Inflammation is Correlated with Abnormal Functional Connectivity in Unmedicated Bipolar Depression: A Resting State FMRI Study

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Abstract

Objectives Inflammation might play a role in bipolar disorder (BD), but it remains unclear the relationship between inflammation and brain structural and functional abnormalities in patients with BD. In this study, we focused on the alterations of functional connectivity (FC), peripheral pro-inflammatory cytokines and their correlations to investigate the role of inflammation in FC in BD depression.

Methods In this study, 42 unmedicated patients with BD II depression and 62 healthy controls (HCs) were enrolled. Resting-state-functional magnetic resonance imaging (rs-fMRI) was performed in all participants and independent component analysis (ICA) was used. Serum levels of Interleukin-6 (IL-6) and Interleukin-8 (IL-8) were measured in all participants. Correlation between FC values and IL-6 and IL-8 levels in BD was calculated.

Results Compared with the HCs, BD II patients showed decreased FC in the left orbitofrontal cortex (OFC) implicating the limbic network and the right precentral gyrus implicating the somatomotor network (SMN). BD II showed increased IL-6 (P = 0.039), IL-8 (P = 0.002) levels. Moreover, abnormal FC in the right precentral gyrus were inversely correlated with the IL-8 (r=-0.458, P = 0.004) levels in BD II. No significant correlation was found between FC in the left OFC and cytokines levels.

Conclusions Our findings that serum IL-8 levels is associated with impaired FC in the right precentral gyrus in BD II patients suggest that inflammation might play a crucial role in brain functional abnormalities in BD.

1. Introduction

Bipolar disorder (BD) is a severe psychiatric disease characterized by recurrent periods of mania and depression (BD I) or hypomania and depression (BD II). It is a leading cause of disability in young people as they can lead to cognitive and functional impairment and increased mortality, particularly from suicide and cardiovascular disease[1]. Although abnormalities in specific brain regions and connections in BD have been reported by growing structural and functional neuroimaging studies, the neuropathology of BD is still not fully understood.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive neuroimaging technique that has been used to investigate abnormal regional function and functional connectivity (FC) in BD [2]. Two methods widely used in FC studies include seed-based correlation approach [3, 4] and independent component analysis (ICA) [5, 6]. The ICA is a data-driven approach that do not require prior knowledge of predefined brain regions or voxels when estimating functional networks [7]. Several studies reported altered FC in the default mode network [8, 9], limbic network [10-12], somatomotor network/sensorimotor network (SMN) [6, 13], frontoparietal network [14], and dorsal and ventral attention network [15] in BD. Reasons for the inconsistent findings are as following: heterogeneity of the patients included, different states and subtypes of BD, illness duration, drug administration, multiple comparison correction strategies and metrics of fMRI applied.

Studies investigating systemic inflammation and immune dysregulation have provided important insights into the pathophysiologic processes underlying BD [16-19]. Pro-inflammatory cytokines have been shown to access the brain [20] and interact with neurocircuits to influence the risk for depression [21] and are implicated in many neurobiological processes including neuromodulator effects, neurotransmitter-like effects, regulation of neurogenesis that potentially relevant to psychiatric disorders such as BD [22]. Previous studies examined the relationship between inflammation and BD focusing on abnormal peripheral pro-inflammatory cytokines levels, and found significantly elevated levels of interleukin 6 (IL-6) [23-26] and interleukin 8 (IL-8) [27-29] in BD. Higher baseline IL-6 and IL-8 levels associated with poorer antidepressant responses have been found in BD [30]. Moreover, some studies exhibited increased serum concentrations of cytokines such as IL-8 were associated with cognitive dysfunction, poor performance in the memory and speed domains and in motor function [31, 32]. Another study indicated that inflammation (modulated by IL-6) causes mood deterioration through alterations in emotional processing related neural activity [33].

Previous studies have found that inflammation was associated with abnormal brain activation and functional connectivity in limbic network [34, 35]. The limbic network, which includes the hippocampus, para-hippocampal gyrus, amygdala, orbitofrontal cortex (OFC), cingulate gyrus [36], involves in various functions such as emotional processing and regulation [37, 38] and reward processing [39, 40], and plays a critical role in emotional dysregulation in BD [11, 41]. Additionally, most of depressed patients demonstrate effort-related motivational symptoms, including psychomotor retardation, tiredness, low energy, and listlessness, which is second only to depressed symptoms [42, 43]. Recently, studies found that inflammation could affect cortical reward and motor circuits and was related to such symptoms (anhedonia and motor slowing) in psychiatric diseases such as BD [19, 44, 45]. Also, a recent neuroimaging study found abnormalities of brain regions in SMN correlated with inflammation in BD patients [46].

