Differences of resting fMRI and cognitive function between drug-naïve bipolar disorder and schizophrenia

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Abstract

Background: Bipolar disorder (BD) and schizophrenia (SC) have many similarities in clinical manifestations. The acute phase of BD has psychotic symptoms, while SC also has emotional symptoms during the onset, which suggests that there is some uncertainty in distinguishing BD and SC through clinical symptoms.

Aim: To explore the characteristics of brain functional activities and cognitive impairment between BD and SC.

Methods: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test was performed on patients in drug-naïve BD and SC (50 subjects in each group), and resting-state functional magnetic resonance imaging (rs-fMRI) scanning was performed meanwhile. Rs-fMRI data were routinely preprocessed, and the value of the fractional amplitude of low-frequency fluctuation (fALFF) was calculated. Then each part of the scores of the RBANS and the characteristics of brain function activities were compared between the two groups. Finally used Pearson correlation to analyze the correlation between cognition and brain function.

Results: (1) Compared with BD group, all parts of RBANS scores in SC group decreased; (2) The left inferior occipital gyrus (IOG, peak coordinates −30, -87, -15; t = 4.78, voxel size = 31, Alphasim correction) and the right superior temporal gyrus (STG, peak coordinates 51, -12, 0; t = 5.08, voxel size = 17, Alphasim correction) were the brain areas with significant difference in fALFF values between BD and SC. Compared with SC group, the fALFF values of the left IOG and the right STG in BD group were increased (p < 0.05); (3) Pearson correlation analysis showed that the visuospatial construction score was positively correlated with the fALFF values of the left IOG (r<sub>left IOG</sub> = 0.304, p = 0.003; r<sub>right STG</sub> = 0.340, p = 0.001); The delayed memory (figure recall) score was positively correlated with the fALFF value of the left IOG (r<sub>left IOG</sub> = 0.207, p = 0.044).

Discussion: The cognitive impairment of SC was more serious than BD. The abnormal activities of the left IOG and the right STG may be the core brain region to distinguish BD and SC, and are closely related to cognitive impairment, which provide neuroimaging basis for clinical differential diagnosis and explore the pathological mechanism of cognitive impairment.

Keywords: Bipolar disorder, Schizophrenia, FALFF, Rs-fMRI, Cognition
Introduction
Bipolar disorder (BD) includes type I, defined as manic episode, and type II, defined as one or more hypomanic episodes and severe depressive episode. It is a group of complex and serious chronic mental disorders [1] with cognitive impairment [2, 3]. Schizophrenia (SC) is a mental disease characterized by uncoordinated thinking, cognition, emotion and behavior [4]. It is generally agreed that cognitive impairment is a typical feature of SC [5, 6]. At the same time, the cognitive impairment characteristics of BD are different from those of SC [7–9]. Although the clinical manifestations of the two diseases are different, they also have similarities. Some BD patients have psychotic symptoms in the acute phase [10, 11]. As a subtype of BD, its prognosis is generally worse than that of non-psychotic BD, and its recurrence rate is higher [12]. Meanwhile, SC has emotional symptoms during the onset [13], which suggests that sometimes it is difficult to distinguish BD and SC from clinical symptoms. At present, the research on the etiology and pathogenesis of BD and SC is still a hot spot in the field of psychiatry. Finding neurobiological markers for the diagnosis and differentiation of the two diseases has always been the direction of efforts [14–16]. In recent years, advances in rs-fMRI have rapidly developed. Voxel-based analyses, especially for fALFF, can well reflect the spontaneous activities of neurons by the changes of blood flow signals accurately in a quiet state noninvasively [17]. Previous neuroimaging studies have shown that patients with BD had structural and functional abnormalities in the prefrontal, temporal, insular and marginal lobe [18–20]. The functional activities of the prefrontal cortex and subcortical related brain networks (cingulate gyrus, insula, striatum, etc.) of SC were abnormal [21, 22]. Correlation analysis also found that both BD and SC had abnormal activities in some specific brain regions and were closely related to cognitive impairment, but the research conclusions were inconsistent [23–26]. Therefore we combined cognitive function evaluation and functional imaging methods, analyzed the characteristics of cognitive impairment and neuroimaging differences between drug-naïve BD and SC patients, in order to provide the theoretical basis for the clinical diagnosis and differentiation of BD and SC.

