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Shared and distinct patterns of dynamical degree centrality in bipolar disorder across different mood states

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Background: Previous studies have probed the brain static activity pattern in bipolar disorder across different states. However, human intrinsic brain activity is time-varying and dynamic. There is a lack of knowledge about the brain dynamical pattern in bipolar disorder across different mood states.

Methods: This study used the dynamical degree centrality (dDC) to investigate the resting-state whole-brain dynamical pattern voxel-wise in a total of 62 bipolar disorder [28 bipolar depression (BD), 13 bipolar mania (BM), 21 bipolar euthymia (BE)], and 30 healthy controls (HCs). One-way analysis of variance (ANOVA) was applied to explore the omnibus differences of the dDC pattern across all groups, and Pearson's correlation analysis was used to evaluate the relationship between the dDC variability in detected regions with clinical symptom severity.

Results: One-way ANOVA analysis showed the omnibus differences in the left inferior parietal lobule/middle occipital gyrus (IPL/MOG) and right precuneus/posterior cingulate cortex (PCUN/PCC) across all groups. The *post hoc* analysis revealed that BD showed decreased dDC in the IPL/MOG compared with all other groups, and both BD and BM exhibited decreased dDC in the PCUN/PCC compared with BE and HCs. Furthermore, correlation analysis showed that the dDC variability of the IPL/MOG and PCUN/PCC negatively correlated with the depression symptom levels in all patients with bipolar disorder.

Conclusion: This study demonstrated the distinct and shared brain dynamical pattern of the depressive, manic, and euthymia states. Our findings provide new insights into the pathophysiology of bipolar disorder across different mood states from the dynamical brain network pattern perspective.

KEYWORDS

bipolar disorder, dynamical degree centrality, inferior parietal lobule, precuneus, posterior cingulate cortex, middle occipital gyrus

Introduction

Bipolar disorder (BD) is a mood disorder with alternating periods of depression (hypo) mania [bipolar mania (BM)], and euthymic mood states [bipolar euthymia (BE)] (1). It affects > 1% of the global population and is a leading cause of disability worldwide (2). Previous studies have reported the abnormal structural, activation, and functional connectivity underlying bipolar disorders (3–6). However, limited studies have considered the various mood episodes in bipolar disorders. Therefore, further research is needed to investigate the pathophysiological mechanisms of bipolar disorder across different mood states (7, 8).

Previous studies have explored the distinctive neural mechanism underlying different mood states of bipolar disorder. For example, Martino et al. have reported the sensorimotor and default-mode networks (DMNs) showed opposite variation patterns in BD and BM (9). Russo et al. have documented that BD showed the altered regional homogeneity in the primary sensorimotor cortex, and BM showed altered regional homogeneity and degree centrality (DC) in the medial prefrontal cortex (10). These findings may indicate that the functional connectivity imbalance pattern between the sensorimotor and DMN is related to the clinical mood state of bipolar disorder. Meanwhile, a prior study has reported that both BD and BM showed higher activation in the right insula, right putamen, and left lateral prefrontal cortex when inhibiting sad faces compared with BE and healthy controls (HCs) (11). In addition, compared with HCs, both BD and BM showed reduced activation in the dorsolateral prefrontal cortex during an N-back working memory task, but there were no differences manifested compared with BE (12). These findings indicated that they have shared and distinct brain patterns among the different mood states of bipolar disorder.

It has been reported that the human brain is a highly dynamic and time-varying system and maintains a dynamic balance to ensure effective communication between various brain regions (13–15). The analysis methods of looking into the brain dynamical pattern have been adopted for investigating neural mechanisms of mental disorders (16–18). For example, Fu et al. have reported the dynamical pattern in patients with schizophrenia by using the dynamical low-frequency fluctuation amplitude and dynamical functional connectivity (16), and our prior studies also have investigated the differences between BD and unipolar depression by using the dynamical fractional amplitude of low-frequency fluctuations and dynamical regional homogeneity, respectively (19, 20). However, to the best of our knowledge, no study has investigated the brain dynamical pattern in bipolar disorder across three different mood states. Thus, this study aimed to fill this blank.

