Brain Imaging and Behavior (2019) 13:1789–1798
https://doi.org/10.1007/s11682-019-00117-4

ORIGINAL RESEARCH

Altered regional homogeneity in pediatric bipolar disorder during manic and euthymic state: a resting-state fMRI study

Qian Xiao[1] · Dong Cui[2] · Qing Jiao[2] · Yuan Zhong[3,4] · Weifang Cao[2] · Guangming Lu[3] · Linyan Su[5]

Published online: 23 May 2019

Abstract

Pediatric bipolar disorder (PBD) is a severely debilitating illness, which is characterized by episodes of mania and depression separated by periods of remission. Little is known about the abnormalities in PBD in resting state, especially comparing manic with euthymic state. Resting state brain activity measured by fMRI might help to explore neurobiological biomarkers of the disorder. Regional homogeneity (ReHo) was examined with resting-state fMRI on 22 manic PBD patients, 21 euthymic PBD patients and 19 healthy controls. Compared with control group, manic group presented reduced cortical ReHo signal in the superior temporal gyrus(STG), the superior parietal lobe (SPL), precentral gyrus and altered subcortical ReHo signal in the insula and cerebelum crus I. Compared with control group, euthymic group only presented reduced cortical ReHo signal in the STG and SPL. Compared with euthymic group, we found reduced ReHo signal in insula, the STG and increased ReHo signal in cerebelum crus I in the manic group. The neural regions we found to have altered ReHo signal in the PBD manic and euthymic group are parts of the cortical-limbic systems, which are important for affective and cognitive processing. Importantly, our findings suggested that there was a difference between manic and euthymic PBD in the insula, cerebelum crus I and the STG.

Keywords Resting-state fMRI · Regional homogeneity · Pediatric bipolar disorder · Manic state · Euthymic state

Introduction

Bipolar disorder (BD) is a common and severe psychiatric illness characterized by episodes of extreme changes in mood state, which is characterized by deficits in emotional processing and executive functioning (Murray and Lopez 1997). A better understanding of the cerebral mechanisms and difference between mood states in BD is crucial in order to develop or improve treatments for this disorder. Pediatric/adolescent BD (PBD) may signify a more malignant course of illness in which extensive neurocognitive deficits is early onset and symptoms persist into adulthood (Lim et al. 2013). Surprisingly, however, few studies have examined the neural aberrations particularly in adolescents with BD who are temporally close to the onset of illness and, consequently, are likely to have minimal lifetime exposure to either psychotropic medications or many previous mood episodes (Singh et al. 2013).

There are still many questions concerning the pathophysiology of BD during affective episodes or in the euthymic phase, but new functional magnetic resonance imaging (fMRI) methods can help us better understand the underlying neurobiology of BD. Recent reviews and meta-analysis of task-functional magnetic resonance imaging (task-fMRI) studies concluded that BD may arise from abnormalities within discrete brain networks. That results showed that the cognition-related circuits included the superior parietal lobe, precentral gyrus, prefrontal lobe, insula and the network

✉ Guangming Lu
cjr.luguangming@vip.163.com

✉ Linyan Su
xiaoqian851112@126.com

[1] Mental Health Centre of Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

[2] Department of Radiology, Taishan Medical University, Taian 271016, China

[3] Department of Medical Imaging, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China

[4] School of Psychology, Nanjing Normal University, Nanjing 210097, China

[5] Department of Psychiatry, Mental Health Institute of The Second Xiangya Hospital, National Technology Institute of Psychiatry, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha 410011, Hunan, China

related to emotion regulation, including the superior temporal gyrus, insula, posterior cerebellar lobe and limbic system abnormalities (Blond et al. 2012; Townsend and Altshuler 2012; Hajek et al. 2013). Existing studies on the functional connectivity in the resting state of BD/PBD patients (Chepenik et al. 2010; Dickstein et al. 2010) reported disrupted connections between prefrontal gyrus and temporal/paralimbic cortex, in line with the neurobiological hypothesis of BD. Especially, a review showed the trends for the pediatric and the adult BD studies are similar (Wegbreit and Pavuluri 2012). Recent researches on dynamic brain connectivity/activity in mood disorders showed static and dynamic connectomics were valuable to study the functional connectivity of neural network (Wegbreit and Pavuluri 2012; Liao et al. 2018).

However, few studies have sought to determine a neural signature of BD in different mood states. Manic and euthymic states may differ from neural signature. A meta-analysis study about task-fMRI showed that BD patients showed decreased activity of the right inferior frontal gyrus regardless of current mood state. Unique to euthymia were cortical hyperactivations (left superior temporal, right middle frontal gyri) combined with subcortical hypoactivations (basal ganglia), whereas unique to mania were subcortical hyperactivations (bilateral basal ganglia), combined with cortical hypoactivations (right inferior and medial frontal gyri) (Hajek et al. 2013). However, a review showed no consistency about different mood state in BD (Brady et al. 2014). In speculation, preliminary works suggest that dysfunctional cortical-limbic systems implicated in cognitive and emotional function may represent a mechanistic failure seen in PBD disorder, even in the absence of an acute mood episode (Hulvershorn et al. 2012).

ReHo can be used to investigate the activity of the entire brain (Zang et al. 2004), avoiding potential bias introduced in the selection of "seed" voxels in functional connectivity studies. ReHo analysis was originally proposed for measuring the degree of regional synchronization of fMRI time courses. Therefore, an abnormal ReHo (either increase or decrease) may be a clue that is likely related to unbalanced local functionality or to an uncompensatory reaction of the whole brain network. The ReHo analysis has been used to study BD. Abnormal signals of reho in cerebellar posterior lobe, superior temporal gyrus, insula, precentral gyrus and superior parietal lobe were found in both adults and adolescents with BD (Liu et al. 2012a; Xiao et al. 2013; Liang et al. 2013).