Method
Participants
They were BD/SC patients inpatient or outpatient treated in the department of psychiatry, the Third People’s Hospital of Foshan, Guangdong, People’s Republic of China from July 2016 to September 2021. The acquisition of clinically relevant information was realized through interviews with clinicians. Inclusion criteria: (1) the diagnosis of BD/SC based on the Structured Clinical Interview for DSM-IV-TR (SCID) criteria; (2) 18 ≤ age (years) ≤ 45; (3) education ≥ 9 years; (4) Han nationality, right-handed; (5) drug-naïve, course of disease ≥ 6 months. Exclusion criteria: other mental diseases, brain organic and physical diseases, family history of mental diseases, substance (drugs, alcohol) abuse, brain trauma, neurological diseases, etc.

All subjects volunteered to participate in this study and excluded the contraindications of magnetic resonance imaging (MRI). This study was approved by the ethics committee of the Third People’s Hospital of Foshan, China and the experiments were conducted following the declaration of Helsinki. We obtained written informed consent from all patients before scanning.

Assessments
Scale evaluation and cognitive test: (1) Positive and Negative Syndrome Scale (PANSS) was used to evaluate the mental symptoms of the SC group. Hamilton Depression Scale-24items (HAM-D), Hamilton Anxiety Scale (HAMA) and Bech-Rafaelsen Mania Rating Scale (BRMS) were used to evaluate the BD group. (2) before the assessment of cognitive function, we explained that this cognitive test had no adverse impact on them to eliminate their psychological burdens. The evaluation rules were explained and demonstrated to the subjects with unified guidance, and then the cognition was evaluated with Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [27].

Rs-fMRI: all subjects were scanned in the radiology department of the Third People’s Hospital of Foshan. The MRI equipment is signa pioneer 3.0T MR of GE company in the United States. Subjects were told to close their eyes, keep a quiet supine position and keep consciousness clear. Firstly, T1 positioning image scanning was carried out, and the scanning parameters were as follows: time repetition (TR)=2000 ms, echo time (TE)=30 ms, flip angle (FA)=90°, field of view (FOV)=240 mm * 240 mm, matrix=64 * 64, layer thickness=4 mm, number of layers=36, layer spacing=1 mm, 250 time point data were collected continuously. High resolution T1 scanning parameters: TR=8.6 ms, TE=3.3 ms, FA=12°, FOV=256 mm * 256 mm, matrix=256 * 256, layer thickness=1 mm, layer spacing=0 mm, slice number=172. Data preprocessing: the DPARSF system (based on SPM 8 and REST 1.8 software; http://www.restfmri.net) was used to preprocess all image data. The first 10 sequences of images were deleted to exclude the influence of machine start-up on signal collection, and the remaining 240 sequences were used for data analysis. The preprocessing process included head movement correction and spatial standardization. According to the head movement correction curve, the data of 5 subjects with head movement translation > 2 mm and rotation > 2° were
Table 1: Clinical data and RBANS test between BD and SC

|                         | BD          | SC          | X² / t / p  |
|-------------------------|-------------|-------------|-------------|
| Participants            | 50          | 50          | -           |
| Age (years)             | 30.80 ± 9.56| 33.28 ± 6.44| 1.52 / 0.131|
| Gender (m/f)            | 23 / 27     | 17 / 33     | 1.50 / 0.307|
| Education               | 12.28 ± 2.86| 11.42 ± 2.921| 1.49 / 0.139|
| Course of disease (w)   | 37.18 ± 15.93| 39.80 ± 15.56 | 0.591 / 0.557|
| Psychotic symptoms      | 21          | 50          | -           |
| Manic/depressive episode| 13 / 37     | -           | -           |
| HAMD                    | 16.66 ± 8.11| -           | -           |
| HAMA                    | 11.86 ± 6.77| -           | -           |
| BRMS                    | 15.12 ± 8.03| -           | -           |
| PANSS                   | -           | 65.36 ± 19.44| -           |
| RBANS                   | 23 / 27     | 33.28 ± 6.44| 4.01 / <0.001|
| Immediate memory (Learning) | 21.66 ± 5.52 | 16.50 ± 6.84 | 4.01 / <0.001|
| Immediate memory (Story Memory) | 9.04 ± 4.35 | 5.02 ± 3.80 | 4.74 / <0.001|
| Visuospatial Construction | 16.12 ± 4.66 | 15.78 ± 3.96 | 2.72 / 0.008|
| Language                | 16.11 ± 4.05| 11.50 ± 4.41| 5.25 / <0.001|
| Attention (Digit span)  | 12.83 ± 2.51| 10.50 ± 2.51| 4.47 / <0.001|
| Attention (Coding)      | 40.32 ± 13.33| 27.04 ± 13.32| 4.81 / <0.001|
| Delayed memory (List Recall) | 4.62 ± 2.35 | 2.59 ± 2.54 | 4.01 / <0.001|
| Delayed memory (List Recognition) | 18.51 ± 1.88 | 17.07 ± 3.06 | 2.75 / 0.007|
| Delayed memory (Story Recall) | 4.23 ± 2.90 | 2.35 ± 2.36 | 3.44 / 0.001|
| Delayed memory (Figure Recall) | 10.84 ± 4.10 | 8.78 ± 5.62 | 2.05 / 0.044|

Note: BD: bipolar disorder; SC: schizophrenia; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; BRMS: Bech-Rafaelsen Mania Rating Scale; PANSS: Positive and Negative Syndrome Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; Values are expressed as mean ± standard deviation.

