Abnormal functional connectivity of the intrinsic networks in adolescent bipolar I versus bipolar II disorder

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Research Article

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Abstract

Background: The symptoms of pediatric bipolar disorder (PBD)-I and PBD-II differ, but accurate identification at an early stage is difficult and may prevent effective treatment of this disorder. Therefore, it is urgent to elucidate a biological marker based on objective imaging indicators to help distinguish the two. Therefore, this research aims to compare the functional connectivity between PBD-I patient and PBD-II patient in different brain networks.

Methods: Our study enrolled 31 PBD-I and 23 PBD-II patients from 12 to 17 years of age. They were analyzed by resting state-functional connectivity through Independent component analysis ICA .

Results: We found differences between PBD-I and PBD-II in functional connectivity of the default network, frontoparietal network, salience network and limbic system. In addition, the clinical features, cognitive functions are associated with the functional connectivity of the intrinsic networks in PBD-I and PBD-II separately.

Conclusion: This research is the first to find differences in functional connectivity between PBD-I and PBD-II, suggesting that abnormality of the functional connectivity within large networks may be biomarkers that help differentiate PBD-I from PBD-II in the future.

1 Introduction

Pediatric bipolar disorder (PBD) is presented by recurrent depressive, manic, and hypomanic episodes[1]. The prevalence of PBD in the adolescent population is 1%[1]. PBD differs from adult bipolar disorder (BD) in that its symptoms are more atypical[2]. Because of the atypical symptoms of PBD, the differential diagnosis of PBD-I and PBD-II is more difficult. The presence or absence of manic episode is a major feature for distinguishing PBD-I from PBD-II disorders[1]. It is very important to identify PBD-I versus PBD-II biomarkers. Because PBD-I may begin with depressive episode or hypomanic episode in the early emotional episode, it is very easy to misdiagnose at this time without manic episode[2]. However, PBD-I and PBD-II are different in medication therapy and risk prevention[3], so it is very important to correctly identify them with biomarkers in early stage. Some researches have showed differences in biological mechanisms compared BD-I with BD-II [3, 4]. Psychosis[3], neurotoxic processes[5], neurochemical[6] and cognitive dysfunction[7] are greater common in BD-I than in BD-II. The Magnetic resonance imaging (MRI) researches have showed that there are difference of cortical-subcortical system compared BD-I with BD-II in volumes[8–10], thickness[8, 11], white matter lesions[9], metabolism[12] and functional connectivity[13]. However, studies on MRI differences between PBD-I and PBD-II are obviously lacking.

The emergence of studies have found that researching the functional connectivity of bipolar disorder can clarify the neuropathological mechanism of this disorder. Resting state functional magnetic resonance imaging (fMRI) has been explored to explore bipolar disorder[13, 14]. The statistical dependence of blood oxygen level dependent (BOLD) sign among the two neural regions was hypothesized as a functional connectivity[15]. The latest meta-analysis in 2021 found alteration in functional connectivity of the fronto-parietal network (FPN), default network (DMN), salience network(SN)and limbic system in bipolar disorder[14]. Previous study using resting state-fMRI and ICA has found aberrations in the intrinsic connectivity neural circuits mentioned above in BD[16–19]. To date, few resting state fMRI studies have been conducted specifically in PBD. Our earlier study has adopted the Independent Components Analysis (ICA) to find discrepancy in resting state DMN functional connectivity in PBD[20].

Aberrant functional connectivity of the DMN indicates the shortage of integration of internal thoughts, which may show decreased cognitive flexibility and impaired self-monitoring process of BD[14]. Functional connectivity abnormalities in DMN may provide evidence for clinical symptoms observed in BD, such as working memory dysfunction and rumination[14]. Effective emotional regulation depends on limbic system[21]. Dysfunctional connectivity of the limbic system is related to the severity of manic mood[21]. And SN involved in goal-directed adjustment of external stimulus and internal thought, its dysfunctional connectivity shows imbalanced communication between the neural networks[22]. BD patients will consider emotional information as external stimulation rather than emotion itself, which further explains the emotional dysregulation in BD[22]. Abnormal functional connectivity within FPN is also commonly found in BD patients[23]. The abnormal functional connectivity of the FPN in BD subjects may be the basis of impulsivity and attention deficit in BD[14, 23]. In recent years, many studies have found that PBD is similar to adult BD in functional connectivity of the DMN, FPN, SN, and limbic system[24–26].

However, no studies have analyzed the functional connectivity in the DMN, FPN, SN, and limbic system compared PBD-I with PBD-II patients. The clinical manifestations of PBD-I were found to be more severe than PBD-II in terms of manic symptoms and cognitive dysfunction[27], but whether the functional connectivity of the neural circuits serves as the neural underpinning is not clear and need to be explored. To detect whole-brain connectivity mode, we used the model-free methods to explore connectivity patterns without defining prior seed regions. Comparing with the seed-based approach, the model-free approach aims to find widespread mode of connectivity in the whole brain. The ICA-based approach is probably the most generally used and has been demonstrated a high degree of consistency [28].

In this research, our aim was to compare differences in functional connectivity comparing PBD-I with PBD-II. Our hypothesis was that there might be differences in functional connectivity of the DMN, FPN, SN and limbic system compared PBD-I with PBD-II. Furthermore, we examined the correlation among manic symptoms, depressive symptoms, sleep quality, suicide risk, cognitive function and the functional connectivity of the intrinsic networks, to see if differences in fMRI indicators were related to clinical symptoms and cognitive impairment. To our knowledge, this was the first functional connectivity research to assess wide neural circuits compared PBD-I with PBD-II.