The aim of the current study is to test for the ReHo variation in the neural networks, both across as well as within the different mood states of PBD during resting-sate. Based on previous findings, we expected that, both euthymia and manic patients with PBD would show ReHo variation of brain areas related with cortico-limbic dysregulation relative to healthy individuals. In the meanwhile, we expected certain regional synchronization may uniquely change depending on different mood state.

Materials and methods

Subjects

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Xiangya Hospital,and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consents were obtained from both the children and their parents. 12 to 17-year old outpatients were enrolled at adolescent psychiatric clinic of the Second Xiangya Hospital, Changsha, China. 43 PBD patients were included for this study. The inclusion criteria were: meeting DSM-5-TR criteria for bipolar disorder(BD), including at least one episode meeting full DSM-5-TR criteria for hypomania (≥4 days) or mania (≥7 days). The following exclusion criteria were applied in this study: (a) BD not otherwise specified, (b) IQ ≤ 80, (c) autistic or Asperger's disorder; (d) schizophrenia; e) schizoaffective psychosis; (f) medical illness that was unstable or could cause psychiatric symptoms; (g) pregnancy; (h) substance abuse within ≤2 months of participation. We also excluded attention deficit hyperactivity disorder(ADHD) and obsessive-compulsive disorder(OCD).

Manic pediatric bipolar disorder (manic PBD) was defined using DSM-5-TR criteria for mania or hypomania on the day of screening, but was not met DSM-5-TR criteria for depressive symptom. Euthymic pediatric bipolar disorder (euthymic PBD) was defined as being in remission for at least four weeks. Remission was not met DSM-5-TR criteria for depression, dysthymia, mania or hypomania. According to these criteria, 22 patients were diagnosed as manic PBD, and 21 patients as euthymic PBD.

19 age-and sex-matched healthy controls (HC) were recruited through local middle school by advertisements. The inclusion criteria were a negative history of psychiatric illness in the subject and his/her first-degree relatives. Exclusion criteria were IQ ≤ 80; ongoing medical or neurological illness; pregnancy; or past/present psychiatric or substance disorder.

All participants were evaluated by a board-certified child psychiatrist using the Affective Disorders and Schizophrenia Scale for School-Age Children-Present and Lifetime Version (K-SADS-PL) administered to parents and children separately (Kaufman et al. 1997). Information from this interview and all other available clinical information were reviewed to make a consensus clinical diagnosis. Comorbid diagnosis for BD

youths was assessed by inquiring about symptoms during a time of relative euthymia to ensure that the PBD symptoms were not double-counted.

All participants were completed the Wechsler Abbreviated Scale of intelligence as an overall measure of cognitive function (D, W 1999). All participants were also completed the evaluation of Young Mania Rating Scale (YMRS) (Young et al. 1978) and the Mood and Feelings Questionnaire (MFQ) (Wood et al. 1995). All the scales were completed on the day of scanning. Handedness was assessed using the Edinburgh Inventory (Oldfield 1971).

fMRI data acquisitions

Functional images were obtained on a 3-Tesla scanner (Siemens Trio) using a standard whole-head coil. Functional images were acquired by using of single-shot gradient echo-echo imaging (GRE-EPI) sequence (repetition time: 2000 ms; echo time: 30 ms; slices: 30; thickness: 4 mm; gap: 0.4 mm; field of view: 240 mm × 240 mm; in-plane resolution: 64 × 64; flip angle: 90°).

Structural images were acquired by using a three-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time: 2300 ms; echo time: 2.98 ms; inversion time: 900 ms; field of view: 256 mm × 256 mm; flip angle: 9°; in-plane resolution: 256 × 256). During the scanning, all subjects were informed to relax, hold still, keep their eyes closed without falling asleep and think of nothing in particular.

fMRI data preprocessing

Spatial preprocessing of fMRI data was done using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). The fMRI images were corrected for the acquisition delay between slices and for the head motion. The participants whose head motion exceeded 1.5 mm or rotation exceeded 1.5° during fMRI scanning were excluded. The fMRI images were normalized to a standard SPM8 echo planar imaging template, resampling to $3 \times 3 \times 3$ mm^3. Data were temporal band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and physiological high-frequency noise, the linear trend was removed and regress out the head motion parameters (Wu et al. 2009).

Regional homogeneity analysis

Kendall's coefficient concordance (KCC) can measure the similarity of a number of time series. It has been used for purifying a given cluster in functional MRI (fMRI). In the regional homogeneity (ReHo), KCC was used to measure the similarity of the time series of a given voxel to those of its nearest neighbors in a voxel-wise way. ReHo can consider as a complementary method to model-driven method, and it could help reveal the complexity of the human brain function.

Regional homogeneity analysis was performed with software REST (http://www.resting-fmri.sourceforge.net). ReHo maps were generated for each subject by calculating KCC of the time series of a given voxel and the nearest voxels (26 voxels) in a voxelwise analysis (Zang et al. 2004). The KCC value was calculated to this voxel, and an individual KCC map was acquired for each participant. Then a mask (made from the MNI template to assure matching with the normalization step), in the REST software, was used to remove non-brain tissue and for standardization purposes. Each individual ReHo map was divided by its own global mean KCC value within the mask (Wu et al. 2009). Finally, the data were smoothed with a Gaussian filter of 4 mm full width at half-maximum (FWHM) to reduce noise and residual differences in gyral anatomy.