In this study, we used the voxel-wise dynamic degree centrality DC (dDC) approach to explore the dynamical pattern of the resting-state whole-brain functional connectome in

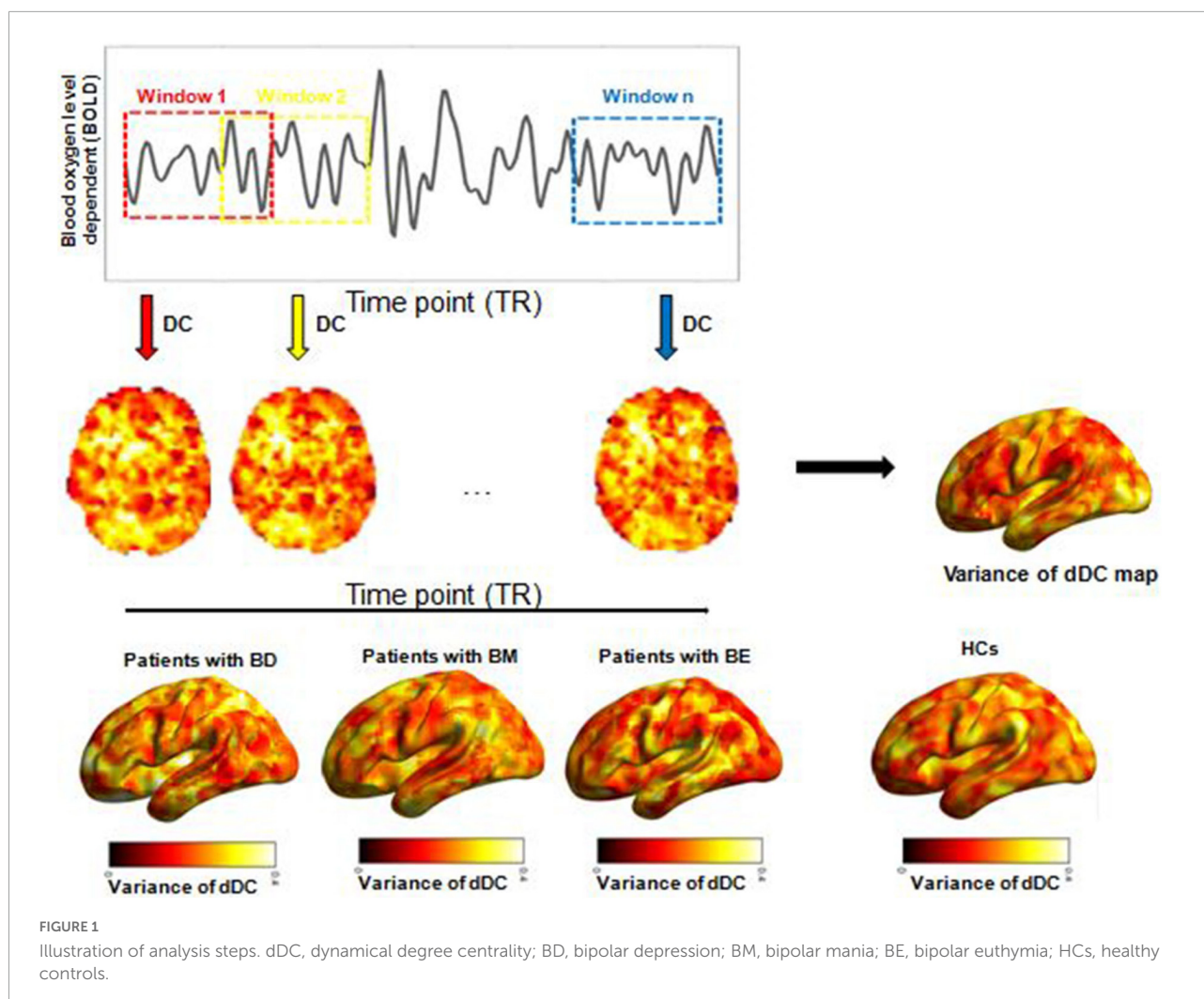
bipolar disorder across three states. DC is an index of the total weight of connections for a given node (15) and has been widely used in psychiatric disorders as an analytic measurement to reveal the core-hub architecture of brain networks (21–23). The dDC approach adds the sliding-window step to measure the time-varying features of the DC maps (24). By adopting this method, we first hypothesized that the dynamical pattern of the whole-brain functional connectome will be distinctive across three mood states (i.e., mania, depression, euthymia), and it will be strongly related to the severity of the clinical symptoms. We further hypothesized that the distinctive dDC value across three states would tend to be distributed in the DMN and sensorimotor areas that have been repeatedly reported in previous studies. By studying the differences in bipolar disorder across different mood states in terms of dDC, we can have a more comprehensive understanding of the bipolar disorder.