2 Materials And Methods

2.1 Participants

We collected 31 PBD-I and 23 PBD-II adolescents in the outpatient service of pediatric psychiatry, Xiangya Second Hospital, China. Xiangya Hospital Research Ethics Committee approved this research. The process of this study obeyed the 1964 Helsinki ethical statement. Each subject and their parents agreed to join in the research and signed informed consent.

This research used the DSM-5 criteria to diagnose PBD-I and PBD-II patients. Exclusion criteria as following: (a) autism spectrum disorder; (b) Wechsler intelligence total score ≤ 80; (c) schizophrenia spectrum disorder; (c) mental disorders due to physical diseases; (d) other specific/unspecific bipolar disorder; (e)in pregnancy; (f) Psychoactive drug use in the two months.

2.2. Emotional and cognitive features

2.2.1. Mood assessments and Demographics

Structured interviews were conducted with PBD patients by the K-SADS-PL[29]. Two subtypes of PBD were included type I and type II. The key difference comparing PBD-I with PBD-II was that there was no full-blown manic episode in PBD-II. The consistency between psychiatrists was proved to be good. The clinical features of all the PBD patients was assessing using Wechsler Abbreviated Scale of Intelligence (WASI) [30], the Mood and feelings Questionnaire (MFQ) [32], Young Mania Rating Scale (YMRS)[31], Beck Suicide Ideation Scale (BSIS)[34] an Pittsburgh Sleep Quality Index (PSQI)[33]. We used the Edinburgh Inventory to determine handedness[35]. All interviews and assessments were conducted on the right day of the MRI acquisition to improve accuracy.

2.2.2 Cognitive Function Test

To measure the patient's cognitive function, cognitive test including: Stroop color-word test (SCWT), digit span test (DST), trail making test (TMT), and visual reproduction immediate recall test (VR I). These tests were operated by trained psychiatrists. The brief descriptions of the cognitive tests were following:

(1) Stroop Color-word Test (SCWT)

This SCWT [36] could measure participants' attention and response inhibition. It contained three subtasks, such as reading characters (SCWT-A), reading colour (SCWT-B), and reading colour disturbance (SCWT-C). SCWT-A included 100 words which participants read in 45 s. SCWT-B contained 100 symbols that participants named color correctly in 45 s. SCWT-C included 100 colored words that subjects named color within 45 s.

(2) Trail Making Test (TMT)

TMT consisted of TMT-A and TMT-B[37]. The first test demanded the participants to link the scattered numbers in order (1–25), and the second test asked the participants to connect a line sequentially through the 13 numbers (from 1 to 13) and 12 English alphabet (from A to L) alternately. TMT scores were the whole times for participants to accomplish these tasks. TMT-A measured processing speed and attention, as well as TMT-B measured cognitive flexibility[37].

(3) Digit Span Subtest (DST)

The participants were required to recite the assigned number forwards (DST-A) and to recite the assigned number backwards (DST-B). The scores were based on the longest sequence of numbers recited. DST-A could measure attention level and DST-B could assess ability of working memory [30].

(4) Visual Reproduction Immediate test (VR I)

This test was operated to measure visual memory. Evaluators showed patients three geometric images, one page each time. At first, participants were asked to view each picture for 10 seconds. Then, the participants were asked to draw the image and details as correctly as possible according to the memory[38].

2.3 MRI Acquisition

MRI images were collected by a 3.0-Tesla Siemens scanner. Functional image was collected by a single-shot gradient echo-echo imaging sequence. The parameters is: echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, slice thickness = 4 mm, slices = 30, field of view (FOV) = 240×240 mm^2, gap = 0.4 mm, matrix = 64×64, flip angle = 90°.

The acquisition of structural images was used a 3-dimensional T1-weighted sequence. The following parameters: TE = 2.03ms, TR = 2300 ms, matrix = 256×256, slices = 176, slice thickness = 1.0 mm, FOV = 256×256 mm2, flip angle = 9°. Overall, 250 volumes were acquired in 500s. During the acquisition, all patients were demanded to hold still, relax, close their eyes, not think special. We used the foam padding to reduce head motion.

2.4 Data Preprocessing

This study used Statistical Parametric Mapping software SPM12 to preprocess MRI Data. For head motion correction, slice timing and realignment were used. Any patients whose head rotation more than 1.0°or motion more than 1.0 mm was excluded.

We applied the standard Montreal Neurological Institute (MNI) template within SPM12 to normalize MRI images. This research used the voxel size of 3 mm×3 mm×3 mm to resample. For minimizing spatial noise, the normalized data were smoothed by convolution with the isotropic Gaussian kernel (8 mm full-width at half-maximum). At every process, the output was proved, and data were excluded if their quality did not meet standard.

2.5 Group ICA and recognition of the intrinsic networks

The fMRI Toolbox Spatial ICA was performed to determine independent components (ICs) for all subjects (GIFT, version 4.0b). We measure the number of ICs using the dimension estimation by the minimum length criteria[39]. In the two groups, the numbers of ICs were 40. We could make sure that the neural circuits shared the semblable spatial mode in the two groups.

This study used normative means of denying factitious ICA neural circuits. We visually identified neural circuits to exclude those obviously showing artifacts. Then the default mode network (DMN), fronto-parietal network (FPN), salience network (SN) and limbic system of the two groups were chosen according to the biggest spatial correlation with a previous pattern[40].