Statistics analysis

One way ANOVA was applied to compare the results of ReHo between PBD patients and HCs. The F-map was set at a corrected significance level of $p < 0.01$ (a minimum cluster size of 53 voxels). We built mask according to the results of variance analysis and use the mask to limit the result of posteriori test. The two-sample t-test was performed to determine the significant differences in ReHo between patients with manic PBD and euthymic PBD and HCs. The t-map was set at a corrected significance level of $p < 0.01$ (a minimum cluster size of 20 voxels). Threshold correction was performed by using Monte Carlo simulation (AlphaSim: individual voxel p value = 0.01, 1000 simulations, FWHM = 4 mm, with mask) in the DPABI 3.0 software. One way ANOVAs, independent-sample t-tests and chi-square tests were used to compare demographic, clinical and cognitive differences between groups. Relationship between the neuropsychological tests scores and activity of brain areas was assessed using Spearman's correlation analysis of SPSS software (v21.0, IBM Corporation, NY, USA). Individual's age, gender and years of education were included as nuisance covariates.

Results

Demographics and clinical data for PBD manic group、euthymic group and healthy controls were summarized in Table 1. There were no significant differences in age ($p = 0.191$), gender ($p = 0.385$), IQ ($p = 0.121$), education ($p =$

Table 1 Sample characteristics. Demographics and clinical data of patients with pediatric bipolar disorder and healthy controls

Characteristics	manic PBD ($n = 22$)	euthymic PBD ($n = 21$)	HC ($n = 19$)	F /T /χ2	*P*
Gender(male/female)	9/13	12/9	7/12	1.909*	0.385
Age(years)	14.91 ± 1.72	15.10 ± 1.76	14.16 ± 1.57	1.705&	0.191
Education (years)	8.13 ± 1.67	8.52 ± 1.88	7.47 ± 2.22	1.508&	0.230
IQ	103.50 ± 12.05	109.71 ± 9.46	105.32 ± 7.51	2.189&	0.121
YMRS scores	36.25 ± 4.85	10.48 ± 4.14	7.90 ± 3.70	283.633&	0.000
MFQ scores	8.95 ± 4.13	6.62 ± 4.63	7.32 ± 5.23	1.426&	0.248
Onset age (year)	14.18 ± 1.79	13.95 ± 1.55	–	0.445#	0.659
Illness duration (months)	15.00 ± 12.62	20.95 ± 18.01	–	−1.260#	0.215
Onset frequency	3.00 ± 1.63	4.81 ± 7.36	–	−1.125#	0.267
The first episode bipolar disorder(mania/depression)	9/13	6/15	–	0.720*	0.396
Psychotic symptoms (yes/no)	10/12	10/11	–	0.020*	0.887
BP-I/BP-II	18/4	13/8	–	2.118*	0.146
Familial BD history (yes/no)	5/17	5/16	–	0.007*	0.933
Medications					
Lithium	9 (40.9%)	7(33.3%)	–	–	–
Atypical antipsychotics	15 (68.2%)	14 (66.7%)	–	–	–
Antidepressants	2 (9.1%)	0	–	–	–
Valproate	12 (54.5%)	16(76.2%)	–	–	–

Data are presented as mean ± standard deviation. * Pearson chi-square test; & ANOVA (one way analyses of variance); # Independent Sample *T* Test

Abbreviations: *BP-I* bipolar disorder type I, *BP-II* bipolar disorder type II

0.230) among the three groups. The YMRS scores among the three groups showed significant difference ($p = 0.000$). The MFQ scores among the three groups showed no significant difference ($p = 0.248$). There are no statistical difference in manic PBD and euthymic PBD with regard to onset age, illness duration, onset frequency, the first episode bipolar disorder(mania/depression), psychotic symptoms, BP-I/BP-II, familial BD history (Table 1).

The result of variance analysis indicated significant differences of ReHo in the brain regions, the right

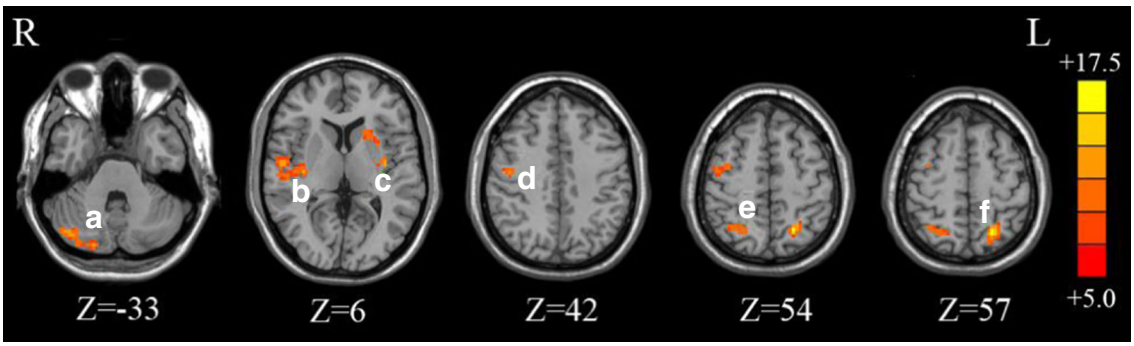

Fig. 1 ANOVA analysis among three groups. Notes: The result of variance analysis indicated significant differences of ReHo in the brain regions, the right Cerebelum_Crus1 (A), the right Superior Temporal Gyrus (B), the left Insula (C), the right precuneus (D), the right Superior Parietal Lobule (E) and the left Superior Parietal Lobule (F)