Data analysis: SPSS 21 (https://www.ibm.com/analytics/spss-statistics-software) was used to analyze the score of clinical scale. SPM 8 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm8) was used to conduct two sample t-test on two groups of standardized fALFF images. The mean value of head movement parameters, gender, age and years of education of each subject were taken as covariates, and the threshold level was set as p<0.001 (Alphasim correction). Finally, Pearson correlation analysis was carried out to test the cognitive function score and the fALFF value of different brain regions.

Result
Clinical data and cognitive function test
There was no significant difference between BD and SC in age, gender, years of education and course of disease (p>0.05). While there were significant differences in immediate memory (learning and story memory), visuospatial construction, language, attention (digit span), and delayed memory (list Recall, list Recognition, story recall and figure recall), which belong to the RBANS test (p<0.05). Compared with BD, the cognition of SC generally decreased (p<0.05). (Table 1)

fALFF
Compared with SC, the brain areas with significant differences in BD were the left inferior occipital gyrus (IOG, peak coordinates of −30, −87, −15; t=4.78, voxel size=31, p<0.05, Alphasim correction) and the right superior temporal gyrus (STG, peak coordinates of 51, −12, 0; t=5.08, voxel size=17, p<0.05, Alphasim correction). (Fig. 1)

Pearson correlation analysis
The fALFF values of the left IOG and the right STG were positively correlated with visuospatial construction score (r<sub>left IOG</sub> = 0.304, p=0.003; r<sub>right STG</sub> = 0.340, p=0.001). The fALFF values of the left IOG were positively correlated with delayed memory (Figure Recall) score (r<sub>left IOG</sub> = 0.207, p=0.044). (Fig. 2)

Discussion
At present, it is generally believed that BD and SC have cognitive impairment in the course of disease to some extent [28–30]. The difference in cognition is of great significance in the differential diagnosis between them. Previous studies had found that SC performed worse than BD in executive function, working memory, IQ, association, attention concentration and perceptual motor function [31–33]. Our study showed that the cognitive test score of SC was lower than BD, which was partially similar to previous studies, suggested that the cognitive impairment of SC was more serious than BD. And although BD and SC sometimes have the same cognitive impairment, their recovery after treatment is still different [34]. A longitudinal study suggested that after standardized clinical treatment, BD patients could get cognitive recovery, left slight cognitive damage, and could be repaired to a certain extent through follow-up cognitive exercise [35]. However, the cognitive impairment of SC was usually considered irreversible because...
it was considered to be related to nerve injury [36–39]. Therefore, cognitive testing is helpful to distinguish the diagnosis of these two diseases.

Our study also showed that the fALFF values of the left IOG and the right STG in BD were higher than SC. According to Zhang et al’s study [40], there were a large number of nerve fiber connections between temporal and occipital lobes, which would be damaged by neurological and mental diseases. Meanwhile, the results of an Asian population study suggested that SC has significant functional impairment in the temporal and occipital lobes[41]. The dysfunction of these brain regions was

Fig. 1  FALFF abnormalities in the BD compared with SC. (A) The left inferior occipital gyrus (IOG), \( t = 4.78 \), cluster size = 31; (B) The right superior temporal gyrus (STG), \( t = 5.08 \), cluster size = 17; \( p < 0.05 \), AlphaSim correction

Fig. 2  A/B The fALFF values of the left IOG and the right STG were positively correlated with visuospatial construction score (\( r_A = 0.30, p_A = 0.003; r_B = 0.34, p_B = 0.001 \)). C The fALFF values of the left IOG were positively correlated with delayed memory (Figure Recall) score (\( r_C = 0.20, p_C = 0.044 \))
related to the dysfunction of language, attention and higher-level visual and auditory comprehensive processing [42]. What’s more, emotional perception was an effective tool to distinguish SC from BD, and the fronto-temporal occipital circuit was considered to be related to impaired emotional perception [25]. Ehrminger et al’s research indicated that the impairment of cognitive function was partly reversible in the course of BD [35]. Therefore, it can be understood that the signal activity of the BD brain area is more active than that of SC’s, which also supports ours results.

