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Surface-based regional homogeneity in bipolar disorder: A resting-state fMRI study

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ABSTRACT

Surface-based, two-dimensional regional homogeneity (2dReHo) was used in the current study to compare local functional synchronization of spontaneous neuronal activity between patients with bipolar disorder (BD) and healthy controls (HC), rather than volume-based, three-dimensional regional homogeneity (3dReHo) methods that have been previously described. Seventy-one BD patients and 113 HC participated in structural and resting-state fMRI scans. Participants ranged in age from 12 to 54 years. All subjects were rated with the Young Mania Rating Scale and the Hamilton Depression Rating Scale. BD patients showed reduced surface-based ReHo across the cortical surface, both at the global level and in the left ventral visual stream (VVS). Additionally, ReHo value across the cortical surface showed a significant negative correlation with age in both groups at the global level. Abnormal activity in the left VVS cortex may contribute to the pathogenesis of BD. Therefore, surface-based ReHo may be a useful index to explore the pathophysiology of BD.

1. Introduction

Bipolar disorder (BD) is one of the most challenging psychiatric disorders to manage, with both periods of depression and elevated mood. BD patients without a history of mania are frequently misdiagnosed, leading to inadequate treatment (Parker, 2000). Furthermore, the pathophysiology underlying BD remains unclear.

Resting-state functional magnetic resonance imaging (rfMRI) evaluates regional interactions in the brain that occur when an individual is not performing an explicit task (Biswal, 2012). Several recent studies have reported functional abnormalities in patients with BD using rfMRI (Minuzzi et al., 2017; Wang et al., 2017). Among several functional homogeneity measures of rfMRI, regional homogeneity (ReHo) is the most widely used to provide information about local activity within a small region of the brain (Zang et al., 2004) and is strongly recommended as an algorithm for BD studies (Vargas et al., 2013).

As such, ReHo has been widely used to investigate BD within the past decade (Gao et al., 2014; Liang et al., 2013; Liu et al., 2012). To our knowledge, all previous fMRI studies examining ReHo in BD patients to determine local synchronization of spontaneous neuronal activity have done so via three-dimensional (3D) ReHo (Lin et al., 2018; Wei et al., 2018). Despite variation among different research designs, results consistently suggest extensive brain regions with altered local synchronization of spontaneous neuronal activity exist in patients with BD (Gao et al., 2014; Lim et al., 2013; Syan et al., 2018). Altered regional brain activity presents evidence for abnormality in BD during a resting state, providing fresh insights into the possible pathophysiological mechanisms underlying BD, as well as potential treatment options. However, voxels close to the boundaries between gray and white matter show remarkable partial volume effects. It has been demonstrated that

Abbreviations: 2dReHo, two-dimensional regional homogeneity; 3D, three-dimensional; ANCOVA, Voxelwise one-way analysis of covariance; BBR, boundary-based registration; BD, bipolar disorder; BOLD, blood oxygen level dependent; CCS, Connectome Computation System; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th; EPI, echo planar imaging; FSPGR, fast-spoiled gradient echo; FWE, family-wise error; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Rating Scale; HC, healthy control; K-SAD-PL, Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version; maxRot, maximum rotational degree; maxTran, maximum translational distance; mcBBR, minimal cost of the BBR co-registration; meanFD, mean frame-wise displacement; *n*, number

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compared with 3dReHo, two-dimensional (2d) ReHo is more specific to the intrinsic functional organization of the cortical mantle and has higher test-retest reliability at the cost of restricting analyses to the cortical mantle (Jiang and Zuo, 2016).

In the present study, two-dimensional regional homogeneity (2dReHo) was used to detect abnormalities of local functional synchronization of spontaneous neuronal activity in BD. We compared the resting-state local functional homogeneity of patients with BD to those of healthy participants. As ReHo serves as an index to demonstrate the temporal synchronization of regional blood oxygen level dependent (BOLD) signals and reflect the coordination of local neuronal activity, we hypothesized that patients with BD would demonstrate abnormal local synchronization of spontaneous neuronal activity across the global cortex mantle, if a global difference existed. However, if a local cluster difference was observed, this would imply that the specific region may be involved in the neuropathophysiological mechanisms underlying BD. Specifically, 2dReHo has been associated with some phenotypic variables, such as age (Jiang et al., 2015). Previous correlation studies have demonstrated that the normal aging process may disrupt local homogeneity at the millimeter scale (Fair et al., 2009; Lopez-Larson et al., 2011; Wu et al., 2007); however, the exact correlation between age and ReHo still remains unclear. Therefore, the present study also aimed to detect the correlation tendency between ReHo and age, both for patients with BD and healthy controls (HC).