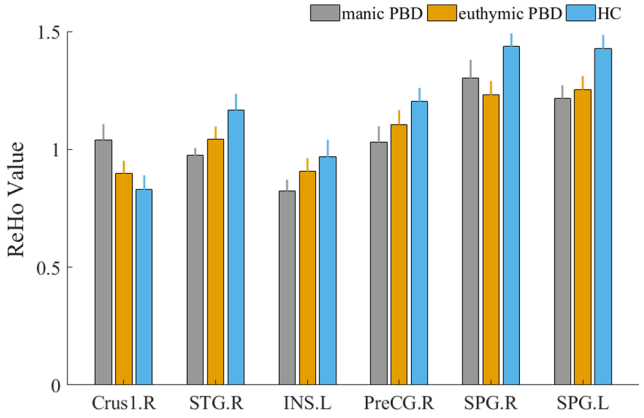

Fig. 2 Difference of ReHo value among the three groups. Note: Crus1.R (Right Cerebelum Crus1), STG.R (Right Superior Temporal Gyrus), INS.L (Left Insula), PreCG.R (Right Precentral Gyrus), SPG.R (Right Superior Parietal Gyrus), SPG.L (Left Superior Parietal Gyrus)

Cerebelum_Crus1, the right Superior Temporal Gyrus, the left Insula, the right precuneus and the left/right Superior Parietal Lobule (Figs. 1 and 2, Table 2).

Compared with that of HCs, the manic group showed decreased ReHo in the right superior temporal gyrus, the left insula, the right precuneus and the left superior parietal lobule and increased ReHo in the Cerebelum_Crus1 (Fig. 3, Table 3). Compared with that of HCs, the euthymic group showed decreased ReHo in the right superior temporal Gyrus and the left/right superior parietal lobule (Fig. 4, Table 4). Compared with that of euthymic patients, manic patients displayed decreased ReHo in the right superior temporal gyrus and left insula, and increased ReHo in Cerebelum_Crus1 (Fig. 5; Table 5). ($P < 0.01$, AlphaSim corrected).

Correlations between ReHo and clinical feature

The score of YMRS in PBD manic group revealed significant negative correlation with ReHo value in the right precentral gyrus($r = -0.633$, $p = 0.002$) (Fig. 6). Negative relationship between ReHo value and course of disease was found in the right superior temporal gyrus in the PBD manic group ($r = -0.589$, $p = 0.004$) (Fig. 7).

Discussion

To the best of our knowledge, our study is the first one that visualize the whole brain ReHo profiles of PBD manic and euthymic patients during brain spontaneous activity using fMRI. Our analysis of ReHo profiles in PBD manic and euthymic patients showed that they shared some similarities in ReHo abnormalities in the cortical-limbic system. Meanwhile, each group also showed some unique changes. There were brain regions which showed unique ReHo variation comparing manic with euthymic state, including insula, Cerebellum Crus I and superior temporal gyrus.

Insula

Interestingly, our study demonstrated decreased ReHo in the insula, when manic PBD group compared with euthmic/healthy group. Whereas euthymic subjects did not show insula alteration than the healthy controls. The human insula which links to numerous cortical areas through different neural pathways, may have multiple functional roles, including emotion, cognition, and sensory perception (Nieuwenhuys 2012).

As one of the core regions in the limbic system, the insular cortex may be implicated in the etiology of BD. Meta-analysis of voxel based morphometry studies in BD found that the most consistent abnormalities involved gray matter reduction in anterior insula (Bora et al. 2010). Compared with control group, BD (Hulvershorn et al. 2012) and PBD (Chang et al. 2004) revealed significant increased activity of insula in varied tasks. In resting-state, researches showed increased ALFF/coherence/ReHo in the insula of patients with bipolar disorder

Table 2 Regions showing significant differences in ReHo between PBD and HC

Brain regions of ReHo	Hemisphere	Cluster size	Peak MNI coordinate			*F* value
			x	y	z	
Cerebelum Crus1	Right	141	42	−78	−33	11.56
Superior Temporal Gyrus	Right	154	57	−12	6	10.96
Insula	Left	92	−36	−12	6	9.57
Precentral Gyrus	Right	62	45	−12	42	8.88
Superior Parietal Lobule	Right	53	27	−60	54	8.66
Superior Parietal Lobule	Left	75	−21	−60	57	17.45

Abbreviations: *PBD* pediatric bipolar disorder, *HC* healthy controls, *MNI* Montreal Neurological Institute

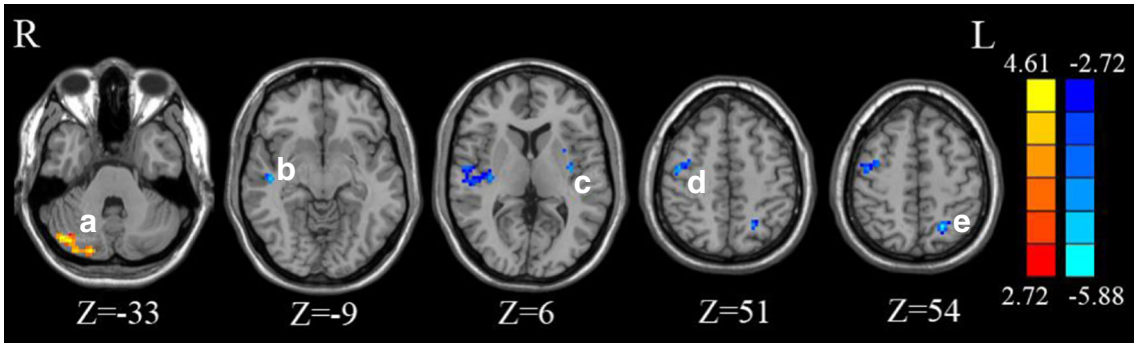

Fig. 3 Significant Between-Group Differences in ReHo between manic PBD and HC. Notes: The ReHo showed decrease (cold colors) in the right Superior Temporal Gyrus (B), the left Insula (C), the right precuneus (D) and the left Superior Parietal Lobule (E). An increase (hot colors) in the Cerebelum_Crus1 (A)