Materials and methods

Participants

A total of 77 patients with bipolar disorder were enrolled in this study, including 32 patients with BD, 20 patients with BM, and 25 patients with BE. All patients were recruited from the inpatient or outpatient department of the Second Xiangya Hospital, Central South University. To reduce the heterogeneous impact of different typing patients with bipolar disorder, our study only included patients with type I bipolar disorder (25). They were diagnosed as bipolar disorder type I (including the BD, BM, or BE) using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P) (26). The clinical symptoms were comprehensively assessed by two experienced psychiatrists using the Hamilton Depression Scale (HAMD) (27), Young Mania Rating Scale (YMRS) (28), Hamilton Anxiety Rating Scale (HAMA) (29), and Brief Psychiatric Rating Scale (BPRS) (30), respectively. HAMD is the most commonly used scale to clinically assess depression status and its severity. HAMA is mainly used to assess the severity of anxiety symptoms in patients. YMRS is mainly used to assess manic symptoms and their severity. BPRS is mainly used to assess the severity of the patient's psychiatric symptoms. The inclusion criteria were the HAMD score ≥ 17 and the YMRS score < 6 for BD; the YMRS score ≥ 12 and the HAMD score < 8 for BM; the HAMD score < 8 and the YMRS score < 6 for BE (31, 32).

A total of 35 HCs were recruited from the local universities and communities through advertisement and using the Structured Clinical Interview for DSM-IV, Non-patient Edition (SCID-I/NP). To better understand our sample, all participants were assessed by using the Wechsler Adult Intelligence Scale (WAIS) (33), including WAIS-Knows and WAIS-Digit symbol.



All participants were excluded if they had any of the following: (1) < 18 years old or > 45 years old; (2) previous neurological diseases or serious physical illness; (3) previous alcohol or other psychoactive substance abuse; (4) previous electroconvulsive therapy; and (5) had taken benzodiazepines within 24 h before scanning or any other contraindications to MRI.

This study was conducted in accordance with the ethical guidelines of the medical ethics committee of the Second Xiangya Hospital, Central South University, and in strict accordance with the Declaration of Helsinki. Participants were informed and agreed to participate in the study and were free to withdraw from the research at any time.

Data acquisition and preprocessing

All MRI data were collected as soon as possible after the patient's first visit to the clinic using a 3.0 Tesla Philips Gyrosan Achieva (Amsterdam, The Netherlands) scanner. In

the scanning, all participants were explicitly instructed to keep their eyes closed and stay awake. A gradient-echo echo-planar imaging sequence was used with the following parameters: axial slice = 36, matrix = 64×64 , repeat time = 2,000 ms, echo time = 30 ms, field of view = $240 \text{ mm} \times 240 \text{ mm}$, flip angle = 90° , slice thickness = 4 mm, scanning interval = 0 mm, in a total of 250 total volumes.

Data preprocessing was carried out using DPABI¹ (34). The first 10 volumes were removed to allow magnetization balance and adaptation to the environment (35). The remaining 240 functional scans were done with the following analyses: all participants had < 3 mm maximum displacement in x, y, or z and less than 3° of angular rotation about each axis, spatial normalization of the Montreal Neurological Institute (MNI), resampled to the voxel size of $3 \times 3 \times 3 \text{ mm}^3$ then the BOLD signal of each voxel was detrended to abandon linear trends and passed through a bandpass filter (0.01–0.08 Hz).

¹ <http://rfmri.org/dpabi>

We also employed the scrubbing step by removing outlier volumes with frame-wise displacement (FD) > 0.5 mm. Finally, interference covariates were regressed out from the BOLD signals, including six head motions and their temporal first derivatives (36), global mean signals, white matter signals, and cerebrospinal fluid signals.

A total of 20 participants were excluded due to their excessive head movement or inability to cooperate during fMRI scanning. After data quality control, 92 subjects (including 28 patients with BD, 13 patients with BM, 21 patients with BE, and 30 patients with HCs) participated in the following analyses.