In this study, we tried to detect brain FC alterations in limbic network and SMN based on ICA approach. Because medication use and different subtypes of patients could confound the findings, all the BD II patients recruited in the present study were unmedicated. We hypothesized that patients with BD II would show disrupted FC patterns in regions of the limbic network or SMN compared to healthy controls (HCs), and elevations of pro-inflammatory markers IL-6 and IL-8 would exist in BD groups. Additionally, we sought to determine whether abnormal FC in BD would correlate with inflammation (as identified by changes in pro-inflammatory markers).

2. Materials And Methods

2.1 Participants

A total of 42 right-handed, currently depressed individuals diagnosed with BD II were recruited from the psychiatry department, First Affiliated Hospital of Jinan University, Guangzhou, China. The patients were aged from 18 to 55 years. All patients met Diagnostic and Statistical Manual of Mental Disorders, Fifth

Edition (known as DSM-V) criteria for BD II according to the diagnostic assessment by the Structured Clinical Interview for DSM-V Patient Edition (SCID-P) by two experienced psychiatrists (Y.J. and S.Z., with 21 and 6 years of experienced clinical psychiatry, respectively). The clinical state was assessed by using the 24-item Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) during the 3-day period prior to the imaging session. The inclusion criterion for the depressed patients with BD II was a total HDRS-24 score > 21 and YMRS score < 7. The exclusion criteria were patients with other Axis-I psychiatric disorders, a history of electroconvulsive therapy, neurological disorders, any history of organic brain disorder, mental retardation, pregnancy, alcohol/substance abuse, cardiovascular diseases or any presence of a concurrent and major physical illness. At the time of testing, all patients were either medication-naïve, or were not medicated for at least six months. In addition, 69 right-handed HC were recruited via local advertisements. They were carefully screened through a diagnostic interview, the Structured Clinical Interview for DSM-V Nonpatient Edition (SCID-NP), to rule out the presence of current or past history of any psychiatric illness. Further exclusion criteria for HCs were any history of psychiatric illness in first-degree relatives, current or past significant medical or neurological illness.

2.2 MR Imaging Data Acquisition and Preprocessing

All MRI data were obtained on a GE Discovery MR750 3.0T System with an eight-channel phased-array head coil. The participants were scanned in a supine, head-first position with symmetrically placed cushions on both sides of the head to decrease motion. During the scanning, the participants were instructed to relax with their eyes closed without falling asleep. After the experiment, each participant confirmed not having fallen asleep.

The rs-fMRI data were acquired using a gradient-echo echo-planar imaging sequence with the following parameters: time repetition (TR)/time echo (TE) = 2000/25 ms; flip angle = 90°; voxel size = 3.75 × 3.75 × 3 mm^3; field of view (FOV) = 240 × 240 mm^2; matrix = 64 × 64; slice thickness/gap = 3.0/1.0 mm; 35 axial slices covering the whole brain; and 210 volumes acquired in 7 min. In addition, a three-dimensional brain volume imaging (3D-BRAVO) sequence covering the whole brain was used for structural data acquisition with the following parameters: TR/TE = 8.2/3.2 ms; flip angle = 12°; bandwidth = 31.25 Hz; slice thickness/gap = 1.0/0 mm; matrix = 256 × 256; FOV = 240 × 240 mm; NEX = 1; and acquisition time = 3 min 45 s. Routine MRI examination images were also collected for excluding any anatomic abnormality. All participants were found by two experienced neuroradiologists (YM and YS, with 8 and 3 years of experience in neuroimaging, respectively) to confirm the absence of any brain structural abnormalities.

2.3 Functional Image Preprocessing

The preprocessing was carried out using Data Processing Assistant for Resting-State fMRI (DPABI_V3.0, http://restfmri.net/forum/DPABI) [47] which is based on Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/). For each subject, the first 10 images of the rs-fMRI dataset were discarded to ensure steady-state longitudinal magnetization. The remaining 200 images were first slice-

time corrected and then were realigned to the first image for correcting for inter-TR head motion. This realignment correction provided a record of the head motion within the rs-fMRI scan. All subjects should have no more than 2 mm maximum displacement in any plane, 2° of angular motion as well as 0.2 mm in mean frame-wise displacement (FD) [48]. The individual T1 structural images were segmented (white matter, gray matter, and cerebrospinal fluid) using a segmentation toolbox. Then, the DARTEL toolbox was used to create a study specific template for the accurate normalization. Then, resting-state functional images were coregistered to the structural images and transformed into standard Montreal Neurological Institute (MNI) space, resliced to a voxel size of 3×3×3 mm^3 resolution and smoothed using a 6 mm full width at half maximum (FWHM) Gaussian kernel. The data were removed linear trend and passed through band-pass filtered of 0.01-0.1 Hz.