relative to healthy controls (Liu et al. 2012a; Liang et al. 2013; Yip et al. 2014). According to a meta-analysis, changes uniquely associated with euthymia and mania. Unique to manic participants showed increased activations relative to controls in insula (Hajek et al. 2013). Our result also supported that compared with euthymic and healthy group, manic group had abnormal fMRI signal in insula. Taken together, these findings suggest that insular dysfunction may play a role in the pathogenesis of PBD, especially in manic state.

Posterior cerebellar lobe

Our study showed increased ReHo in the right Cerebelum Crus1 when manic PBD participants relative to both euthymic subjects and healthy controls. Cerebellum may play an important role in the pathophysiology of BD (Kim et al. 2013). Cognitive impairments occur when posterior lobe lesions affect lobules VI and VII (including Crus I and Crus II), disrupting cerebellar modulation of cognitive loops with cerebral association cortices (Stoodley and Schmahmann 2010).

Results from these studies mostly support our findings that BD patients have decreased posterior cerebellar volumes (Mills et al. 2005) and density (Kim et al. 2013). One ALFF study also found decrease in amplitude of fluctuation in cerebellum posterior lobe in bipolar disorder patients (Liu et al. 2012b). A recent topographic meta-analytic approach to functional neuroimaging studies has demonstrated that this posterior cerebellar hemispheric region might be involved in higher-level tasks including language and executive functions. The posterior cerebellum have also been implicated in processing as a part of the cerebellar–limbic circuitry (Stoodley and Schmahmann 2010). Taken together, the posterior cerebellum, which is reciprocally linked to other prefronto–limbic brain areas, may work en bloc to modulate cognitive and emotional processing (Stoodley and Schmahmann 2010; Konarski et al. 2005). Our result suggest that manic group of patients have cerebellar dysfunction.

Superior temporal gyrus (STG)

Whether manic and euthymic group relative to healthy controls, reduced ReHo was found in the right superior temporal gyrus (STG) in this study. However, manic showed more reduced ReHo in STG compared with euthymic patients. The

Table 3 Significant between-group differences in ReHo between manic PBD ($n = 22$) and HC ($n = 19$)

Brain regions of ReHo	Hemisphere	Cluster size	Peak MNI coordinate			*T* value
			x	y	z	
Cerebelum Crus1	Right	126	42	−78	−33	4.61
Superior Temporal Gyrus	Right	127	48	−18	−9	−4.95
Insula	Left	25	−36	−12	6	−4.46
Right Precentral Gyrus		62	45	−9	51	−4.81
Superior Parietal Lobule	Left	54	−21	−60	54	−5.58

Abbreviations: *PBD* pediatric bipolar disorder, *HC* healthy controls, *MNI* Montreal Neurological Institute

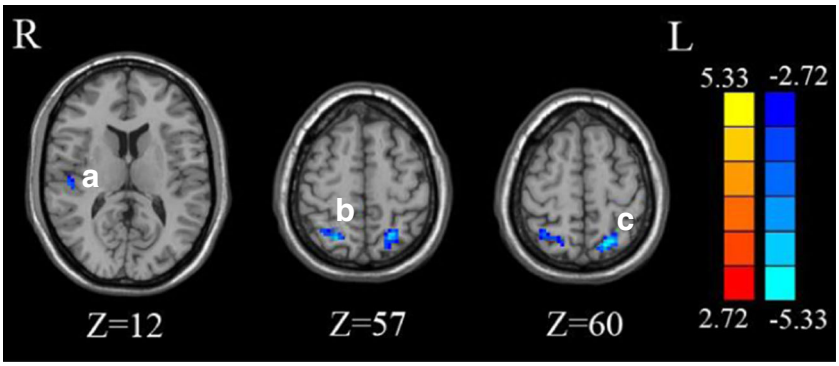

Fig. 4 Significant between-group differences in ReHo between euthymic PBD and HC. Notes: The ReHo showed decrease (cold colors) in the right Superior Temporal Gyrus (A), the left Superior Parietal Lobule (B) and the left Superior Parietal Lobule (C)

temporal pole is considered part of the extended limbic system, along with its tight connectivity to limbic and paralimbic regions. The STG are associated with complex language, interoceptive, affective, and reward processing (Lim et al. 2013). Some studies observed increased GMV in the superior temporal gyrus in PBD patients (Gogtay et al. 2007; Lisy et al. 2011). In resting-state networks, young adult participants compared with controls with BD-II had increased coherence in the STG (Yip et al. 2014). One study explored functional abnormalities in three different mood states (euthymic, depressed, and manic) associated with BD. Similar to this finding, manic and euthymic patients showed reduced activation compared with healthy control (Van der Schot et al. 2010). In the resting state, PBD showed altered connectivity between the STG and Prefrontal/limbic areas (Dickstein et al. 2010). Finally, our data indicate that euthymic patients show activation levels resembling those of manic patients in the STG. As such, our data support the finding of abnormal emotional reactivity in euthymic patients. Therefore, our data appear to provide neurophysiological support for the notion that euthymic BD patients are at risk for developing manic episode (Van der Schot et al. 2010).