2. Materials and methods

2.1. Participants

The Ethics Committee of the First Hospital of China Medical University approved this study. A total of 184 individuals were enrolled in the present study, including 71 patients with BD (49 subjects with BD type I, 22 subjects with BD type II) who were recruited from the outpatient facility of the Department of Psychiatry, in the Mental Health Center of the Shenyang and the First Affiliated Hospital of China Medical University. The BD diagnosis for adult patients was individually determined by two professional psychiatrists with the use of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th (DSM-IV) criteria. Adolescent patients were diagnosed via the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version (K-SAD-PL). HC (n = 113) were recruited from the community of Shenyang, China. All HC were interviewed to confirm that they were without any DSM-IV disorders in their first-degree relatives. Neuropsychological tests, including the Young Mania Rating Scale (YMRS), Hamilton Anxiety Scale (HAMA), and the Hamilton Depression Rating Scale (HAMD), were used to assess mood state on the day of the scan for all individuals. Inclusion criteria for all participants were between ages 12 and 54, right-handed, no history of neurological disorders or head trauma with loss of consciousness lasting more than 5 min, no history of drug or alcohol abuse, no major medical condition, no physical illness of any kind, and no contraindications for MRI. Participants were excluded when head translation or rotation movement $>$ 2.0 mm or 2.0° occurred during scanning. Eighteen (25.4%) BD patients met DSM-IV criteria for a manic, mixed, or hypomanic episode; 38 (53.5%) for a depressive episode; and 15 (21.1%) were euthymic on the day of the scan. To avoid risk of mood destabilization, participants with BD in our study were allowed to continue any other psychotropic medications. At the time of the study, 26 patients in the BD group were without medication, and 45 were medicated, including mood stabilizers, antidepressants, antipsychotics, anxiolytics, and/or benzodiazepines. We also verified that the medication status of all patients was stable during the past two months and that all patients were currently experiencing a clinically stable mood status for the MRI scan, despite the manic or mixed state shown in the neuropsychological tests. After receiving a complete outline of the study, all adult participants, and parents of adolescent participants, provided written informed consent.

2.2. MRI data acquisition

Each participant was scanned with a GE Signa HDX 3.0 Tesla MR Scanner in the Department of Radiology of the First Affiliated Hospital of China Medical University. Head motion was reduced by applying foam pads. Three-dimensional, T1-weighted images were collected in a sagittal plane by use of a fast-spoiled gradient echo (FSPGR) sequence (TR 7.1 ms, TE 3.2 ms, FOV 240 × 240 mm, FA 15°, matrix 240 × 240, 1 mm slice thickness with no gap). Scanning time lasted for 8 min and 28 s. Functional resting-state images were acquired with the use of a gradient echo planar imaging (EPI) sequence (TR 2000 ms, TE 30 ms, FOV 240 × 240 mm, FA 90°, matrix 64 × 64, 3 mm slice thickness with no gap, 35 slices). Scanning time lasted for 6 min and 40 s. All participants were instructed to lie still with their eyes closed and to let their mind wander during the scan.

2.3. Data processing

For each participant, all image data were preprocessed by the Connectome Computation System (CCS; http://zuolab.psych.ac.cn/ccs.html), which was based on FCP scripts (http://www.nitrc.org/frs/downloadlink.php/2628) by integrating AFNI (Cox, 2012), FSL (Isler and Neugebauer, 2013), and FreeSurfer (Fischl, 2012) software with shell, as well as MATLAB scripts in the Dell Blade Cluster System at the Institute of Psychology, Chinese Academy of Sciences. The CCS pipeline (Xu et al., 2015) provides a data-preprocessing platform for both structure and function (Jiang et al., 2015; Zuo et al., 2013). The structural image processing steps were as follows: (1) MRI spatial noise removal (Zuo and Xing, 2011); (2) intensity correction; (3) brain extraction and tissue segmentation; (4) cutting plane generation; (5) mesh tessellation and deformation; and (6) individual surface normalization. The functional image processing steps consisted of (1) time series despiking; (2) slice timing; (3) volume aligning; (4) Four-dimensional global mean imaging intensity normalization; (5) head motion and noise elimination (Satterthwaite et al., 2013; Yan et al., 2013); (6) multiple linear regression (Yan et al., 2013; Zuo et al., 2013); (7) temporal filtering; and (8) alignment of spatial correspondences between individual structural and functional images by use of a boundary-based registration (BBR) algorithm (Greve and Fischl, 2009).