Temporal variability of the dynamical degree centrality

As mentioned earlier, DC is a widely used method to describe intrinsic brain connectivity at a global level (37). In this study, by using the Dynamic Brain Connectome (DynamicBC) toolbox, the temporal variability of voxel-wise dDC was calculated according to the sliding-window approach. According to the recommendations of the previous studies (38), we used a window length of 50 TRs (100 s) to calculate the temporal variability of dDC. We obtained a dDC map for each sliding window and then computed the coefficient of variation across all sliding windows to explore the dDC variability of the four groups. Finally, the dDC map was smoothed with full-width at half maximum = 6 mm. The analytical steps of this study are illustrated in [Figure 1](#).

Validation analyses

To validate our main findings, we reperformed the analysis by using a sliding-window length of 70 TRs (140 s).

Statistical analysis

The demographic and clinical characteristics of the four groups have been analyzed using SPSS 21.0. Differences in age, education, illness duration, age of onset, manic episodes times, depressive episodes times, mean FD, WAIS-Knows, WAIS-Digit symbol, HAMD, YMRS, HAMA, BPRS, and chlorpromazine (CPZ) equivalents (39) were analyzed with a one-way analysis of variance (ANOVA). A chi-square test was used to calculate the differences in gender across all groups.

The dDC variability among the four groups was performed using Statistic Parameter Mapping 8 software.² One-way ANOVA was carried out to compare the dDC variability among

the four groups voxel-wise with age, gender, and education years as nuisance covariates. Then, by applying the significant voxels that survived in one-way ANOVA analysis as the mask, the *post hoc t*-tests were performed between any two groups. The threshold was set at voxel-level $p_{\text{voxel}} < 0.005$ and cluster size > 60 (AlphaSim corrected, $p_{\text{cluster}} < 0.05$).

Finally, Pearson's correlation analysis was used to evaluate the relationship between the altered dDC variability with the HAMD score and YMRS score.

Results

Demographic and clinical characteristics

No significant differences were detected for age [$F_{(3,91)} = 0.710$, $p = 0.548$], gender ($\chi^2 = 0.174$, $p = 0.677$), education [$F_{(3,91)} = 2.440$, $p = 0.070$], mean FD [$F_{(3,91)} = 1.517$, $p = 0.216$], and WAIS-knows [$F_{(3,91)} = 1.216$, $p = 0.309$] in all groups. However, WAIS-Digit symbol score of the three patient groups was lower than that of HCs [$F_{(3,91)} = 11.507$, $p < 0.001$]. Three patient groups were matched with illness duration [$F_{(3,91)} = 1.374$, $p = 0.261$], age of onset [$F_{(3,91)} = 0.116$, $p = 0.891$], manic episodes times [$F_{(3,91)} = 0.576$, $p = 0.565$], and depressive episodes times [$F_{(3,91)} = 1.153$, $p = 0.323$]. In addition, BD showed a higher score of HAMD [$F_{(3,91)} = 122.500$, $p < 0.001$], HAMA [$F_{(3,91)} = 33.129$, $p < 0.001$], BPRS [$F_{(3,91)} = 13.874$, $p < 0.001$] than that of BM and BE, while BM showed a higher score of YMRS [$F_{(3,91)} = 140.063$, $p < 0.001$] than that of BD and BE. Moreover, significant differences were found for CPZ equivalents [$F_{(3,91)} = 7.413$, $p = 0.001$] in three patient groups, and BE took more antipsychotics than that of BD ($t = 2.80$, $p = 0.014$) and BM ($t = 1.917$, $p = 0.073$). Detailed results are shown in [Table 1](#) and [Supplementary Table 1](#).

Temporal variability of the dynamical degree centrality

One-way ANCOVA showed significant dDC variability differences among the four groups in left inferior parietal lobule/middle occipital gyrus (IPL/MOG; MNI [$x = -36$, $y = -72$, $z = 33$]; $F_{(3,91)} = 9.58$; see [Figure 2](#) and [Table 2](#)) and right precuneus/posterior cingulate (PCUN/PCC; MNI [$x = 15$, $y = -60$, $z = 15$]; $F_{(3,91)} = 9.04$; see [Figure 2](#) and [Table 2](#)). The *post hoc t*-tests revealed that BD showed decreased dDC in the IPL/MOG compared with BM ($t = -3.76$), BE ($t = -4.66$), and HCs ($t = -4.77$). The *post hoc t*-tests revealed that BD showed decreased dDC in the PCUN/PCC compared with BE ($t = -4.26$) and HCs ($t = 4.21$), and BM showed decreased dDC in the PCUN/PCC compared with BE ($t = -3.85$). In addition,