Superior parietal lobule(SPL)

Both manic and euthymic group relative to healthy controls, reduced ReHo was found in the superior parietal lobule. Some studies have demonstrated reduced activity/ReHo in the superior parietal gyrus in bipolar disorder patients (Liang et al. 2013; Rey et al. 2014). The neural changes of parietal lobe suggest that it is probably involved in information transmission and inhibitory functions (Hajek et al. 2013). Neurocognitive and functional imaging studies thus far have focused on deficits in response inhibition as a core component of mood dysregulation in children with bipolar disorder (Wu et al. 2013). Some studies have suggested that in bipolar disorders (BD) impulsivity, a construct encompassing impaired inhibitory functions, may remain elevated during euthymia (Henna et al. 2013). In this study, the ReHo value was decreased in the superior parietal lobe in PBD manic and euthymic patients, suggesting that patients with parietal cortex dysfunction probably have attenuated ability of receiving new information and inhibitory function.

Precentral gyrus

While manic group relative to healthy controls, reduced ReHo was found in the precental gyrus in this study. The increased connectivity in the precental gyrus may arise from the prominent motoric symptoms of increased agitation, restlessness and excessive motor activity during episodes of mania (Wu et al. 2013). Compared with control group, manic BD patients showed reduced activity in the precentral gyrus in fMRI-task study (Rey et al. 2014).

Table 4 Significant between-group differences in ReHo between euthymic PBD ($n = 21$) and HC ($n = 18$)

Brain regions of ReHo	Hemisphere	Cluster size	Peak MNI coordinate			T value
			x	y	z	
Superior Temporal Gyrus	Right	24	51	−24	12	−3.74
Superior Parietal Lobule	Right	52	24	−63	57	−4.61
Superior Parietal Lobule	Left	66	−21	−63	60	−5.33

Abbreviations: *PBD* pediatric bipolar disorder, *HC* healthy controls, *MNI* Montreal Neurological Institute

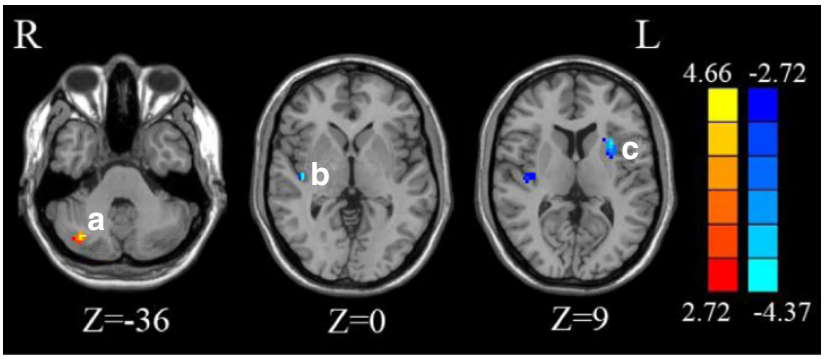

Fig. 5 Significant between-group differences in ReHo between manic PBD and euthymic PBD. Notes: The ReHo showed decrease (cold colors) in the right superior temporal gyrus (B) and left Insula (C). An increase (hot colors) in the Cerebelum_Crus1

In this study, abnormal signals of ReHo in the white matter were found in both the manic and the euthymic state. There are also some researches applied resting-state fMRI to investigating the in function of white matter in brain disorders (Ji et al. 2019). White matter abnormality has been paid more and more attention in the pathogenesis of mental disorders.

ReHo and manic clinical feature

We found negative correlation of ReHo value in the right precentral with the manic severity (YMRS Score) in the PBD manic group. We also showed negative value correlation between abnormal ReHo value in the right superior temporal gyrus(STG) and the course of disease in the PBD manic group. The manic patients who had more serious manic symptom may have lower ReHo value in the precentral gyrus. The precental gyrus may correlated with the prominent motoric symptoms of increased agitation, restlessness and excessive motor activity during episodes of mania (Wu et al. 2013). Longer course of disease may have lower ReHo value in the STG, which is associated with complex language, interoceptive, affective, and reward processing (Lim et al. 2013).

Limitation We could not control for potential effects of medication. However, many studies have found no significant effect of medication (Wessa et al. 2007; Strakowski et al. 2011; Phillips et al. 2008). Medication has been shown to obscure behavioral and neural differences between patient groups and controls (Hafeman et al. 2012), so that this confound is unlikely to explain our main findings. This sample is small. In the future, we will expand our sample number to solve the limitation.

Summary The regions we found to have altered ReHo signal in the PBD manic and euthymic Group are parts of the cortical-limbic systems, which are important for affective and cognitive processing. Importantly, our findings suggested

Table 5 Significant between-group differences in ReHo between manic PBD ($n = 22$) and euthymic PBD ($n = 21$)

Brain regions of ReHo	Hemisphere	Cluster size	Peak MNI coordinate			*T* value
			x	y	z	
Cerebelum crus1	Right	36	36	−72	−36	4.66
Superior temporal gyrus	Right	33	42	−18	0	−4.26
Insula	Left	43	−30	12	9	−4.37

Abbreviations: *PBD* pediatric bipolar disorder, *HC* healthy controls, *MNI* Montreal Neurological Institute