Following the preprocessing steps to exclude subjects with low-quality multimodal imaging datasets, such as bad brain extraction or surface construction, from further analyses, CCS pipeline provides a quality control procedure (QCP; http://zuolab.psych.ac.cn/ccs/QC.html) for both structural and functional images. The QCP included image screenshots for visual inspection of (1) skull stripping or brain extraction; (2) segmentation of brain tissue; (3) head motion blurring during rfMRI; (4) reconstruction of pial and white surfaces; (5) functional image registration based on BBR and other quality metrics (Jiang et al., 2015). These quality metrics included (1) head movement, including the maximum translational distance (maxTran) and the maximum rotational degree (maxRot); (2) mean frame-wise displacement (meanFD) (Patriat et al., 2013); and (3) the minimal cost of the BBR co-registration (mcBBR) (Greve and Fischl, 2009). All datasets matched the following criteria: (1) maxTran $\leq$ 2 mm; (2) maxRot $\leq$ 2°; (3) meanFD $\leq$ 0.2 mm; and (4) mcBBR $<$ 0.6. All participants passed QCP for subsequent analyses.

2.4. Surface-based local functional homogeneity: 2dReHo

Due to its robustness against various types of noise (Zuo and Xing, 2014), surface-based 2dReHo metrics (Zuo et al., 2013) were applied to characterize the local short-range functional homogeneity by integrating noise-filtering operations in both spatial and temporal domains on the cortical surface. To calculate 2dReHo for a given vertex on

the surface grid of interest (*fsaverage5*), we identified its 6 nearest-neighbor vertices and computed KCC of the rfMRI time series for all seven vertices, as in Eq. (1), where K is the number of neighbors of the voxel, n is the number of time points, R_i ($i = 1, \ldots n$) is the ranks of its BOLD time series, $\bar{R}_i$ is the mean rank at the ith time point across its neighbors, and $\bar{R}$ is the overall mean rank across all time points and neighbors. This procedure was repeated for each vertex of the global brain surface to form a vertex-wise 2dReHo map. Spatial smoothing steps were followed for all the participants, with a Gaussian kernel, with 10-mm full width at half maximum, on fsaverages5.

$$KCC = \frac{\sum_{i=1}^{n} R_i^2 - n(\bar{R})^2}{\frac{1}{12}K^2(n^3 - n)} = 12\frac{\sum_{i=1}^{n}(\bar{R}_i)^2}{(n^3 - n)} - 3\frac{(n+1)}{(n-1)} \quad (1)$$

2.5. Statistical analysis

SPSS was used to compare differences between groups. Independent t tests were used for continuous variables, and chi-square tests were used for categorical variables. The level of two-tailed statistical significance was set at $p < 0.05$ for all tests. Voxelwise one-way analysis of covariance (ANCOVA) tests (covariates: age, gender, mcBBR, and rmsFD) were used for analyses of 2dReHo differences between the BD and HC groups. To correct for multiple comparisons, we employed a cluster-level correction algorithm. Specifically, this algorithm used a threshold of the uncorrected $p < 0.001$ to format the clusters, which were further cleaned by a family-wise error (FWE) correction of $p < 0.05$ (Bernal-Rusiel et al., 2010). The Pearson and Spearman correlation coefficients between each vertex on the surface and age and clinical scale score were calculated. For this analysis, we again employed a cluster-level FWE correction for multiple comparisons.

3. Results

3.1. Demographic data

Demographic data are shown in Table 1. BD and HC groups were well-matched in age and gender. Moreover, medication status, age of illness onset, YMRS, HAMD, and HAMA score of BD patients are also included in Table 1.

3.2. Surface-based regional homogeneity differences between BD and HC

In comparison with HC at the global level, BD patients showed reduced surface-based ReHo across the cortical surface (Fig. 1). At the cluster level, patients with BD showed lower 2dReHo than HC in the left ventral visual stream (VVS) cortex (Fig. 2). Results of the independent sample t tests are shown in Table 2.

