, *P* < 0.001*** slow-3: BD = HC, *P* = 0.757 slow-2: BD > HC, *P* = 0.010***

Note: BD: Patients with bipolar disorder; HC: Healthy controls; PCu/PCC: Precuneus/Posterior cingulate cortex; ALFF: Amplitude of low-frequency fluctuations.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

decreased dALFF values in the PCu/PCC (Gong et al., 2020a; Liang et al., 2020; Luo et al., 2021). Based on these previous findings, the PCu/PCC seems to be the most vulnerable brain region in BD. In the current study, a decreased dALFF was also found in the PCu/PCC of patients with BD in the routine frequency band (0.01–0.1 Hz). This result is consistent with those of two previous studies that used a routine frequency band (Gong et al., 2020a; Luo et al., 2021). Together, these results suggest that decreased dALFF in the PCu/PCC prominently exists across the lower frequency bands but disappears in the higher frequency bands during rest in patients with BD. Thus, lower-frequency bands may be more sensitive for exploring PCu/PCC alterations in patients with BD. Moreover, the decreased dALFF in the PCu/PCC across the lower frequency bands was independent of patients' mood states. In a previous study, a decreased dALFF in the routine frequency band was also found in PCu/PCC in patients with manic BD (Liang et al., 2020). Therefore, we speculated that the decreased dALFF across the lower frequency bands in the PCu/PCC may be a trait-like variant in BD, regardless of patients' mood states, although further studies recruiting patients with manic, depressed, and euthymic BD are needed to test this speculation.

Functionally, PCu/PCC is a key node of the default mode network, which is activated during rest (Raichle et al., 2001). It is implicated in internally oriented tasks (like the retrieval of autobiographical episodic memory) and suppressed in externally oriented tasks (like working memory) (Elton and Gao, 2015). Compared with HCs, abnormalities in the PCu/PCC have been frequently reported in patients with depressed or euthymic BD, such as decreased static ALFF values (Liu et al., 2012; Zhang et al., 2022; Zhong et al., 2019), decreased activation during a self-reflection task (Zhang et al., 2015) and emotion-related tasks (Rey et al., 2014; Sepede et al., 2015; Tesli et al., 2015), and decreased gray matter volume (Nugent et al., 2006) and cortical thickness (Knochel et al., 2016). These results support that PCu/PCC indeed plays an important role in the pathogenesis of BD. Our results further depicted the frequency-specific characteristics of the oscillation amplitude of the PCu/PCC in patients with BD. In other words, compared with HCs, patients with BD showed less dynamic segregation (i.e., more stable) of the oscillation amplitude of the PCu/PCC across the lower frequency bands but comparable dynamic segregation across the higher frequency bands. This has deepened our understanding of the internal pathological mechanisms underlying BD. In addition, we noted that, limited to the lower frequency bands (0.01–0.1 Hz), decreased dALFF variability in the PCu/PCC can also be observed in patients with schizophrenia (Li et al., 2020) and major depressive disorders (Luo et al., 2021; Yao et al., 2020). Thus, we speculate that decreased dALFF variability in the PCu/PCC across the lower frequency bands (0.01–0.1 Hz) may not be specific to BD but a cross-diagnosis characteristic that commonly exists in major mental illness. Although studies across the higher frequency bands are lacking, findings obtained in the lower frequency bands highlight the pivotal role of time-variable brain activity of the PCu/PCC in BD, schizophrenia, and major depressive disorders.

Frequency-universal alterations in the dynamic oscillation amplitude of spontaneous brain activity have also been observed in patients with BD. In all the validation analyses conducted across the whole frequency range, the most consistent results were that patients with BD showed increased dALFF (i.e., more dynamic segregation) in the thalamus and left cerebellum anterior lobe and decreased dALFF in the medial superior frontal gyrus. This result indicated that the abnormal dALFFs in these three clusters were independent of the frequency bands. Furthermore, we found that these results were independent of patients' mood states. To the best of our knowledge, no study has reported abnormalities in the dALFF across the entire frequency range in BD. However, restricted to the routine frequency band, one study recruited patients with BD in depressed, euthymic, and manic mood states and found that these patients had an increased dALFF in the thalamus (Zhang et al., 2021a). To a certain extent, this study supports our findings. From a functional point of view, the thalamus is a relatively complex structure related to impaired function in BD. For example, patients with BD show decreased activation of the thalamus when completing tasks related to working memory, emotion, and sensory processing (Pomarol-Clotet et al., 2015; Rey et al., 2014; Shaffer et al., 2018). The cerebellum is regarded as an "emotional pacemaker" in BD (Minichino et al., 2014). Similar to PCu/PCC, the medial superior frontal gyrus is another key node in the default mode network (Franco et al., 2009). Several previous studies have provided clues to understand the abnormalities of these three clusters in the current study. Specifically, compared with HCs, patients showed decreased cerebral blood flow within these three clusters (Culha et al., 2008; Zhao et al., 2016, 2017). However, cerebral glucose metabolism is increased within the thalamus and cerebellum anterior lobe and decreased within the medial superior prefrontal gyrus (Ketter et al., 2001). Decreased cerebral blood flow may result from decreased gray matter volume and cortical thickness (Cho and Goghari, 2020; Kandilarova et al., 2019; Poletti et al., 2016; Zhang et al., 2021b). The abnormal pattern of cerebral glucose metabolism was similar to the