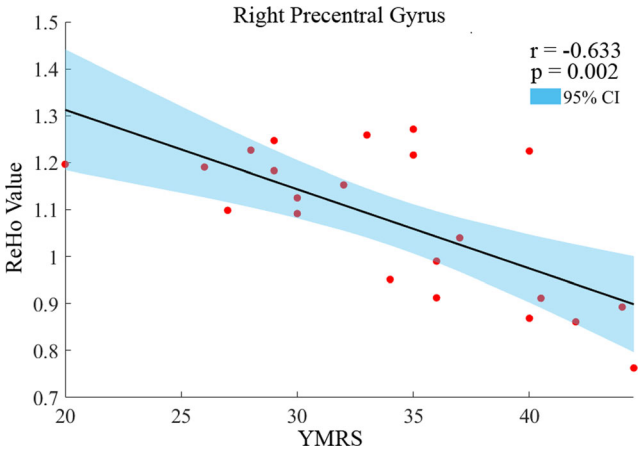

Fig. 6 The score of YMRS in manic PBD group revealed significant negative correlation with ReHo value in the right precentral gyrus (YMRS:Young Mania Rating Scale)

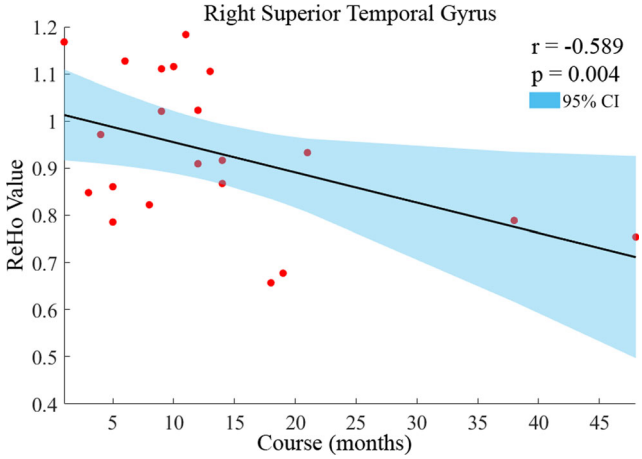

Fig. 7 Negative relationship between ReHo value and course of disease was found in the right superior temporal gyrus in the manic PBD group

that there was a difference between manic and euthymic PBD in the insula, cerebelum crus I and the STG.

Funding This study was funded by Natural Science Foundation of Hunan Province: No. 2018JJ3832, National Natural Science Foundation of China (81371531,81171291, 81201077), the Natural Science Foundation of Jiangsu Province (BK20161109).

Compliance with ethical standards

Conflict of interest No conflict exists: Author Qian Xiao declares that she has no conflict of interest. Author Dong Cui declares that he has no conflict of interest. Author Qing Jiao declares that she has no conflict of interest. Author Yuan Zhong declares that he has no conflict of interest. Author Guangming Lu declares that he has no conflict of interest. Author Linyan Su declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Blond, B. N., Fredericks, C. A., & Blumberg, H. P. (2012). Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala-anterior paralimbic neural system. *Bipolar Disorders, 14*(4), 340–355.

Bora, E., Fornito, A., Yücel, M., & Pantelis, C. (2010). Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biological Psychiatry, 67*(11), 1097–1105.

Brady, R. J., Ongur, D., & Keshavan, M. (2014). Neurobiology of mood-state shifts in bipolar disorder: a selective review and a hypothesis. *Harvard Review of Psychiatry, 22*(1), 23–30.

Chang, K., Adleman, N. E., Dienes, K., Simeonova, D. I., Menon, V., & Reiss, A. (2004). Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. *Archives of General Psychiatry, 61*(8), 781–792.

Chepenik, L. G., Raffo, M., Hampson, M., Lacadie, C., Wang, F., Jones, M. M., Pittman, B., Skudlarski, P., & Blumberg, H. P. (2010). Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Research, 182*(3), 207–210.

D, W. (1999). *Wechsler abbreviated scale of intelligence*. San Antonio: The Psychological Corporation.

Dickstein, D. P., Gorrostieta, C., Ombao, H., Goldberg, L. D., Brazel, A. C., Gable, C. J., Kelly, C., Gee, D. G., Zuo, X. N., Castellanos, F. X., & Milham, M. P. (2010). Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. *Biological Psychiatry, 68*(9), 839–846.

Gogtay, N., Ordonez, A., Herman, D. H., Hayashi, K. M., Greenstein, D., Vaituzis, C., Lenane, M., Clasen, L., Sharp, W., Giedd, J. N., Jung, D., Nugent III, T. F., Toga, A. W., Leibenluft, E., Thompson, P. M., & Rapoport, J. L. (2007). Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *Journal of Child Psychology and Psychiatry, 48*(9), 852–862.

Hafeman, D. M., Chang, K. D., Garrett, A. S., Sanders, E. M., & Phillips, M. L. (2012). Effects of medication on neuroimaging findings in bipolar disorder: an updated review. *Bipolar Disorders, 14*(4), 375–410.

Hajek, T., Alda, M., Hajek, E., & Ivanoff, J. (2013). Functional neuroanatomy of response inhibition in bipolar disorders–combined voxel based and cognitive performance meta-analysis. *Journal of Psychiatric Research, 47*(12), 1955–1966.

Henna, E., Hatch, J. P., Nicoletti, M., Swann, A. C., Zunta-Soares, G., & Soares, J. C. (2013). Is impulsivity a common trait in bipolar and unipolar disorders? *Bipolar Disorders, 15*(2), 223–227.

Hulvershorn, L. A., Karne, H., Gunn, A. D., Hartwick, S. L., Wang, Y., Hummer, T. A., & Anand, A. (2012). Neural activation during facial emotion processing in unmedicated bipolar depression, euthymia, and mania. *Biological Psychiatry, 71*(7), 603–610.

Ji, G. J., Ren C., Li Y., Sun J., Liu T., Gao Y., Xue D., et al. (2019). Regional and network properties of white matter function in Parkinson's disease. *Human Brain Mapping, 40*(4), 1253–1263.

Kaufman, J., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980–988.