Table 1
Demographic data for BD versus HC participants.

Characteristics	BD (n = 71)	HC (n = 113)	t/x^2	p
Age (years)	26.11 (9.15)	26.61 (8.99)	0.401	0.69
Sex, n	28:43 (male: female)	46:67 (male: female)	0	0.99
YMRS	8.12 (10.63)	–	–	–
HAMD	12.83 (10.05)	–	–	–
HAMA	10.51 (9.90)	–	–	–
Medication (yes/no)	45/26	–	–	–
Illness duration (month)	16.85 (18.19)	–	–	–

Parentheses numbers denote standard deviations. BD, bipolar disorder; HC, healthy control; n, number; NA, not applicable; YMRS, Young Mania Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Rating Scale.

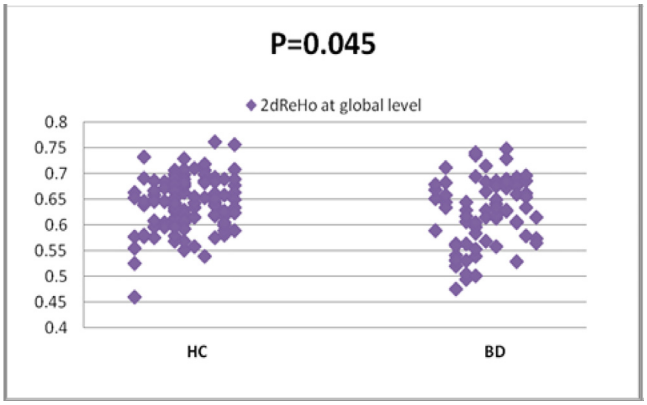

Fig. 1. BD patients showed reduced 2dReHo compared with HC at the global level ($p = 0.045$) across the cortical surface. 2dReHo, two-dimensional regional homogeneity; BD, bipolar disorder; HC, healthy control.

3.3. Correlation analysis

For the BD group, no significant correlations were found between 2dReHo values in the left VVS cortex and clinical scale score (YMRS, HAMD, HAMA) or illness duration. Moreover, there were no significant differences in 2dReHo values either between two BD types (type I/type II: 49/22) or two medication status (on/off: 45/26). There were no significant differences in 2dReHo among three states (manic or hypomanic episode/depressive episode/euthymic: 18/38/15).

The surface-based ReHo value across the cortical surface was significantly correlated with age negatively both in the BD and HC group at the global level (Table 3: BD: $r = -0.363$, $p = 0.002$*; Table 4: HC: $r = -0.232$, $p = 0.013$*).

4. Discussion

ReHo is defined as a local measure for quantifying functional synchronizations between neighboring vertices, which is distinct from remote functional-connectivity measures (Jiang and Zuo, 2016). Abnormal ReHo suggests that there are changes in spontaneous neuronal activity at the local level, or that there are atypical patterns of neuronal synchrony across global networks. With its ability to detect unpredicted hemodynamic responses, ReHo could help us to better understand highly complex brain computations. ReHo was originally proposed in 3D volumetric imaging by Zang and colleagues (Zang et al., 2004). In recent years, with further development of ReHo methodologies, Zuo et al. (2013) extended computations onto a sheet-like 2D cortical mantle. 2dReHo has been recommended instead of 3DReHo (Zuo et al., 2013) due to its higher specificity of the intrinsic functional organization of the cortical mantle and its higher test-retest reliability (Jiang and Zuo, 2016). Observations in healthy subjects have suggested that 2dReHo could serve as a standard neuroimaging marker for investigating human brain function (Jiang et al., 2015) and that this method could be extremely useful for researchers aiming to integrate various measures of both structure and function of the cortical surface (Zuo et al., 2013).

To the best of our knowledge, this is the first study of 2dReHo in patients with BD. BD patients demonstrated decreased vertex-wise functional homogeneity across the cortical surface, both at the global level and in the left VVS cortex. Our findings at the global level reveal that patients with BD exhibited decreased local synchronization of spontaneous neuronal activity across the global cortical mantle.