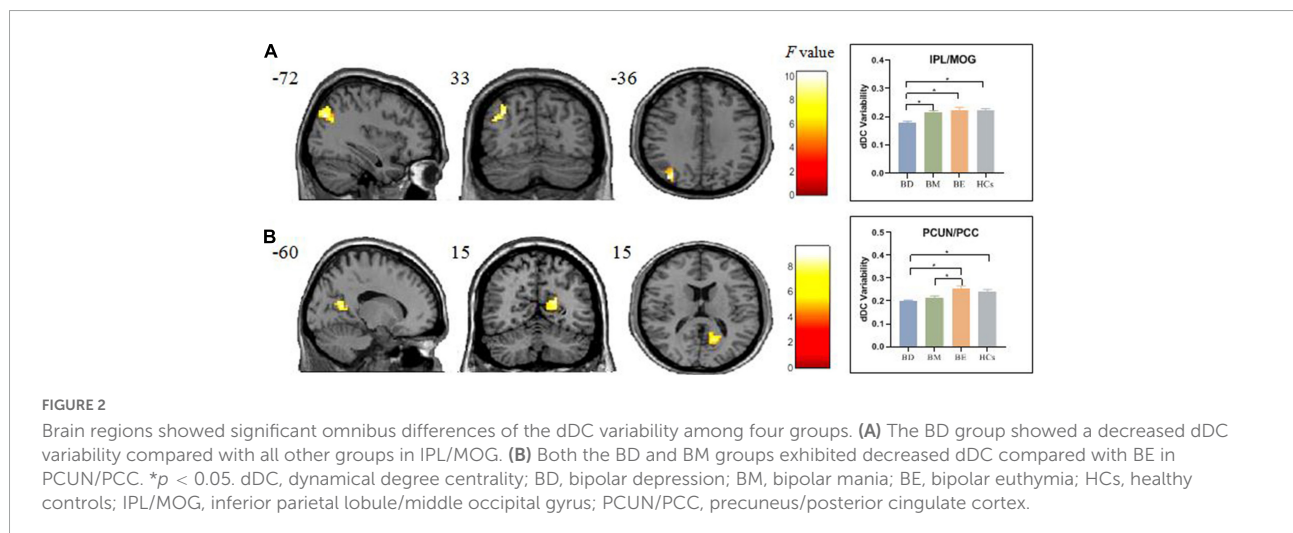
² www.fil.ion.ucl.ac.uk/spm

TABLE 1 Cohort demographics and clinical characteristics.

Characteristics	BD (n = 28)	BM (n = 13)	BE (n = 21)	HCs (n = 30)	F/ χ^2	P
Age (years)	26.50 ± 6.76	27.69 ± 7.34	26.95 ± 6.25	24.93 ± 6.17	0.710	0.548 ^b
Gender (M/F)	12/16	5/8	11/10	15/15	0.174	0.677 ^a
Education (years)	13.04 ± 3.05	11.31 ± 3.01	13.98 ± 2.60	12.73 ± 2.69	2.440	0.070 ^b
Illness duration (months)	52.83 ± 53.16	78.38 ± 91.57	42.86 ± 40.47	N/A	1.374	0.261 ^b
Manic episodes (times)	2.32 ± 2.93	3.38 ± 3.20	2.67 ± 2.82	N/A	0.576	0.565 ^b
Depressive episodes (times)	3.54 ± 3.17	2.08 ± 2.33	4.05 ± 4.92	N/A	1.153	0.323 ^b
Age of onset (years)	21.43 ± 4.29	21.75 ± 6.59	22.15 ± 5.25	N/A	0.116	0.891 ^b
WAIS-Knows	19.64 ± 4.74	18.05 ± 4.98	20.37 ± 4.38	20.69 ± 4.33	1.216	0.309 ^b
WAIS-Digit symbol	65.29 ± 18.29	62.83 ± 14.87	73.33 ± 13.39	84.97 ± 10.31	11.507	<0.001 ^b
CPZ-equivalents (mg)	13.10 ± 51.39	50.00 ± 99.54	149.89 ± 188.18	N/A	7.413	0.001 ^b
Mean FD	0.12 ± 0.36	0.12 ± 0.03	0.14 ± 0.59	0.15 ± 0.10	1.517	0.216 ^b

^ap-value for chi-square test.