2.6 Statistical Analysis

Clinical features, demographics and cognitive function were statistically analyzed by SPSS version 22.0. FMRI images were calculated by SPM12. To explore the intrinsic networks differences between PBD-I and PBD-II, two-sample T test was calculated of the DMN, FPN, SN and limbic system in the voxel-by-voxel pattern [P<0.05, using family-wise error (FWE) correction]. Head motion, gender and age were performed as covariates in our statistical analysis. Additionally, correlation between variations in DMN, FPN, SN, limbic system z values and clinical/cognitive scores were performed by Spearman's rank correlation within both PBD-I and PBD-II. Correlation analysis was calculated by SPSS 22.0 (threshold, P<0.05, uncorrected).

3 Result

3.1 Subjects' Demographics, Clinical Features and Cognitive Functions

The demographics, symptomatic characteristics and cognitive function were described at Table 1. There was no obvious differences in age (t = 0.86, p = 0.40), education level (t = 0.75, p = 0.46), gender (chi-square = 1.00, p = 0.32), intelligence (t =-1.06, p = 0.30), BSIS(t = 0.40, p = 0.70), PSQI(t = 0.46 ,p = 0.65) ,MFQ (t =-0.41 ,p = 0.68), YMRS (t = 1.70, p = 0.10), age of onset (t =-0.08, p = 0.94), with psychotic symptoms (chi-square = 0.04, p = 0.85), onset frequency (t =-0.48, p = 0.64), and familial psychiatric history (chisquare = 0.08, p = 0.78).

Table 1
Clinical characteristics and cognitive function of PBD-I and PBD-II

	PBD-I Mean (SD)	PBD-II Mean (SD)	$t/^2$	*P* value
Age	15.16 (1.95)	14.74 (1.54)	0.857	0.395
Gender (male/female)	15/16	10/13	1.000	0.317
Education (years)	8.19 (1.94)	7.83 (1.56)	0.747	0.458
IQ	101.68 (13.13)	105.35 (11.85)	-1.058	0.295
BSIS	3.10 (4.57)	2.64 (3.81)	0.386	0.701
PSQI	6.61 (3.67)	6.14 (3.73)	0.463	0.646
MFQ	13.42 (12.97)	14.87 (12.60)	-0.411	0.683
YMRS	17.00 (14.73)	10.74 (12.31)	1.699	0.095
Course of disease (months)	19.65 (13.32)	11.78 (13.67)	2.12	0.039
Age of onset (years)	13.61 (1.71)	13.65 (2.01)	-0.077	0.939
Onset frequency	3.71 (2.27)	4.36 (7.17)	-0.477	0.635
Familial BD history (yes/no)	6/25	7/16	0.077	0.782
Psychotic symptoms (yes/no)	15/16	14/9	0.034	0.853
Medication, n (%)	23 (74.2%)	15 (65.2%)	1.684	0.194
SCWT-A	53.29 (15.16)	51.59 (14.04)	0.414	0.680
SCWT-B	66.97 (19.02)	67.82 (20.87)	-0.154	0.878
SCWT-C	31.10 (8.54)	28.95 (8.28)	0.911	0.367
TMT-A	39.06 (13.69)	38.36 (9.40)	0.208	0.836
TMT-B	98.03 (45.44)	83.95 (25.52)	1.312	0.196
VR I	9.71 (2.69)	9.32 (4.47)	0.367	0.716
DST-A	8.23 (1.43)	8.55 (1.54)	-0.778	0.440
DST-B	4.65 (1.50)	4.91 (2.02)	-0.547	0.587

In the PBD-I group, subjects were taking valproate (n = 15), lithium (n = 10), antipsychotics (n = 22), and antidepressants (n = 1). PBD-II subjects were taking valproate (n = 10), lithium (n = 7), antidepressants (n = 3) and antipsychotics (n = 14). There was no obvious difference in medication between PBD-I and PBD-II (chisquare = 1.68, p = 0.19).

No significant differences were exhibited in the Stroop Color-word test (SCWT)-A (t = 0.41, p = 0.68), SCWT-B (t =-0.15, p = 0.88), SCWT-C (t = 0.91, p = 0.37), Trail making tes(TMT)-A (t = 0.21, p = 0.84), TMT-B (t = 1.31, p = 0.20), VR I (t = 0.37, p = 0.72), DST-A (t =-0.78, p = 0.44) and DST-B (t =-0.55, p = 0.59)(see Table 1).

3.2 Between-Group ICA Analyses

The findings showed significant differences in the default network (DMN), fronto-parietal network (FPN), salience network (SN) and limbic system compared PBD-I with PBD-II ($p < 0.05$, FWE corrected). Intra-network functional connectivity compared PBD-I with PBD-II are shown in Table 2, as following:

Table 2
Different functional connectivity in the intrinsic networks comparing PBD-I with PBD-II