2.4 Component selection

Following preprocessing, images were processed in the Group ICA FMRI Toolbox (GIFT) (http://icab.sourceforge.net). Data were first prewhitened and dimensions reduced via a 2-step principal component analysis [49]. Estimation showed an estimate of 82 components. Then, images of all subjects were decomposed into a set of 82 spatially independent components by the Infomax algorithm. Each independent component (IC) depicted a distinct network of brain regions that have the same pattern of homodynamic change over time, and robustness of the component was achieved by running ICASSO [50] (http://www.cis.hut.fi/projects/ica/icasso) for 100 iterations. We then chose the components using *component labeler* in GIFT. The *component labeler* option is provided to label components given the templates of interest. Each component is correlated with the given templates and best template is selected based on the maximum correlation value. The 7-network templates used for sorting were created by yeo (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011), and the networks including Visual Network, Somatomotor Network, Dorsal Attention Network, Ventral Attention Network, Limbic Network, Frontoparietal Network, and Default Network. After this procedure, nine and eight of components were respectively identified as components of the Somatomotor Network and Limbic Network.

Individual maps of each group were subjected to a random effect one sample *t*-test in SPM12. Deemed significant at uncorrected $p<0.01$ with a minimum extent threshold of 10 contiguous voxels and created a group-specific component map. These two maps of BD patients and HCs were combined as a mask for group analyses.

2.5 Pro-inflammatory Cytokines Measures

Blood samples from BD patients and HCs were obtained in the morning under fasting condition, abstained from alcoholic beverages for at least one day prior to testing and processed (then frozen) by technicians. Fasting serum samples were collected in serum tubes, clotted for 30 min, and stored at -80℃ until use. Levels of pro-inflammatory cytokines, including IL-6 and IL-8 levels were determined from

serum by the Bio-Plex Pro Human Cytokine Assay kit (Bio-Rad). According to manufacturer's directions using a Bio-Plex 200 array reader (Bio-Rad). Bio-Plex Manager Software, version 6.1, was used for data acquisition (Bio-Rad).

2.6 Group comparison and Correlation analyses

Independent-sample *t*-test (normal variable) and Mann-Whitney U test (skewed variables) were used to compare demographic data (except gender) and levels of serum pro-inflammatory cytokines between the two groups with SPSS 19.0 software (SPSS, Chicago, IL, USA). A chi-squared test was performed to compare gender distribution. All tests were two-tailed, and $P < 0.05$ was considered statistically significant. The two-sample *t*-test was performed to assess the significant differences of the interest component between BD II patients and HCs within the union mask of one-sample *t*-test results of both groups. Age, gender, years of education and the mean FD were included as nuisance covariates in the comparisons. Statistical maps were thresholded using permutation tests (PTs) as implemented in PALM and integrated into DPABI. The threshold-free cluster enhancement (TFCE) and voxel wise correction (VOX) with PT were tested at two-tailed $P < 0.05$ for multiple comparisons. The number of permutations was set at 1000. Previous study observed that permutation test with TFCE, a strict multiple comparison adjustment strategy, reached the best balance between family-wise error rate (under 5%) and test-retest reliability and replicability [51].

When statistically significant group differences were observed in brain regions and pro-inflammatory cytokines levels, partial correlation analysis was used to compute the correlation between FC values and inflammatory cytokines levels in BD II depression whilst controlling for the effect of gender, age and years of education. Also, the partial correlation coefficients were calculated between the clinical variables and abnormal FC values, abnormal inflammatory cytokines levels in BD II group. These clinical variables included onset age of illness, number of episodes, duration of illness, 24-item HDRS scores and YMRS scores.

3. Results

3.1 Demographic and Clinical Characteristics

Table 1 presents the demographic and clinical data of all participants. No significant differences were found between the BD II group and the HCs group in sex, age, or FD parameters ($P > 0.05$). The HCs group received a significantly higher level of education than the BD II group ($P < 0.001$).

Table 1
Demographic and clinical data for patients with Bipolar II disorder and healthy controls

	Bipolar II disorder	Control	*p* value
	Mean (SD) or Median (LQ, UQ)		
Demographic			
Number of subjects	42	69	
Age (years)	26.95 (8.21)	31.48 (11.62)	0.075*
Gender (male/female)	19/23	33/36	0.791†
Education (years)	12.50 (3.29)	15.35 (3.29)	0.000*
Age at onset (years)	23.60 (8.11)	n/a	
Number of episodes	2.81(1.67)	n/a	
24-item HDRS score	26.55 (8.37)	n/a	
YMRS score	6.14 (7.55)	n/a	
Duration of illness (months)	36.99 (51.58)	n/a	
FD	0.05(0.03)	0.05(0.03)	0.258*
Biomarkers of inflammation			
IL_6	2.89(2.18, 2.83)	2.48(2.05, 2.57)	0.039*
IL_8	19.81(7.85, 24.45)	21.94(6.49,11.00)	0.003*

HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FD, framewise displacement for in-scanner head motion.