^bp-values for one-way ANOVA. Values are presented by mean ± standard deviation. BD, bipolar depression; BM, bipolar mania; BE, bipolar euthymia; HCs, healthy controls; WAIS, Wechsler Intelligence Scale; CPZ, chlorpromazine; FD, frame-wise displacement; N/A, not available.



we did not observe any significant correlations between the dDC variability of areas with omnibus differences and mean FD in all participants (see [Supplementary Figure 1](#)).

Validation results

We also observed the omnibus dDC differences in IPL/MOG and PCUN/PCC using 70 TRs. The results were essentially in agreement with that of 50 TRs, and the details are summarized in [Supplementary Table 2](#).

Correlation analysis

Correlation analyses revealed significant negative correlations between the HAMD score and the dDC variability of the IPL/MOG ($r = -0.439$, $p < 0.001$) and PCUN/PCC ($r = -0.458$, $p < 0.001$), but no significant correlation was

found between the YMRS score and the dDC variability of the IPL/MOG ($r = 0.192$, $p = 0.138$) and PCUN/PCC ($r = 0.177$, $p = 0.172$) (see [Figure 3](#) and [Table 3](#)).

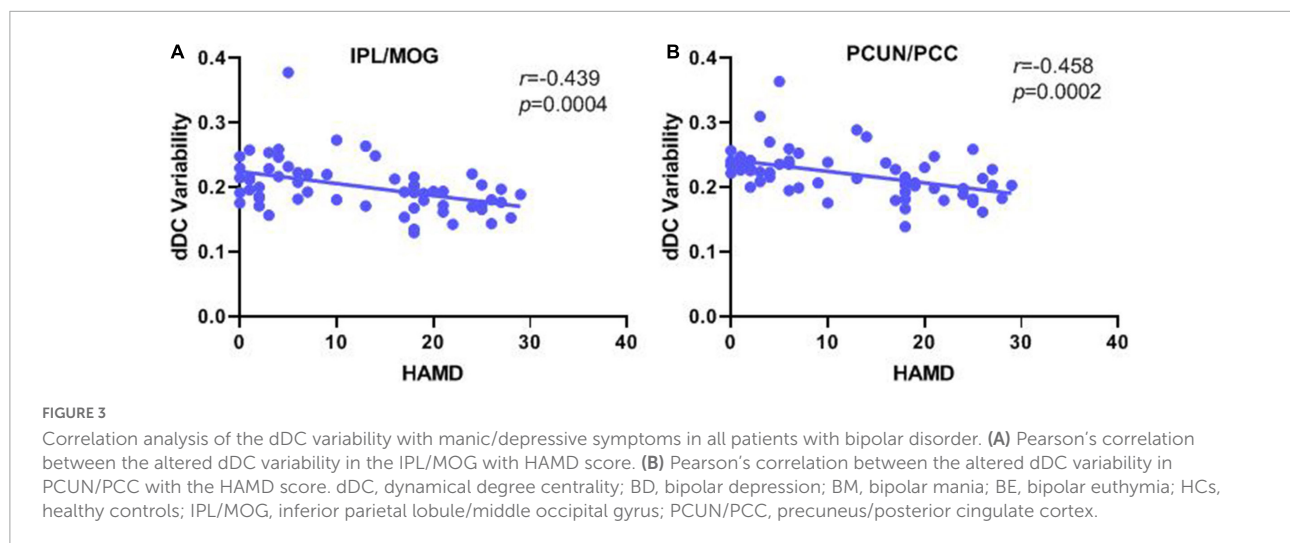
Discussion

To the best of our knowledge, this is the first study to investigate the dDC variability of the whole-brain functional connectome at the voxel-wise across all diagnostic groups. We found significant dDC differences among all groups in the IPL/MOG and PCUN/PCC. More specifically, the BD group showed a decreased dDC in the IPL/MOG compared with all other groups. Both the BD and BM groups exhibited decreased dDC in PCUN/PCC compared with BE. Furthermore, correlation analysis showed that dDC variability of the IPL/MOG and PCUN/PCC negatively correlated with scores of depressive symptoms in all patients.

TABLE 2 Brain regions with significant dDC difference among the four groups.

Brain region	MNI			BA	Voxels	F	Post hoc analysis	
	X	Y	Z				Comparisons	T
IPL/MOG	-36	-72	33	19	62	9.58	BD < BM BD < BE BD < HCs	-3.76 -4.66 -4.77
PCUN/PCC	15	-60	15	30	63	9.04	BD < BE BD < HCs BM < BE	-4.26 -4.21 -3.85

dDC, the dynamical degree centrality; BD, bipolar depression; BM, bipolar mania; BE, bipolar euthymia; HCs, healthy controls; MNI, Montreal Neurological Institute; BA, Brodmann area; IPL/MOG, inferior parietal lobule/middle occipital gyrus; PCUN/PCC, precuneus/posterior cingulate cortex.