VVS is associated with visual representations and object recognition. Visual information enters the VVS through the primary visual cortex (V1). Information from V1 projects to the secondary visual cortex (V2), which then proceeds to the fourth visual area (V4) on the lateral and ventromedial surfaces of the hemisphere. Subsequently, V4

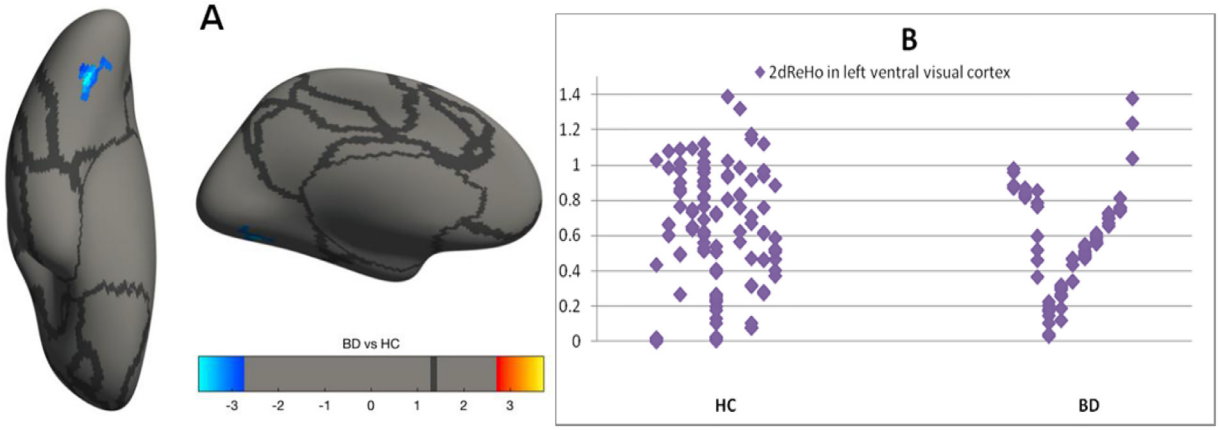

Fig. 2. Reduced 2dReHo in left VVS cortex in BD patients was visualized across the cortical surface and compared with that of HC ($p = 0.001$). The cluster in Fig. 2A showed a major decrease in 2dReHo located in the left VVS cortex. The cluster-level scatter gram (Fig. 2B) was derived from the group comparisons using vertex-wise statistical tests. 2dReHo, two-dimensional regional homogeneity; BD, bipolar disorder; HC, healthy control.

Table 2
Independent sample *t*-test results of 2dReHo values between HC and BD groups.

	Diagnosis	*n*	Mean value	Standard deviation	*t*	*p*
Global 2dReHo	HC	113	0.639969	0.049646	2.022	0.045
	BD	71	0.621799	0.064704		
Cluster 2dReHo	HC	113	0.619322	0.357010	3.257	0.001
	BD	71	0.405718	0.474685		

2dReHo, two-dimensional regional homogeneity; BD, bipolar disorder; HC, healthy control; *n*, number.

Table 3
Pearson correlation results between 2dReHo values and age in the BD group.

		gReHo (BD)	Age (BD)
gReHo (BD)	Pearson Correlation	1	−0.363**
	Sig. (2-tailed)		.002
	n	71	71
Age (BD)	Pearson Correlation	−0.363**	1
	Sig. (2-tailed)	.002	
	n	71	71

2dReHo, two-dimensional regional homogeneity; BD, bipolar disorder.
** Correlation is significant at the 0.01 level (2-tailed).

Table 4
Spearman's correlation results between 2dReHo values and age in the HC group.

			gReHo (HC)	Age (HC)
Spearman's rho	gReHo (HC)	Correlation Coefficient	1.000	−0.232*
		Sig. (2-tailed)		.013
		n	113	113
	Age (HC)	Pearson Coefficient	−0.232*	1.000
		Sig. (2-tailed)	.013	
		n	113	113

2dReHo, two-dimensional regional homogeneity; HC, healthy control.
* Correlation is significant at the 0.05 level (2-tailed).

projects to the inferior temporal lobe, which is putatively one of the final visual areas related to object recognition within the VVS. Recent studies on morphology and visual function have revealed that visual deficits might participate in the pathophysiology of BD. Patients with BD present quantifiable thinning of the macular retinal nerve-fiber layer, ganglion cell layer, inner plexiform layer, and peripapillary retinal nerve-fiber layer (Garcia-Martin et al., 2018). Another study on visual-processing deficits demonstrated that initial eye acceleration was decreased and the ability to adjust eye acceleration to increasing target acceleration was impaired in patients with BD, which might reflect a fundamental imbalance between processing external input and acting according to internal preferences (Trillenberg et al., 2017).