*The p values were obtained by Mann-Whitney U tests.

†The p value for sex distribution was obtained by chi-square test.

3.2 Independent components and Group differences

Of the interest components, two independent components (IC 1 and IC 5) were interpreted as meaningful neural network components (Figure 1). IC 1 consisted of the bilateral precentral and postcentral gyrus, which are related to the SMN. IC 5 consisted of the bilateral medial frontal gyrus and the bilateral posterior cingulate, which are related to the limbic network. The significant IC1 implicating the SMN showed decreased FC in the right precentral gyrus, and IC 5 implicating the limbic network showed

decreased FC in the left OFC in BD II group compared to the HCs ($P < 0.05$, TFCE corrected) (Table 2 and Figure 2).

Table 2
The areas of significantly different FC between the BD II patients and the HCs. (p < 0.05, TFCE corrected)

location in the cerebrum	Brodman Area	Montreal Neurological Institute Coordinates			Peak t Value	Cluster Size (voxel numbers)
		X	Y	Z		
L Frontal_Med_Orb	11	-6	60	-9	-3.7512	26
R precentral gyrus	6	45	-3	24	-4.4288	13

FC= functional connectivity; BD= bipolar disorder; HCs= healthy controls; TFCE= threshold-free cluster enhancement; L (R)= left (right) hemisphere.

3.3 Group differences of peripheral cytokine levels

The levels of IL-6 and IL-8 of the two groups were shown in Table 1. Compared with the HCs group, the BD II group showed increased IL-6 ($P = 0.039$) and IL-8 ($P = 0.002$) levels.

3.4 Correlation analyses

The IL-8 levels were significantly inversely correlated with FC in the right precentral gyrus in the patients with BD II ($r = -0.458$, $P = 0.004$) (Figure 3). No significant correlation result was found between FC in the left OFC and pro-inflammatory cytokines. In addition, there was no significant correlation between cytokines levels and clinical variables, or between FC and clinical variables (24-item HDRS score, YMRS score, number of episodes, onset age of illness, duration of illness) in the patients with BD II ($P > 0.05$).

4. Discussion

The main findings are the following: (i). decreased FC in the left OFC implicating the limbic network, and in the right precentral gyrus implicating the SMN in unmedicated BD II depression. (ii). increased IL-6 and IL-8 levels in BD II depression. (iii). negative correlation between the right precentral gyrus FC and IL-8 levels in BD II depression. This study is among the first to investigate the FC in unmedicated BD patients using ICA methods combined with inflammation markers, which may improve our understanding of the neuropathological mechanisms underlying BD from the perspective of neuro-inflammation.

4.1 Decreased FC in the left OFC

In this study, the BD II patients showed hypoconnectivity in the left OFC compared with the HCs, suggesting disrupted FC in the limbic network in BD. The OFC is a part of the limbic network which is known to be involved in emotion processing [52] and regulation [53], reward value encoding [54], and decision making including the vulnerability to suicidal behavior [55]. A previous rs-fMRI study found decreased FC between the left OFC and left anterior cingulate cortex in BD using seed-based correlation approach [12], which may be associated with dysfunction in emotion processing and decision making in BD. In addition, several studies found reduced regional homogeneity (ReHo) [56, 57], amplitude of low-frequency fluctuations (ALFFs) [58], and regional blood flow (rCBF) [59] in the OFC in BD. Task-based fMRI research also demonstrated hypoactivation in the OFC during emotion processing and reward-related tasks in BD [60, 61]. Structural MRI studies also showed reduced gray matter volume (GMV) [62, 63] and gray matter density [64] in the left OFC in BD. Moreover, BD patients with a prior suicide attempt had lower fractional anisotropy (FA) within the left OFC white matter [65, 66]. These findings may reflect a potential structural basis for functional abnormalities in the left OFC in BD. Several studies reported that the OFC was associated with affective liability [67], emotional dysregulation [68], and reward processing [69]. Taken together, our findings suggested that abnormal FC in the left OFC could contribute to the neuropathology of BD and result in characteristic behavioral abnormalities associated with BD such as emotional lability, emotional dysregulation and heightened reward sensitivity.