PBD-I vs PBD-II												
DMN				FPN				SN				Limbic sys
Brain regions	MNI x, y, z	Peak t value	Volume	Brain regions	MNI x, y, z	Peak t value	Volume	Brain regions	MNI x, y, z	Peak t value	Volume	Brain regions
Increased connectivity				Increased connectivity				Increased connectivity				Increased connectivit
PCC (L/R)	-5,-47,23/ 5,-42,28	4.30/ 5.90	20/ 28	MTG (R)	52,-57,15	7.00	80	AIn (L/R)	-35,16,-9 37,10,-6	7.70 5.17	530/ 500	PoG (L)
AnG (L/R)	-45,-63,42 49,-57,39	8.40/ 5.45	25/ 21	dlSFG (R)	16,65,10	5.41	180	IFG (L/R)	-50,34,1 50,34,-1	9.47 8.76	530/ 500	MFOr (L)
				FOr (L/R)	-37,50,-12 33,54,-12	8.10/ 10.43	97/ 223					IFOr (R)
												PHG (L/R)
Decreased connectivity				Decreased connectivity				Decreased connectivity				Decreased connectivit
SPG (L/R)	-29,-59,52 29,-61,52	-5.6/ -4.5	19/ 18	SPG (R)	30,-56,55	-8.56	530	ACC (L/R)	-6,34,15 6,25,24	-4.20 -6.44	500/ 530	olf (L/R)
PrCu (L/R)	-9,-54,34/ 7,-56,31	-5.45/ -6.61	21/ 28	dlSFG (L)	-20,64.9	-11.97	115	MCC (L/R)	-7,10,49 7,12,35	-5.67 -6.12	500/ 530	GR (L/R)

Abbreviations: PBD, pediatric bipolar disorder; MNI, the Montreal Neurological Institute; L, left; R, right; PCC, posterior cingulate gyrus; AnG angular gyrus; SPG, precuneus; MTG, middle temporal gyrus; dlSFG, dorsolateral superior frontal gyrus; FOr, orbitofrontal gyrus; AIn, anterior insula; IFG, inferior frontal gyrus; ACC middle cingulate gyrus; PoG, posterior central gyrus; MFOr, middle orbitofrontal gyrus; IFOr, inferior orbitofrontal gyrus; PHG, parahippocampal gyrus; Olf, olfa

1. DMN: Compared with PBD-II, PBD-I subjects presented greater connectivity in the posterior cingulate gyrus and bilateral angular gyrus, while reduced connectivity in the bilateral superior parietal gyrus and bilateral precuneus (see Fig. 1).
2. FPN: Compared to PBD-II, PBD-I presented increased connectivity in the right middle temporal gyrus, right dorsolateral prefrontal gyrus and bilateral orbitofrontal gyrus, meanwhile reduced connectivity in the right superior parietal gyrus, left dorsolateral prefrontal gyrus (see Fig. 2).
3. SN: Compared to PBD-II, PBD-I showed greater connectivity in the bilateral anterior insula and bilateral inferior frontal gyrus, while reduced connectivity in the bilateral anterior cingulate gyrus and bilateral middle cingulate gyrus (see Fig. 3).
4. Limbic system: Compared to PBD-II, PBD-I exhibited greater connectivity in the left postcentral gyrus, left middle orbitofrontal cortex, right inferior orbitofrontal cortex, and bilateral parahippocampal gyrus, meanwhile reduced connectivity in the bilateral olfactory cortices and bilateral rectus gyrus (see Fig. 4).

3.3 Correlation Analysis

The correlation between clinical characteristics, cognitive function and intrinsic network connectivity were as following ($p<0.05$):

1. Correlation in DMN connectivity. In PBD-I group, connectivity of the posterior cingulate cortex was positively related with forward order recite (DST-A)($r = 0.49, p = 0.009$), and the left angular gyrus was positively related to reverse order recite (DST-B) ($r = 0.42, p = 0.030$). In PBD-II group, the connectivity of the posterior cingulate cortex was negatively related to suicidal ideation (BSIS) ($r=-0.69, p = 0.003$), and the right precuneus was negatively associated with depression (MFQ) ($r=-0.53, p = 0.017$) (see Fig. 1C).
2. Correlation in FPN connectivity. No correlation was exhibited between FPN connectivity and mood symptoms in PBD-I and PBD-II. In PBD-I, visual memory (VR I)($r = 0.48, p = 0.007$), working memory (DST-B)($r = 0.37, p = 0.044$)was found to be positively associated with right superior parietal gyrus. In PBD-II

group, attention (SCWT-A/B) (r = 0.64, p = 0.005/ r = 0.53, p = 0.029), response inhibition (SCWT-C)(r = 0.65,p = 0.005)and cognitive flexibility (TMT-B) was positively related to the left orbitofrontal cortex(r = 0.62,p = 0.007), as well as visual memory (VR I) was negatively related to the right dorsolateral prefrontal cortex(r=-0.54,p = 0.026)(see Fig. 2C).

3. Correlation in SN connectivity. In PBD-I group, the connectivity of the right anterior insula was correlated with attention (Stroop-A) (r=-0.44,p = 0.016), processing speed (TMT-A) (r = 0.54,p = 0.002) and working memory (DST-B) (r=-0.42,p = 0.029). In PBD-II, correlation in SN connectivity as following: 1.Depression (MFQ) (r=-0.48,p = 0.030)was negatively correlated with the left anterior insula; 2.Attention (Stroop-A, Stroop-B) (r=-0.61,p = 0.009; r=-0.52,p = 0.034), response inhibition (Stroop-C) (r=-0.50,p = 0.040)and cognitive flexibility (TMT-B) (r = 0.50,p = 0.042)was correlated with bilateral anterior insula; 3.Attention (Stroop-B) (r = 0.53,p = 0.028)and visual memory (VR I) (r = 0.58,p = 0.028) was positively related to the left inferior frontal gyrus; 4. Attention and processing speed (TMT-A) was negatively correlated with the middle cingulate gyrus (r=-0.51,p = 0.037) (see Fig. 3C).
4. Correlation in limbic system connectivity. In the PBD-I group, sleep quality (PSQI) was positively correlated with the left postcentral gyrus (r = 0.40,p = 0.028). Visual memory (VR I) (r=-0.56,p = 0.002) and working memory (DST-B) (r=-0.42,p = 0.039)were negatively correlated with the right parahippocampal gyrus, as well as cognitive flexibility (TMT-B) (r=-0.41,p = 0.035),working memory (DST-A) (r = 0.47,p = 0.014)were associated with the left middle orbitofrontal gyrus in PBD-I. Within PBD-II group, sleep quality (PSQI) was positively correlated with the bilateral parahippocampal gyrus (r = 0.53,p = 0.028), as well as manic symptom (YMRS) was positively associated with the left middle orbitofrontal gyrus(r = 0.68,p = 0.008), right inferior orbitofrontal gyrus(r = 0.56,p = 0.039)and bilateral rectus gyrus connectivity(r = 0.58,p = 0.029). Additionally, response inhibition (Stroop-C) was negatively correlated with the left parahippocampal gyrus in PBD-II (r=-0.67,p = 0.003) (see Fig. 4C).