We made a correlation analysis between the cognitive scores in RBANS and the fALFF values of the left IOG and the right STG. The results showed that there was a significant positive correlation between the visual construction score and the abnormal activities of that two brain regions. Previous studies had suggested that SC has significant impairment of visual breadth cognitive function [43–45], which would affect the prognosis of patients [46], and which might also be one of the factors for the poor prognosis of SC compared with BD. Therefore, the evaluation of visual construction cognition plays an important role in the diagnosis and prognosis of SC. Besides, We also found that the delayed memory (figure recall) score was closely related to the brain function signals of the left SOG. As we know, the occipital lobe has extensive connections with other regions of the two cerebral hemispheres and plays an important role in the integration of visual information with information gathered by other sensory systems. At the same time, it also connects visual information with brain processing systems of other executive functions. The study indicated that the microstructure of frontal occipital white matter bundle was closely related to object working memory. When its microstructure was damaged (such as multiple sclerosis and other diseases), object working memory would be affected [47], which confirmed our results from the side.

In conclusion, this study suggests that cognitive function test can be used as one of the important differential indexes between BD and SC in clinic. The abnormal activities of the left IOG and the right STG may be the core brain region to distinguish BD and SC, and are closely related to cognitive impairment, which provide neuroimaging basis for clinical differential diagnosis and explore the pathological mechanism of cognitive impairment.

At the same time, there are some limitations in this study: BD and SC have many similarities in the early stage of onset. In order to reduce the possibility of diagnostic errors, we had to limit the course of the patient to more than 6 months and exclude the patients who are seriously ill and can not cooperate to complete the test, which might skew the results of the data.

In addition, this study only analyzed the characteristics of low-frequency amplitude activity of brain function, which can be further discussed in combination with other brain function indexes, such as regional homogeneity, degree centrality, functional connection and so on.

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Authors’ contributions
Liang Jiaquan and Wensheng Chen made great contributions to the conception, design and writing of the works; Other authors have provided assistance in the acquisition, analysis or interpretation of data. All authors approve the publication of the manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality but are available from the corresponding author upon reasonable request.

Declarations
Ethics approval and consent to participate
We obtained written informed consent from all patients. This study was approved by the ethics committee of the Third People’s Hospital of Foshan, China and the experiments were conducted following the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors have no potential or actual conflicts of interest.

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References
1. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, Malhi GS, Nierenberg AA, Rosenblat JD, Majeed A, et al. Bipolar disorders. Lancet. 2020;396(10265):1841–56.
2. Roux P, Etain B, Cannavo AS, Aubin V, Anzisrare B, Azorin JM, Bellivier F, Belzeaux R, Bougerol T, Cussac I, et al. Prevalence and determinants of cognitive impairment in the euthymic phase of bipolar disorders: results from the FACE-BD cohort. Psychiatr Med. 2019;49(3):519–27.
3. Mann-Wrobel MC, Camero JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord. 2011;13(4):334–42.
4. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia Lancet. 2022;399(10323):473–86.
5. Karantonis JA, Carruthers SP, Burdick KE, Pantelis C, Green M, Rossell SL, Hughes ME, Cropley V, Van Rheenen TE. Brain Morphological Characteristics of Cognitive Subgroups of Schizophrenia-Spectrum Disorders and Bipolar Disorder: A Systematic Review with Narrative Synthesis. Neuropsychology review 2022.
6. Lynham AJ, Jones IR, Walters JTR. Web-Based Cognitive Testing in Psychiatric Research: Validation and Usability Study. J Med Internet Res. 2022;24(2):e28233.
7. Zanelli J, Reichenberg A, Sandin S, Morgan C, Dazzan P, Pilecka I, Marques TR, Morgan K, Young AH, Mollon J. Dynamic and Static Cognitive Deficits in Schizophrenia and Bipolar Disorder After the First Episode. Schizophr Bull. 2022;48(3):590–8.
8. McPhery G, Nabuli L, Kilmartin L, O’Hara D, Donoghue S, Tronchin G, Costello L, Nair P, Ambati S, Nielsen G, et al. Neuroanatomical Disconnectiv-
ity Underlying Cognitive Deficits in Bipolar Disorder. Biol psychiatry Cogn Neurosci. 2020;5(2):152–62.

9. McPhery G, Nabuli L, Kilmartin L, Whittaker JR, Martyn FM, Hallahan B, McDonald C, Murphy K, Cannon DM. Resting-State Network Patterns Under-
lying Cognitive Function in Bipolar Disorder: A Graph Theoretical Analysis. Brain Connect. 2020;10(7):355–67.