4.2 Decreased FC in the right precentral gyrus

We observed significantly decreased FC in the right precentral gyrus in BD II patients, suggesting disrupted FC in SMN in BD. The precentral gyrus, consists of the primary motor cortex, is a sub-region of SMN implicated in volitional control of motor output [70]. Growing number of studies have shown the precentral gyrus playing an important role in emotional-affective processing [71, 72] and motor performance/activity [73, 74] in mood disorders. Two rs-fMRI studies have found decreased FC in the precentral gyrus in BD [75, 76], which supported our findings. Previous neuroimaging studies found decreased neural activities [56, 77, 78], structural abnormalities in the precentral gyrus in BD [63, 79, 80], and the genetic risk to develop BD was associated with reduced gray matter volumes [81] and decreased grey matter density [82, 83] in the right precentral gyrus, further suggesting the involvement of the precentral gyrus in the pathogenesis of BD. A task-based fMRI study examined the emotionality of autobiographical memory in BD found decreased activation in the precentral areas compared with the control group [84]. In another task-based fMRI study, decreased activation in the precentral gyrus was found in BD during self-paced finger tapping, which may result in impairments in preparation, control, and execution of movement in BD [85]. Additionally, motor retardation is a characteristic feature of BD [86]. Therefore, in combination with our findings, disrupted FC in SMN may contribute to the typical symptoms of emotion dysregulation and motor retardation in BD II patients.

4.3 Correlation between FC in the right precentral gyrus and IL-8 levels

In this study, we found increased pro-inflammatory cytokine levels of IL-6 and IL-8 in BD group when compared to HC, which was consistent with previous studies [26, 28, 30, 87, 88]. Furthermore, we found elevated levels of IL-8 correlated with the reduction of FC in the right precentral gyrus within SMN in BD. IL-8 is a pro-inflammatory cytokine that facilitates blood-brain barrier migration of leukocytes and may sustain brain neuroinflammation resulting in neurotoxic effects [89]. Additionally, IL-8 is associated with blood-brain barrier dysfunction and nerve growth factor production [90]. Recent structural MRI studies showed that IL-8 was associated with reduced gray matter volumes (GMV) in the left OFC in schizophrenia [91] and bilateral hippocampus in old rhesus macaques [89], which implicated inflammation might contribute to structural abnormalities. Another structural MRI study showed that GMV in the precentral gyrus negatively correlated with pro-inflammatory cytokine levels in BD patients [92], further supporting the idea that inflammation might contribute to structural abnormalities in the right precentral gyrus. A diffusion tensor imaging study found that higher levels of IL-8 were associated with lower fractional anisotropy values across the brain including the corticospinal tract [93], which suggested inflammation might contribute to white matter abnormalities and possibly impair the neural function of the precentral gyrus, for the reason that outputs of voluntary movements are controlled by the precentral gyrus through the corticospinal tract [94]. However, the relationship between IL-8 and neural function is little known. In the present study, increased IL-8 levels was associated with reduced FC in the right precentral gyrus in unmedicated BD II patients, suggested that inflammation may be related to disrupted neural function in BD. Moreover, it was noted that IL-8 were associated with psychomotor speed [95] and motor activity [96], severity of depressive symptoms [97, 98], and cognitive dysfunction [22]. Taken together, increased levels of IL-8 possibly impair the FC in the precentral gyrus, and further resulted in affective, cognitive and psychomotor function in BD.

5. Limitations

The findings of this study should be interpreted in light of several limitations. First, the sample size was relatively small. Second, owing to the cross-sectional study, we could not further study the causality between aberrant FC and inflammation. Hence, longitudinal research is warranted to confirm the role cytokines play in brain function. Third, for ethical reasons, we did not measure pro-inflammatory cytokines level in cerebrospinal fluid. In addition, although we controlled for some confounders, peripheral inflammatory cytokines may also be affected by other factors, such as stress and physical activity. However, peripheral cytokines level remains the main stay of assessment because of the ethical considerations involved in obtaining the cerebrospinal fluid or brain tissue. Peripheral cytokine levels may not exactly reflect the brain cytokine levels but can affect the production of cytokines in the brain.

6. Conclusion

In conclusion, our study provided preliminary evidence of the association between brain FC and pro-inflammatory cytokines in unmedicated BD II depression. The current study demonstrated disrupted FC of the left OFC within the limbic network and the right precentral gyrus within the SMN in BD. Moreover, our

results suggest disrupted FC of the precentral gyrus may be associated with pro-inflammatory cytokines in BD, specifically the IL-8 levels. Given that pro-inflammatory cytokines may sustain neuroinflammation resulting in neurotoxic effects, the results provided preliminary evidence that higher levels of serum cytokines may be associated with a more severe deficit in FC abnormalities implicated in BD. Further studies with a larger sample or longitudinal design may confirm the role of pro-inflammatory cytokines in aberrant FC in BD.