4 Discussion

BD-II was used to consider as briefly a 'softer' pattern of BD-I, thus supposing that the identical neuropathological dysfunction underlying BD-I and BD-II. It's just that the degree of the dysfunctions can vary. Recently, this perspective has been challenged through clinical and neurobiological findings. Clinical researches presented that course and severity of symptoms in BD-II were at least as severe as in BD-I [27, 41]. The differences in resting state fMRI comparing BD-I with BD-II were insufficient, particularly in pediatric bipolar disorder (PBD). This research focused on the difference of the functional connectivity in resting state fMRI comparing PBD-I with PBD-II.

In general, Our findings were consistent with prior results of BD, with differences between BD-I and BD-II[13]. PBD-I showed more abnormal functional connectivity within default mode network (DMN), fronto-parietal network (FPN), salience network (SN), and limbic system compared with PBD-II. According to meta-analysis[14, 42], abnormal functional connectivity of the intrinsic networks has been found in adult BD related to healthy control. Besides, we also found that functional connectivity in intrinsic networks were correlated with emotional symptoms and cognitive impairments.

Default mode network (DMN)

Our study found that functional connectivity of posterior cingulate gyrus and bilateral angular gyrus were enhanced, while functional connectivity of bilateral superior parietal cortex and bilateral precuneus were weakened when PBD-I compared with PBD-II. In PBD-I, the posterior cingulate cortex was positively associated with forward order digital recite, and the left angular gyrus was positively correlated with reverse order digital recite. In PBD-II, the posterior cingulate cortex was negatively associated with suicidal ideation, and the right precuneus was negatively associated with depression.

In the latest meta-analysis, the patients of BD exhibited changed functional connectivity in the DMN[14]. The altered functional connectivity within the DMN presented the shortage of integration of inner activity, might show aberrant communication in external cognitive flexibility and internal self-monitoring function[22, 43]. Our previous fMRI research showed weakened functional connectivity of the DMN in the PBD[44].

Working memory and self-reflection processing task-fMRI research in BD-I showed abnormal activation and functional connectivity of the precuneus, which supported the precuneus could be the pathophysiologic mechanism of BD[45, 46]. Precuneus has been shown to involve self-referential processing and depressive rumination[47]. This study exhibited difference of the precuneus connectivity comparing PBD-I with PBD-II, and which was correlated with depression only in PBD-II. This result indicated that PBD-I versus PBD-II had distinction in the functional connectivity of the precuneus.

Disrupted functional connectivity of the posterior cingulate cortex (PCC) was likely to support the evidence for working memory and cognitive function impairment in BD[14]. Our study supported this theory and found that decreased functional connectivity in PCC when PBD-I compared with PBD-II. In PBD-I, PCC was positively associated with attention, and the left angular gyrus was positively correlated with working memory. PCC is also a key nodes of the DMN, the activity of which is involved in emotional processing[48], self-evaluation[48] and suicidal ideation[49] in bipolar disorder. Our study verified this theory and found that PCC connectivity was associated with the suicidal ideation of PBD-II. Overall, our result suggested that difference in DMN connectivity between PBD-I and PBD-II was obvious, which was associated with depressive symptoms, suicidal ideation and cognitive function.

Fronto-parietal network (FPN)

We found both hyper- (FPN seeds and regions of the right middle temporal cortex, right dorsolateral prefrontal gyrus and bilateral orbitofrontal cortex) and hypo-connectivity (FPN region of the right superior parietal gyrus, left dorsolateral prefrontal gyrus) within the FPN while PBD-I compared with PBD-II. The FPN was contributed to varied cognitive function, such as working memory, attention and response inhibition [23, 50–52]. In the correlation analysis of this study, FPN functional connectivity was associated with attention, working memory, cognitive flexibility and response inhibition in PBD-I and PBD-II respectively. Altered resting state-functional connectivity in the FPN are common findings in cognitive dysfunction of BD[23, 50–52]. Our finding presented further evidence for the connectivity difference comparing PBD-I with PBD-II in the FPN.

Salience network (SN)

Salience network (SN) is considered to a core hub in exploring salient stimuli, and modulate the attention and working memory resources for that[53, 54]. The crucial view is the SN mediate dynamic communication between other neural circuits referring to internally oriented attention and externally oriented cognition[53, 55]. This study showed both hyper- (SN seeds and regions of bilateral anterior insula and bilateral inferior frontal gyrus) and hypo-connectivity (SN seeds and region of bilateral anterior cingulate gyrus and middle cingulate gyrus) within the SN compared PBD-I with PBD-II.