Different components of the VVS project to different areas of the brain (Kravitz et al., 2013). The VVS has strong connections with the prefrontal cortex (Kaskan et al., 2016; Takahashi et al., 2013) and the limbic system (McIntosh et al., 1996), which have been implicated in planning complex cognitive behavior, as well as moderating social behavior and emotionality. Due to the neuroanatomical connections of the VVS, the VVS is influenced not only by stimuli in visual receptive fields, but also by other components such as behavior, emotion, and stimulus salience. Thus, the decreased activity that we measured in the VVS cortex of BD patients may be related to their significant mood swings.

Recent fMRI studies have indicated that various parameters in the VVS differ between healthy individuals and clinical populations with schizophrenia (Pirnia et al., 2015; Sehatpour et al., 2010), posttraumatic stress disorder (PTSD) (Mueller-Pfeiffer et al., 2013), and body-dysmorphic disorder (BDD) (Bohon et al., 2012). These observations, together with MRI and electrophysiological evidence, suggest that the VVS is implicated in dysfunctional attentional processes and neurocognitive functions. However, no studies have explored VVS areas in BD patients in terms of local or short-distance neuronal interactions, especially at the scale of millimeters (i.e., the scale used by 2dReHo). The present analyses of functional homogeneity at the cluster level showed that BD patients demonstrated decreased synchronization of spontaneous neuronal activity in the left VVS cortex. This result is partially substantiated by two other studies that suggested that neuropathophysiological mechanisms underlying BD may be related to functional abnormalities within vision-related areas (Garrett et al., 2012; Schallmo et al., 2015). Additionally, decreased 2dReHo in patients with BD may contribute significantly to deficits in perceptual organization and neurocognitive function based on the biological significance of 2dReHo (Jiang et al., 2015). Perceptual organization identifies objects and depends on the function of a distributed network of brain regions, including the VVS. Therefore, dysfunction within this related network involving an impaired VVS may underlie deficits in neurocognitive functions, which supports distributed models of brain dysfunction in BD.

Additionally, correlational analyses in the current study found a decreasing pattern of functional regional homogeneity with age, both in BD patients and HC. During brain development, a transition from local functional connectivity to remote distributed organization has been consistently shown via neuroimaging evidence (Lopez-Larson et al.,

2011; Uddin et al., 2010). ReHo, as an index of local functional connectivity and with its correlation to age, could reflect a developmental transition from local to more remote and distributed functional organization. A ReHo analysis on a resting-state BOLD time series presented findings consistent with our results, which showed a general reduction in ReHo with age throughout the gray matter, with the greatest reduction seen in the cingulate and temporal lobes (Lopez-Larson et al., 2011). Similarly, Wu and colleagues also observed that ReHo in extensive motor regions was significantly decreased in aged subjects (Wu et al., 2007).

5. Limitations

Several limitations should be considered in the interpretation of the findings. First, 45 patients were medicated in the present study, despite their clinically stable mood status, for the MRI scanning. While considering possible effects of medication on ReHo, future studies should focus on mixed-medication effects. Second, our present surface-based ReHo analysis focused only on the cortex rather than subcortical regions, the latter of which has been proven to be crucial in emotional processing and mood regulation (Coenen et al., 2012; Serap Monkul et al., 2003). Third, regarding the correlational analyses between age and surface-based homogeneity across the cortical surface, our linear findings may only reflect a general trend. In the future, participants of different age groups may help to further explore these associations and provide deeper insights into the function-age relationship. Fourth, there may be a potential limitation with the instructions associated with resting-state methods. Previous studies have differed substantially in the instructions provided before MRI data acquisition (Lin et al., 2018; Wei et al., 2018), which might confound a clear interpretation of the ReHo findings.

6. Conclusion

In the present study, patients with BD demonstrated decreased surface-based ReHo across the cortical surface at the global level and lower surface-based ReHo in the left VVS cortex. The abnormal activity in the left VVS cortex may participate in the pathogenesis of BD. As such, surface-based ReHo may be a useful index to explore the pathophysiology of BD.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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