Abbreviations

BD
bipolar disorder; ICA = independent component analysis; OFC = orbitofrontal cortex; SMN = somatomotor network; rs-fMRI = resting-state functional magnetic resonance imaging; FC = functional connectivity; IL = interleukin; DSM-V = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SCID-P = Structured Clinical Interview for DSM-V Patient Edition; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; HC = healthy control; SCID-NP = Structured Clinical Interview for DSM-V Nonpatient Edition; TR = time repetition; TE = time echo; FOV = field of view; 3DBRAVO = three dimensional brain volume imaging; FD = frame-wise displacement; MNI = Montreal Neurological Institute; FWHM = full width at half maximum

Declaration

Ethics approval and consent to participate

This study was approved by the Ethics Committee of First Affiliated Hospital of Jinan University, Guangzhou, China. All subjects were right-handed and signed a written informed consent form after a full written and verbal explanation of the study. Two senior clinical psychiatrists confirmed that all subjects had the ability to consent to participate in the examination.

Consent for publication

Not applicable

Availability of data and material

The data supporting our findings will not be shared. Some of the co-authors do not wish to share their data for privacy.

Competing interests

The authors have declared that no competing interest exists.

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Authors' contributions

Ying Wang design the study; Guanmao Chen, Ying Wang contribute to data sources and study selection; Guanmao Chen, Guixian Tang, Pan Chen, Jiaying Gong, Yanbin Jia, Shuming Zhong, Feng Chen, Jurong Wang, Zhenye Luo, Zhangzhang Qi contribute to data acquisition; Guanmao Chen, Pan Chen contribute to data analysis; Guixian Tang, Pan Chen, write the manuscript; Guanmao Chen, Guixian Tang, Pan Chen, Jiaying Gong, Li Huang, Ying Wang revise the manuscript. All authors contribute to and have approved the final manuscript.