The inferior frontal cortex, anterior insula, and anterior cingulate cortex are significant node of a "salience network" which helps extract the most relevant information in the stimuli to regulate behavior[53]. Taken together, the observed hyper-functional connectivity in anterior insula and inferior frontal gyrus between the PBD-I and PBD-II might show the imbalanced communication between cognitive and affective network[53]. This study also exhibited hypo-connectivity within the anterior cingulate cortex and bilateral middle cingulate cortex comparing PBD-I with PBD-II. Anterior cingulate gyrus involves in conducting salience, which present disrupted coordination with neural circuits involved in internal oriented thought and external goal-oriented control[56]. This study provided a further explanation for more dysfunction of the cognitive function and emotion regulation in contrast PBD-I with PBD-II[57, 58].

It is worth emphasizing that anterior insula is crucial in the regulating negative emotion[59]. This study supported this perspective, and we found functional connectivity of the left anterior insula was related to depression in PBD-II. Besides, anterior insula, as a core node of SN, plays an important effect in high-level cognitive and attentional process[56]. In this research, the functional connectivity of the anterior insula was correlated with attention in both PBD-I and PBD-II. Additionally, the left inferior frontal gyrus was correlated with attention and visual memory, and the middle cingulate gyrus was correlated with attention and processing speed in PBD-II. In general, PBD-I versus PBD-II were found to differ in functional connectivity of the salience network, and which was associated with mood and cognitive dysfunction.

Limbic system

A meta-analysis study found that prefrontal-limbic system dysfunction was an important pathological mechanism of PBD[21]. This study exhibited that PBD-I had different functional connectivity of the limbic system compared with PBD-II (enhanced functional connectivity in the left postcentral cortex, left middle orbitofrontal cortex, right inferior orbitofrontal cortex, and bilateral parahippocampal gyrus; weakened functional connectivity in the bilateral olfactory cortices and bilateral rectus gyrus). In previous comparative studies of BD-I and BD-II, distinction were reported in the structure[8],functional connectivity and anatomical connectivity[13] of the limbic system. Our study confirmed that PBD-I versus PBD-II had altered functional connectivity in the limbic system as those in adult patients [13]. It could be seen that limbic systems had significant differences based on functional connectivity comparing PBD-I with PBD-II.

Additionally, we found an association between functional connectivity of the left postcentral cortex and sleep quality in PBD-I; and the functional connectivity of the bilateral parahippocampal gyrus of PBD-II was correlated with sleep quality. It has been proposed that the postcentral gyrus and parahippocampal gyrus in the limbic system participate in the regulation of sleep in adolescents[60]. Clinical observation has proved that children with severe insomnia due to brain surgery injury to the limbic system[61]. Therefore, abnormal functional connectivity of the limbic system in PBD may be the mechanism of the common sleep problems in PBD patients.

Besides, the functional connectivity in the left middle orbitofrontal gyrus, right inferior orbitofrontal cortex and bilateral rectus cortex were correlated with manic symptoms. Manic symptoms are the core emotional symptoms of PBD-I and the key difference between PBD-I and PBD-II (only hypomanic episodes occur in PBD-II)[27]. The orbitofrontal gyrus in the frontal-limbic system is known to be referred to emotional processing[62]. The fact that the symptoms of mania was correlated with the functional connectivity in the orbitofrontal gyrus suggested that the possible mechanism underlying the difference in manic mood comparing PBD-I with PBD-II.

In the correlation of cognitive function and functional connectivity, PBD-I found that the right parahippocampal gyrus was correlated with visual memory and working memory; and the left orbitofrontal gyrus was correlated with cognitive flexibility, working memory and attention. PBD-II only found that the left parahippocampal gyrus was associated with response inhibition. The parahippocampal gyrus and the orbitofrontal gyrus in the limbic system is involved in memory processing, and the damage of which structure can cause the abnormality of emotion and memory[63]. Our result suggested that differences in the functional connectivity of the limbic system between PBD-I and PBD-II are associated with cognitive impairment, especially memory dysfunction. The difference of functional connectivity in the limbic system may provide new evidence for the pathological mechanism that PBD-I has more disorganized cognitive function and emotion than PBD-II[27].

Some limitation of our research should be noticed. Firstly, our sample size was not large. If verified in greater PBD sample, this result could propose as the biomarker for the differential diagnosis of PBD-I and PBD-II. Secondly, major PBD subjects were using medication. Prior researches have presented that medication neutralized the aberrant functional connectivity of BD[64]. Although this research showed changed functional connectivity in PBD-I compared with PBD-II, it still needed to be detected how psychoactive medication impacted the functional connectivity of PBD-I and PBD-II.

In summary, this study showed that abnormal functional connectivity in the DMN, FPN, salience network and limbic system when PBD-I compared with PBD-II. Besides, associations between clinical features, cognitive function and changed functional connectivity in the intrinsic networks were presented in PBD subtypes. This study, from the first finding to explore difference of functional connectivity comparing PBD-I with PBD-II, proposed the possibility that altered functional connectivity in the DMN, FPN, salience network and limbic system could exhibit a different neural mechanism between PBD-I and PBD-II.