pattern of abnormal dALFF observed in this study. In short, the current study expanded our knowledge about anomalous dALFF in BD and further confirmed that some meaningful physiological signals related to mental disease exist across the whole frequency band, including higher frequency bands.

Furthermore, we noticed that in patients with BD, brain regions showing frequency-universal (including the thalamus, left cerebellum anterior lobe, and medial superior frontal gyrus) and frequency-specific (including the PCu/PCC) alterations in dALFF also showed similar abnormalities in static ALFF, and these alterations were independent of the patients' mood states (i.e., euthymic and depressed mood states). The only exception was that the frequency-specific alteration of the superior frontal gyrus was only found in static ALFF but not in dALFF. To the best of our knowledge, only two studies on BD conducted both static and dynamic ALFF analyses in the same study (Gong et al., 2020a; Tian et al., 2021), but both focused on the routine frequency band. In these two studies, although similar results were found in their analyses of both static and dynamic ALFF, different results were obtained. For example, among patients with BD who had suicide attempts, suicidal ideation, and without suicidal ideation and HCs, one-way ANOVA analysis of dALFF found significant results at the right temporal pole, right inferior temporal gyrus, right superior temporal gyrus, and PCu/PCC, but a similar analysis of static ALFF found the middle temporal gyrus. Across a certain frequency band, the static ALFF is calculated as the sum of amplitudes in a certain frequency band (Zang et al., 2007), and the dALFF measures the variance (such as the standard deviation) of amplitude changes across time courses. Across a certain frequency band, a higher static ALFF means higher sum of amplitudes of one brain region in a certain frequency band, and a higher dALFF means that amplitudes of one brain region are sometimes very high and sometimes very low (i.e., more dynamic segregation), but the sum of amplitudes (i.e., static ALFF) is not necessarily high. From this perspective, static and dynamic ALFF have different physiological meanings. Similar findings found in both static ALFF and dALFF indicate that both the sum of amplitudes and dynamic segregation of amplitudes were altered in certain regions of BD. The abnormality found in only one index can only indicate a change in one aspect of the oscillation amplitude.

5. Limitation

This study had three limitations. First, the dALFF alterations were not explored in patients with manic BD. However, focusing on the routine frequency band, Liang et al. (2020) recruited patients with BD I, who had a manic mood state, and found that patients showed decreased dALFF in PCC. This finding suggests that the decreased dALFF in the PCu/PCC may be independent of patients' mood states. Future work should verify whether frequency-specific alterations in PCu/PCC are trait-like variants in BD with different mood states. Second, considering that different types of medicines may interfere with normal brain chemistry in different ways (Schulz and Steimer, 2000), and we did not have enough information (dose, variety, and duration of different medications taken, etc.) to explore the medicines' influence on our results, as has been done in previous studies (Almeida et al., 2009; Phillips et al., 2008; Sackeim, 2001), we must admit that different types of medicines may be confounding factors in interpreting our results; however, our results were consistent with those studies recruiting unmedicated patients with BD (Gong et al., 2020a). In any case, the influence of medicines should be reduced or even excluded in future work. Third, the main findings of the entire sample of patients were validated using subgroup analysis. The sample size of each subgroup of patients was relatively small. Future studies should include more patients to make the results more generalizable.

6. Conclusion

This study is the first attempt to reveal the frequency-specific and frequency-universal dynamic characteristics of the oscillation amplitude in patients with BD. These findings open a door to understanding the underlying intrinsic neurobiological mechanism of BD from the perspective of multiple frequencies and dynamic changes, which provided a new idea to further understand the pathological mechanism of BD.

CRediT authorship contribution statement

Zhang Zhi-Fang: Formal analysis, Investigation, Methodology, Project administration, Funding acquisition, Visualization, Writing-original draft. **Bo Qi-Jing:** Formal analysis, Investigation, Methodology, Project administration, Funding acquisition, Writing-original draft. **Li Feng:** Data curation, Resources. **Zhao Lei:** Data curation, Resources. **Gao Peng:** Visualization. **Wang Yun:** Software, Supervision, Validation. **Liu Rui:** Software, Supervision, Validation. **Chen Xiong-Ying:** Software, Supervision, Validation. **Wang Chuan-Yue:** Conceptualization, Funding acquisition, Writing - review & editing. **Zhou Yuan:** Conceptualization, Writing - review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103207.

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