We observed decreased dDC variability of the IPL/MOG in BD compared with other groups, and the dDC variability negatively correlated with the HAMD scores. The IPL/MOG involves emotion regulation, reaction inhibition, and self-circulation processing (40). Qiu et al. have reported that both patients with BD and patients with major depressive disorder showed abnormal fractional ALFF in the IPL/MOG compared with HCs (41). Zhang et al. have documented those patients with BE and BD manifested disrupted functional connectivity in IPL/MOG during resting-state (42). Furthermore, consistent with this study, Luo et al. have adopted the dynamical functional connectivity and observed that both patients with BD and patients with major depressive disorder displayed reduced dynamical functional connectivity between the IPL/MOG and precuneus (43). These studies may suggest that deficits of the static or dynamical regional activity or distal functional connectivity in the IPL/MOG are more pronounced in the depressive state. Accordingly, we speculate that the IPL/MOG would be a potential biomarker that distinguishes BD from BM and BE.

Compared with BE, both BD and BM exhibited decreased dDC in the PCUN/PCC, while no significant difference

was found for BD and BM. Consistent with our results, a meta-analysis based on large samples reported that both BD and BM presented decreased connectivity within the DMN, but BE showed increased connectivity (44). The PCUN/PCC is a crucial component in the DMN and acts as an intermediate hub with other networks (45). Previous studies have documented patients with bipolar disorder manifested imbalanced functional connectivity between DMN and salience network (46). It was reported that BD showed decreased functional connectivity between the perigenual

TABLE 3 Correlation analysis of dDC variability with manic/depressive symptoms in all patients with bipolar disorder.

Variable		IPL/MOG	PCUN/PCC
HAMD	r	-0.439	-0.458
	p	0.000**	0.000**
YMRS	r	0.192	0.177
	p	0.138	0.172

** $p < 0.001$. dDC, the dynamical degree centrality; HAMD, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; IPL/MOG, inferior parietal lobule/middle occipital gyrus; PCUN/PCC, precuneus/posterior cingulate cortex.

anterior cingulate cortex and anterior cingulate cortex, and BM showed decreased functional connectivity between the perigenual anterior cingulate cortex and PCUN/PCC.

We also observed the abnormal dDC in the PCUN/PCC correlated with depressive symptoms. Zhong et al. have documented that patients with BD showed intrinsic activity abnormalities under specific frequency bands in the PCUN/PCC and MOG (47). A prior study has reported that patients with BM showed decreased connectivity within the PCUN/PCC, and it correlated with clinical severity scores (48). Combining with our findings of the shared decreased dDC in the PCUN/PCC between the BD and BM groups, we speculate that this area may have important implications to be a potential intervention target for bipolar disorder during active phases (i.e., BD and BM).

It should be noted that this study has some limitations. First, our small sample size, especially the BM group (the sample size is 13), which may limit the statistic power and easily cause the type I and II errors, and the results should be considered preliminary. In addition, this is a cross-sectional study that can only observe the current time measurements of the brain dynamical connectivity pattern, and we did not collect the longitudinal data of patients with bipolar disorder in different mood states. Therefore, further longitudinal studies with larger samples are needed to verify our results, and any generalization of the findings of this study needs to be carefully made. Finally, considering the drugs taken by the patients at the time of enrollment, we cannot ignore the possible impact of drugs on our results.

Conclusion

Our study investigated the brain dynamical pattern in bipolar disorder across different mood states by using the dDC variability index. We observed the detected dDC abnormalities in IPL/MOG were unique to BD, and the dDC abnormalities PCUN/PCC both manifested in BD and BM. It may indicate that there are common and different patterns of the dynamic brain connectome pattern of bipolar disorder in different states. Our findings provide an insight into the resting-state global brain network dynamics in bipolar disorder.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the medical Ethics Committee of the

Second Xiangya Hospital, Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZL, ZH, and JiY designed the study. FS, JuY, ZF, CX, and PC acquired the data. FS, JuY, and ZF analyzed the data. FS and JiY wrote the article. All authors reviewed the article and authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.941073/full#supplementary-material>

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