Declarations

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- **No conflict exists: None of the authors have a conflict of interest to declare.**
- **Consent to Publish：All the co-authors, including Qian Xiao, Gui Zhang, Yuan Zhong have consented to publish this paper.**
- **Ethical approval: All research process obeyed the standards of the 1964 Helsinki Declaration. The Research Ethics Committee of Xiangya Hospital approved our research.**
- **Consent to Participate: All adolescent and their parent consent to take part in the research and signed written consent.**
- **Contribution：The main contributors are Qian Xiao, Gui Zhang, Yuan Zhong. The contributions of Xiao Qian's are the enrollment of subjects, MRI analysis and paper writing. The contribution of Gui Zhang is the analysis of imaging information and statistical analysis. The contribution of Yuan Zhong is revision of this manuscript.**
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Figures

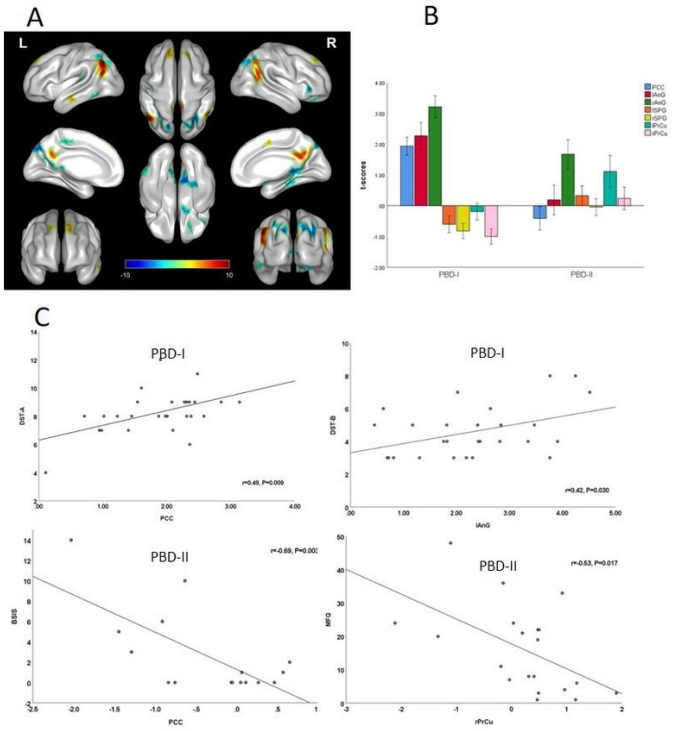

Fig. 1 Comparison of DMN functional connectivity when PBD-I minus PBD-II and correlation analysis

A. Comparison of DMN functional connectivity when PBD-I minus PBD-II ($P < 0.05$, FWE corrected). The color scale represents T values.

B. T scores from two sample T test showed significant difference in the DMN between PBD-I and PBD-II. Histogram was drawn based on the mean value of T. PCC, posterior cingulate gyrus; lAnG, left angular gyrus; rAnG, right angular gyrus; lSPG, left superior parietal gyrus; rSPG, right superior parietal gyrus; lPrCu, left precuneus; rPrCu, right precuneus.

C. In PBD-I group, connectivity of the posterior cingulate cortex was positively correlated with forward order recite (DST-A score), and the left angular gyrus was positively correlated with reverse order recite (DST-B score). In PBD-II, posterior cingulate cortex was negatively associated with suicidal ideation (BSIS score), and the right precuneus was negatively associated with depression (MFQ score). The threshold was set at a significance level of $P < 0.05$ (uncorrected).

Figure 1

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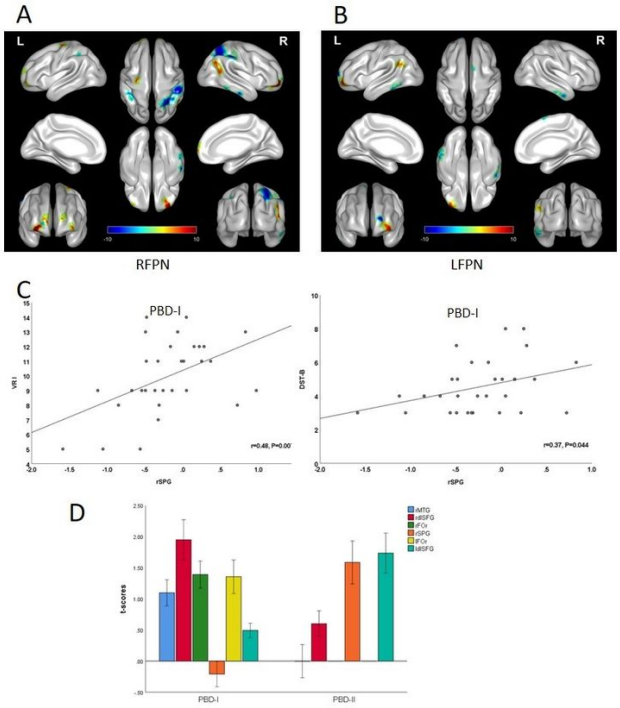

Fig. 2 Comparison of RFPN and LFPN functional connectivity when PBD-I minus PBD-II and correlation analysis

A. Comparison of RFPN functional connectivity between PBD-I and PBD-II. The color scale represents T values ($P < 0.05$, FWE corrected). RFPN, right fronto-parietal network.

B. Comparison of LFPN functional connectivity between PBD-I and PBD-II. The color scale represents T values ($P < 0.05$, FWE corrected). LFPN, left fronto-parietal network.

C. In the PBD-I group, visual memory (VR I score), working memory (DST-B score) was found to be positively correlated with right superior parietal gyrus connectivity. The threshold was set at a significance level of $P < 0.05$ (uncorrected).