Kim, D., Byul Cho, H., Dager, S. R., Yurgelun-Todd, D. A., Yoon, S., Lee, J. H., Hea Lee, S., Lee, S., Renshaw, P. F., & Kyoon Lyoo, I. (2013). Posterior cerebellar vermal deficits in bipolar disorder. *Journal of Affective Disorders, 150*(2), 499–506.

Konarski, J. Z., et al. (2005). Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *Journal of Psychiatry & Neuroscience, 30*(3), 178–186.

Liang, M. J., Zhou, Q., Yang, K. R., Yang, X. L., Fang, J., Chen, W. L., & Huang, Z. (2013). Identify changes of brain regional homogeneity in bipolar disorder and unipolar depression using resting-state FMRI. *PLoS One, 8*(12), e79999.

Liao, W., Li, J., Duan, X., Cui, Q., Chen, H., & Chen, H. (2018). Static and dynamic connectomics differentiate between depressed patients with and without suicidal ideation. *Human Brain Mapping, 39*(10), 4105–4118.

Lim, C. S., et al. (2013). Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: review of the evidence. *Neuroscience and Biobehavioral Reviews, 37*(3), 418–435.

Lisy, M. E., Jarvis, K. B., DelBello, M. P., Mills, N. P., Weber, W. A., Fleck, D., Strakowski, S. M., & Adler, C. M. (2011). Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. *Bipolar Disorders, 13*(4), 396–405.

Liu, C. H., Ma, X., Li, F., Wang, Y. J., Tie, C. L., Li, S. F., Chen, T. L., Fan, T. T., Zhang, Y., Dong, J., Yao, L., Wu, X., & Wang, C. Y. (2012a). Regional homogeneity within the default mode network in bipolar depression: a resting-state functional magnetic resonance imaging study. *PLoS One, 7*(11), e48181.

Liu, C. H., Li, F., Li, S. F., Wang, Y. J., Tie, C. L., Wu, H. Y., Zhou, Z., Zhang, D., Dong, J., Yang, Z., & Wang, C. Y. (2012b). Abnormal baseline brain activity in bipolar depression: a resting state functional magnetic resonance imaging study. *Psychiatry Research, 203*(2–3), 175–179.

Mills, N. P., DelBello, M. P., Adler, C. M., & Strakowski, S. M. (2005). MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *The American Journal of Psychiatry, 162*(8), 1530–1532.

Murray, C. J., & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet, 349*(9063), 1436–1442.

Nieuwenhuys, R. (2012). The insular cortex: a review. *Progress in Brain Research, 195*, 123–163.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Phillips, M. L., et al. (2008). Medication effects in neuroimaging studies of bipolar disorder. *The American Journal of Psychiatry, 165*(3), 313–320.

Rey, G., Desseilles, M., Favre, S., Dayer, A., Piguet, C., Aubry, J. M., & Vuilleumier, P. (2014). Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: preliminary findings from a follow-up state-based fMRI study. *Psychiatry Research, 223*(2), 84–93.

Singh, M. K., Chang, K. D., Kelley, R. G., Cui, X., Sherdell, L., Howe, M. E., Gotlib, I. H., & Reiss, A. L. (2013). Reward processing in adolescents with bipolar I disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(1), 68–83.

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46*(7), 831–844.

Strakowski, S. M., Eliassen, J. C., Lamy, M., Cerullo, M. A., Allendorfer, J. B., Madore, M., Lee, J. H., Welge, J. A., DelBello, M. P., Fleck, D. E., & Adler, C. M. (2011). Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. *Biological Psychiatry, 69*(4), 381–388.

Townsend, J., & Altshuler, L. L. (2012). Emotion processing and regulation in bipolar disorder: A review. *Bipolar Disorders, 14*(4), 326–339.

Van der Schot, A., et al. (2010). Trait and state dependent functional impairments in bipolar disorder. *Psychiatry Research, 184*(3), 135–142.

Wegbreit, E., & Pavuluri, M. (2012). Mechanistic comparisons of functional domains across pediatric and adult bipolar disorder highlight similarities, as well as differences, influenced by the developing brain. *The Israel Journal of Psychiatry and Related Sciences, 49*(2), 75–83.

Wessa, M., et al. (2007). Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *The American Journal of Psychiatry, 164*(4), 638–646.

Wood, A., Kroll, L., Moore, A., & Harrington, R. (1995). Properties of the mood and feelings questionnaire in adolescent psychiatric outpatients: a research note. *Journal of Child Psychology and Psychiatry, 36*(2), 327–334.

Wu, T., Long, X., Zang, Y., Wang, L., Hallett, M., Li, K., & Chan, P. (2009). Regional homogeneity changes in patients with Parkinson's disease. *Human Brain Mapping, 30*(5), 1502–1510.

Wu, M., Lu, L. H., Passarotti, A. M., Wegbreit, E., Fitzgerald, J., & Pavuluri, M. N. (2013). Altered affective, executive and sensorimotor resting state networks in patients with pediatric mania. *Journal of Psychiatry & Neuroscience, 38*(4), 232–240.

Xiao, Q., Zhong, Y., Lu, D., Gao, W., Jiao, Q., Lu, G., & Su, L. (2013). Altered regional homogeneity in pediatric bipolar disorder during manic state: a resting-state fMRI study. *PLoS One, 8*(3), e57978.

Yip, S. W., Mackay, C. E., & Goodwin, G. M. (2014). Increased temporo-insular engagement in unmedicated bipolar II disorder: an exploratory resting state study using independent component analysis. *Bipolar Disorders, 16*(7), 748–755.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry, 133*, 429–435.

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *Neuroimage, 22*(1), 394–400.