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Figures

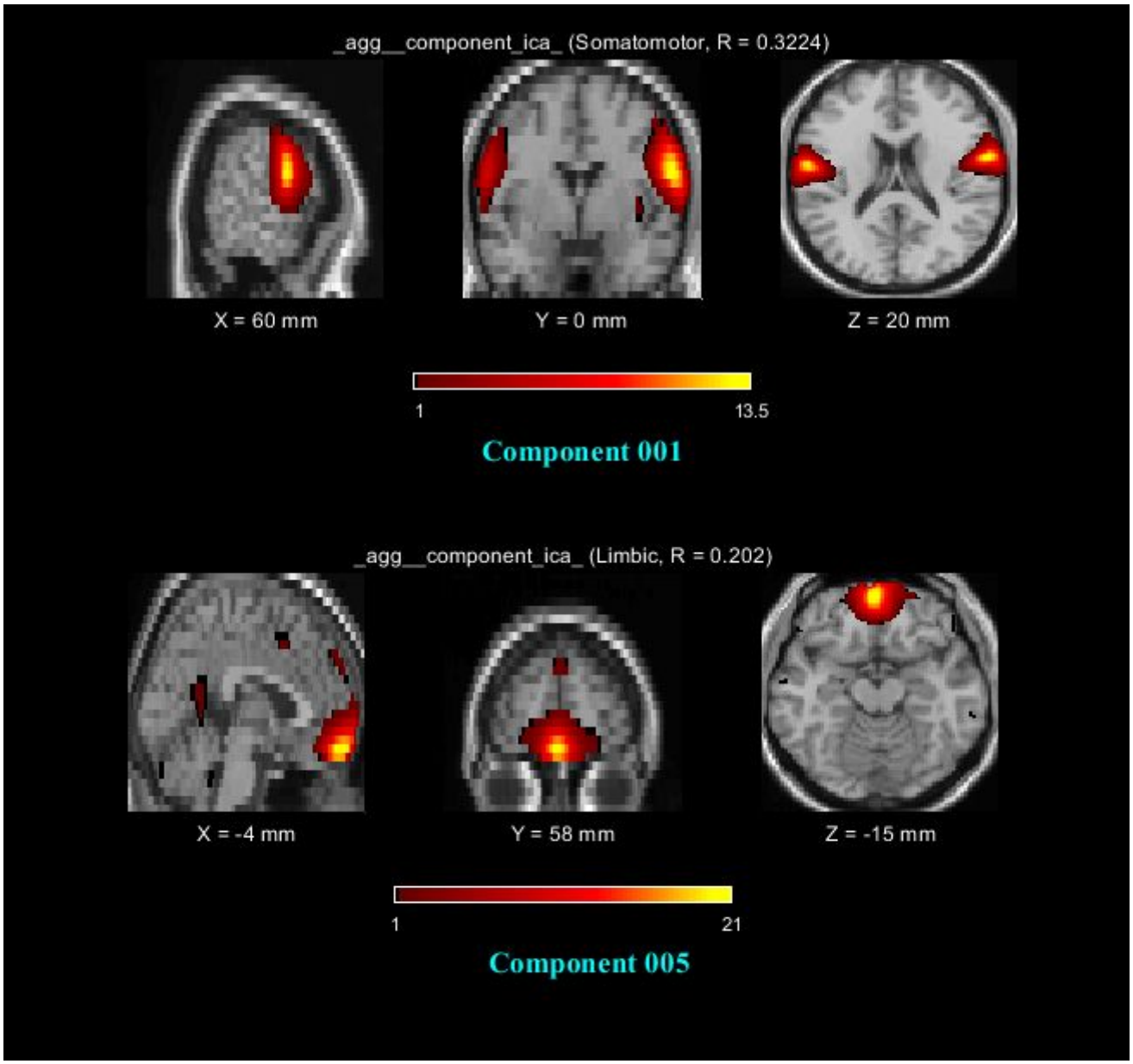

Figure 1

Of the interest components, two independent components (IC 1 and IC 5) were interpreted as meaningful neural network components between BD II and HCs. IC= independent component; BD=bipolar disorder; HCs=healthy controls.

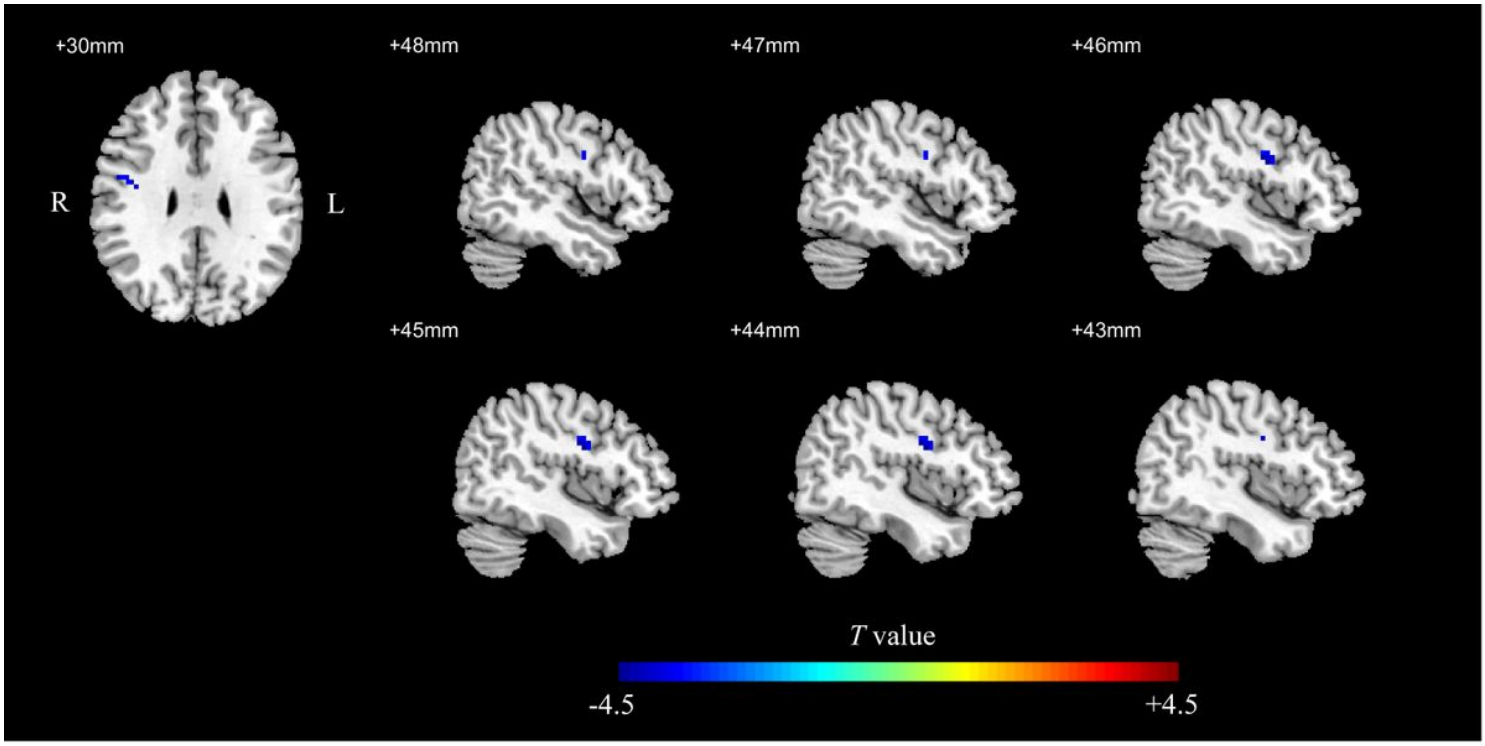

Figure 2

The FC patterns of the left orbitofrontal cortex (OFC) and the right precentral gyrus in BD patients and HCs (P < 0.05, TFCE corrected). The color bar indicates the t values. FC, functional connectivity; BD, bipolar disorder; HCs, healthy controls.