D. T scores from two sample T test showed significant difference in the RFPN and LFPN between PBD-I and PBD-II. Histogram was drawn based on the mean value of T. rMTG, right middle temporal gyrus; rdlSFG, right dorsolateral superior frontal gyrus; rFOr, right orbitofrontal gyrus; rSPG, right superior parietal gyrus; lFOr, left orbitofrontal gyrus; ldlSFG, left dorsolateral superior frontal gyrus.

Figure 2

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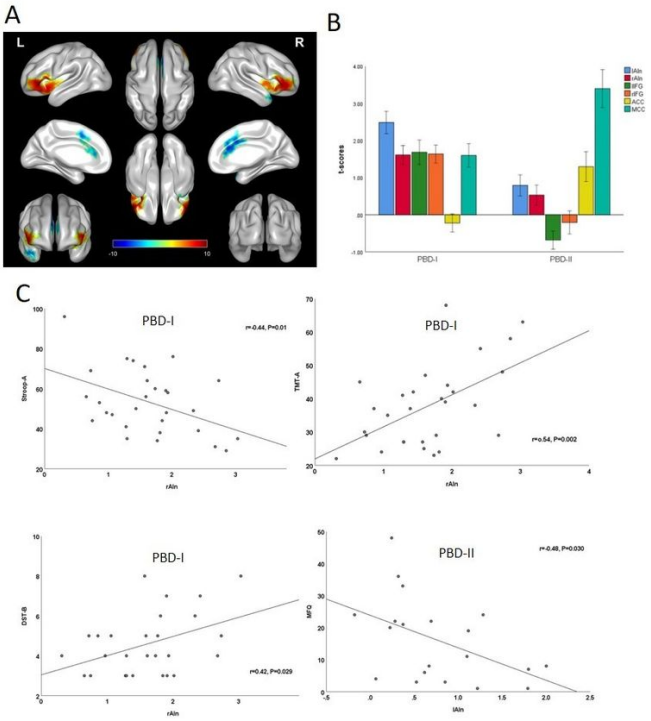

Fig. 3 Comparison of SN functional connectivity when PBD-I minus PBD-II and correlation analysis

A. Comparison of salience network(SN) functional connectivity when PBD-I minus PBD-II ($P < 0.05$, FWE corrected) . The color scale represents T values.

B. T scores from two sample T test showed significant difference in the SN between PBD-I and PBD-II. Histogram was drawn based on the mean value of T. lAIn, left anterior insula; rAIn, right anterior insula; lIFG, left inferior frontal gyrus; rIFG, right inferior frontal gyrus; ACC, anterior cingulate gyrus; MCC middle cingulate gyrus.

C. In PBD-I group, the connectivity of the right anterior insula was correlated with attention (Stroop-A), processing speed (TMT-A score) and working memory (DST-B score). In PBD-II group, depression (MFQ score) was negatively associated with the left anterior insula connectivity.The threshold was set at a significance level of $P < 0.05$ (uncorrected).

Figure 3

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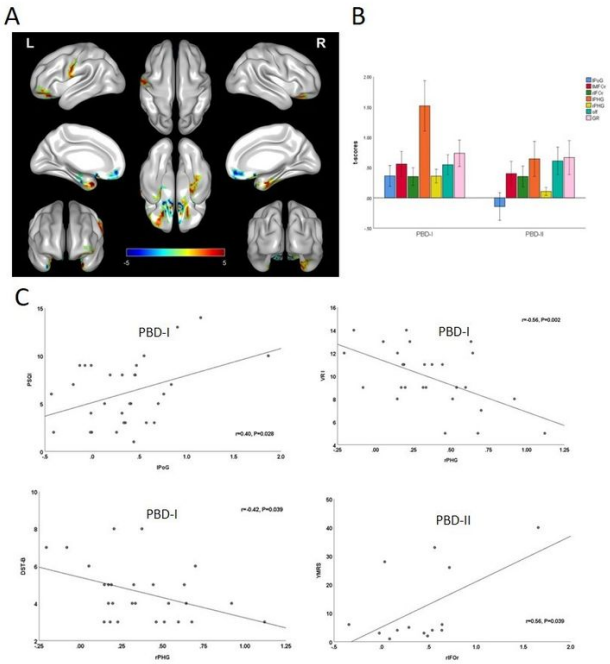

Fig. 4 Comparison of limbic system functional connectivity when PBD-I minus PBD-II and correlation analysis

A. Comparison of limbic system functional connectivity when PBD-I minus PBD-II ($P < 0.05$; FWE corrected) . The color scale represents T values.

B. T scores from two sample T test showed significant difference in the limbic system between PBD-I and PBD-II. Histogram was drawn based on the mean value of T.
lPoG, left posterior central gyrus; lMFOr, left middle orbitofrontal gyrus; rIFOr, right inferior orbitofrontal gyrus; lPHG, left parahippocampal gyrus; rPHG, right parahippocampal gyrus; Olf, olfactory cortex;GR, rectus gyrus.

C. In the PBD-I group, sleep quality (PSQI score) was positively correlated with the left postcentral gyrus connectivity(r=0.40,p=0.028） , as well ad visual memory (VR I score) (r=-0.56,p=0.002) and working memory (DST-B score) (r=-0.42,p=0.039） were negatively correlated with the right parahippocampal gyrus connectivity. In PBD-II group, manic symptom (YMRS score) was positively associated with the right inferior orbitofrontal gyrus(r=0.56,p=0.039） . The threshold was set at a significance level of $P < 0.05$ (uncorrected).

Figure 4

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