10. Allardice J, Leonenko G, Hamshere M, Pardinas AF, Forty L, Knott S, Gordon-
Smith K, Porteous DJ, Haywood C, Di Florio A, et al. Association Between Schizophrenia-Related Polygenic Likelihood and the Occurrence and Level of Mood-Induced Psychotic Symptoms in Bipolar Disorder. JAMA Psychiatry. 2018;75(1):28–35.

11. Nabuli L, McPhery G, Kilmartin L, Whittaker JR, Martyn FM, Hallahan B, McDonald C, Murphy K, Cannon DM. Frontolimbic, Fronto-parietal, and 
Default Mode Involvement in Functional Disconnectivity in Psychotic Bipolar Disorder. Biol psychiatry Cogn Neurosci neuroimaging. 2020;5(2):140–51.

12. Buoli M, Calderoli A, Cumerla Melter C, Serati M, de Nijs J, Altamura AC. Biological aspects and candidate biomarkers for psychotic bipolar disorder: A systematic review. J Neuropsychiatry Clin Neurosci. 2016;70(8):227–44.

13. Herniman SE, Phillips LJ, Wood SJ, Cotton SM, Liemburg EJ, Allott KA. Inter-
pharmacology. 2018;43(3):598–606.

14. Madeira N, Duarte JV, Martins R, Costa GN, Macedo A, Castelo-Branco M. Morn-
morphometry and gyration in bipolar disorder and schizophrenia: A functional magnetic resonance imaging study. NeuroImage Clin. 2020;26:102220.

15. Schubert KD, Focke M, Prehn JH, Cotter DR. Hypothesis review: are clathrin-
mediated endocytosis and clathrin-dependent membrane and protein trafficking core pathophysiological processes in schizophrenia and bipolar disorder? Mol Psychiatry. 2012;17(7):669–81.

16. Chen C, Cheng L, Gremm J, Kibin F, Zhang C, Badner JA, Gershon ES, Liu C. Two gene co-expression modules differentiate psychotics and controls. Mol Psychiatry. 2013;18(1):318–34.

17. Zou QH, Zhu CZ, Yang Y, Zuo XN, Long XY, Cao QJ, Wang YF, Zang YF. An 
analytical approach. J Psychiatr Res. 2021;140:137–60.

18. Nabulsi L, McPhery G, Kilmartin L, Whittaker JR, Martyn FM, Hallahan B, McDonald C, Murphy K, Cannon DM. Frontolimbic, Fronto-parietal, and 
Default Mode Involvement in Functional Disconnectivity in Psychotic Bipolar Disorder. Biol psychiatry Cogn Neurosci neuroimaging. 2020;5(2):140–51.

19. Allardice J, Leonenko G, Hamshere M, Pardinas AF, Forty L, Knott S, Gordon-
Smith K, Porteous DJ, Haywood C, Di Florio A, et al. Association Between Schizophrenia-Related Polygenic Likelihood and the Occurrence and Level of Mood-Induced Psychotic Symptoms in Bipolar Disorder. JAMA Psychiatry. 2018;75(1):28–35.

20. McPhery G, Nabuli L, Kilmartin L, Whittaker JR, Martyn FM, Hallahan B, McDonald C, Murphy K, Cannon DM. Frontolimbic, Fronto-parietal, and 
Default Mode Involvement in Functional Disconnectivity in Psychotic Bipolar Disorder. Biol psychiatry Cogn Neurosci neuroimaging. 2020;5(2):140–51.

21. Magioncalda P, Martino M, Conio B, Lee HC, Ku HL, Chen CJ, Inglese M, Amore 
and neurocognition, symptomatology, functional competences and outcomes in people with schizophrenia - A network analysis perspective. J Psychiatr Res. 2021;144:18–31.

22. Jiménez-López E, Aparicio A, Sánchez-Moría EM, Rodriguez-Jimenez R, Vieta 
E, Santos JL. Neurocognition in patients with psychotic and non-psychotic bipolar disorder. An RDoC Domain Across Bipolar Disorder and Schizophrenia. Neuropsycho 
pharmacology. 2021;2011(4):317–29.

23. Raji TK, Imaiz S, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2009;195(4):286–93.

24. Wei CW, Chen YQ, Ma M, Xiu MH, Zhang XY. Sex differences in the association of body mass index with symptoms and cognitive deficits in Chinese patients with chronic schizophrenia. Transl Psychiatry. 2020;10(3):18.

25. Mora LF, Gold JM, Sullivan SK, Strauss GP. Predictors of neuropsychological 
functioning in bipolar disorder. JAMA Psychiatry. 2020;77(14):1305–13.
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