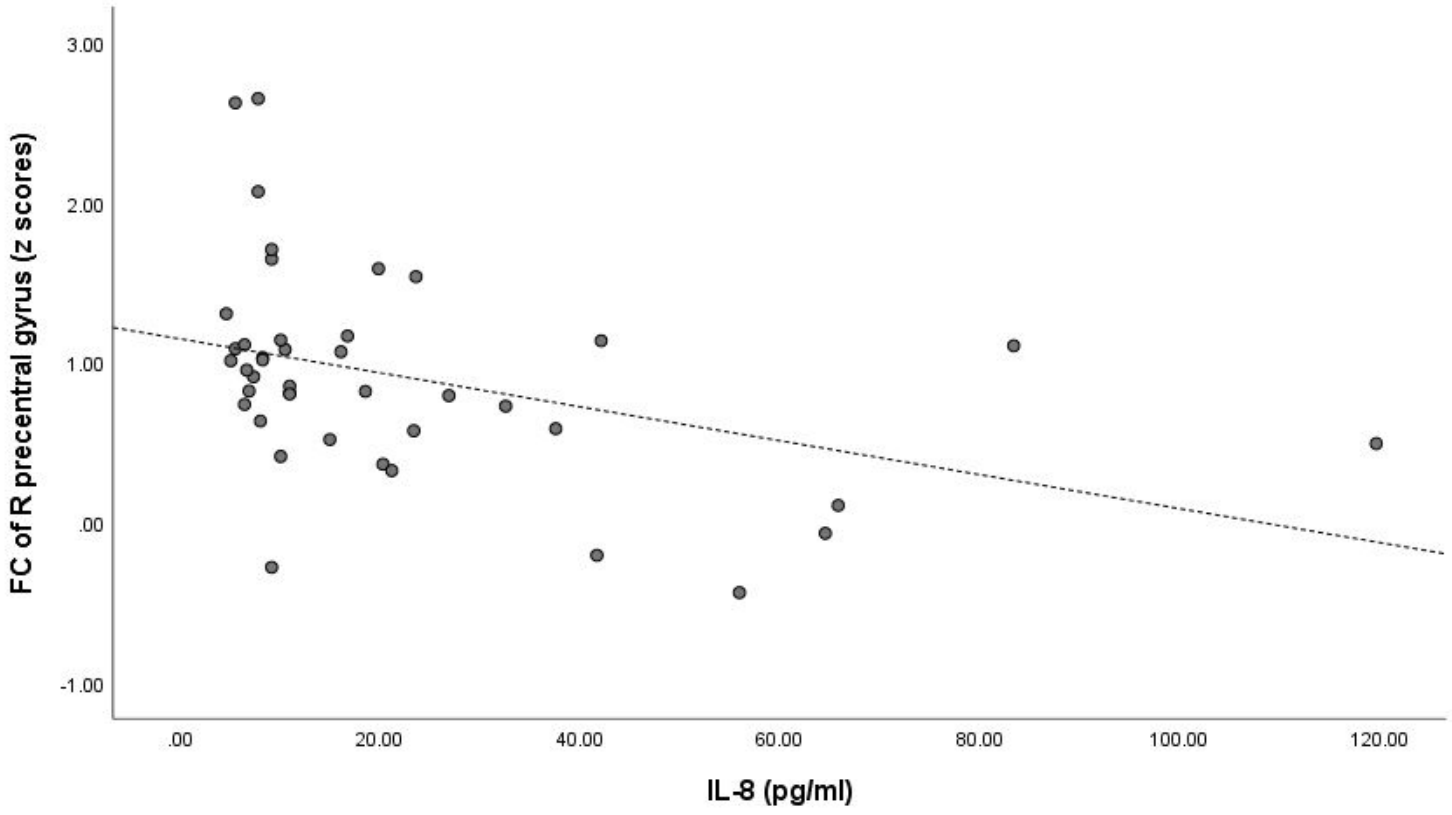

Figure 3

The correlation between abnormal FC values in the right precentral gyrus and IL-8 ($P < 0.05$) levels. FC, functional connectivity; L (R), left (right) hemisphere.