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IMAGE & SIGNAL PROCESSING

Discussion on Patients with Bipolar Disorder and Depressive Episode by Ratio Low Frequency Amplitude Combined with Grey Matter Volume Analysis

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Abstract
In order to explore the brain functional and structural imaging results of patients with bipolar disorder and depressive episode without taking medicine, and to further explore the disease mechanism of bipolar disorder by combining with clinical symptoms and cognitive function (neuropsychological test), DPABI (Data Processing and Analysis (Resting-State) For Brain Image) software is used to pre-process fMRI (functional magnetic resonance imaging) data and calculate fALFF (ratio low frequency fluctuation amplitude) index. In addition, SPM8 is applied for grey matter volume analysis based on voxel morphology. Pearson correlation model is used to analyze the relationship between functional and morphological changes and clinical symptoms and cognitive tests. DPABI software and SPSS 22.0 software are used to analyze the data. The results show that corresponding abnormal brain areas are found in both functional and structural aspects of patients with bipolar disorder and depression, involving LCSPT emotional circuits. More importantly, the superior frontal gyrus shows significant abnormalities in both functional and structural analysis.

Keywords biphasic disorder · resting-state fMRI · fALFF · grey matter volume analysis

Introduction

Bipolar disorder is a common type of disabling condition in mood disorders [1, 2]. Its clinical manifestations are complex, the rate of misdiagnosis and missed diagnosis is very high, and effective treatment is also difficult. Even after effective treatment, there is still a high risk of recurrence [3], with a lifelong suicide risk of about 20%, and an annual death rate of about 0.4%, 20 times higher than that of the general population [4]. Among bipolar disorders, the first episode of depression is the most common, accounting for more than 50% of the patients with bipolar disorders [5]. In bipolar patients with first episode of depression, researchers found that the number of depressive episodes increased significantly compared with the number of manic or hypomanic episodes. Patients will be in a longer course of depressive phase, while manic and hypomanic episodes often occur several years or even more after the first depression [6, 7], which often causes patients to be misdiagnosed as other diseases in the early stage of onset, and the misdiagnosis rate is as high as 69% [8]. Therefore, finding objective image indexes of bipolar disorders as the reference is rather important.

Scholars at home and abroad have emphasized more extensive brain network dysfunction. However, the specific pathological mechanism is not clear, and the high heterogeneity between the studies has also led to more controversy and discussion. For bipolar disorder patients with depressive episodes, there are few studies of functional imaging combined with structural imaging [9]. Based on this, it is intending to analyze the correlation between abnormal brain areas and cognitive status in patients with bipolar disorder and depressive episode, and explore the biological mechanism of cognitive impairment from the aspects of brain imaging, so as to provide

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some basis for the identification of objective image indicators in patients with bipolar disorder and depressive episode.

Methodology

Subject information

Case group: Inclusion criteria: outpatients or inpatients in The First Affiliated Hospital of Harbin Medical University; those who are right-handed; people of Han nationality; aged 18–57 years old; those who are in accordance with the diagnostic criteria of the bipolar disorder in the Handbook for Diagnosis and Statistics of Mental Diseases (Fourth Edition) (DSM-IV) and in the period of depressive episode; those who with Hamilton Rating Scale for Depression (HAMD) score above 17 points; those who with Wechsler Intelligence Test Total IQ (WAIS) higher than 70; those who with the Young Mania Rating Scale (YMRS) not higher than 10; the patients and their families agreed to participate in the study and signed the informed consent. Exclusion criteria: other psychiatric complications: schizophrenia, mental retardation, mental disorders caused by psychoactive substances; traumatic brain injury; other serious organic diseases and various immune diseases; other neurological diseases and skull CT suggesting congenital malformation; taking any antipsychotic drugs before admission to the group, no electroconvulsive therapy; pregnant or lactating women; serious excitement and impulse incompatibility; contraindications of MRI scanning, such as metal teeth or claustrophobia. Informed consent was signed by all patients or their families and this study was approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University, and the informed consent was signed by all participants.

Control group: Inclusion criteria: Han nationality; right-handed; aged 18–57 years old; WAIS higher than 70 points; patients and their family members agreed to participate in the study. Exclusion criteria: Mental disorders; severe neurological disorders; craniocerebral trauma; pregnant or lactating women; severe excitement and impulse incompatibility; contraindications to MRI scanning, such as metal teeth or claustrophobia.

According to statistics, a total of 30 bipolar patients are included, including 15 males and 15 females. There are 31 cases in normal control, including 18 males and 13 females. There is no difference in demographic data between the two groups, as shown in Table 1.

17 items of HAMD-17 are used to assess the severity of depressive symptoms, which are divided into seven factors: cognitive impairment, anxiety/somatic symptoms, sleep disorder, day and night changes, weight, block and despair. The total score is divided into the sum of all items. When the total score is higher than 17, it suggests that there may be mild or moderate depression, and when the total score is higher than 24, there may be severe depression. Psychiatric assessors assess patients' symptoms and input them into a computer-specific database.

RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) includes word learning, story memory, graphic copying, line positioning, number breadth, coding, picture naming, semantic fluency, word recall, word recognition, story recall and picture recall 12 sub-tests. The whole test often lasts about 30 min, which can be summarized into five dimensions: immediate memory, visual space/structure, language, attention and delayed memory. Among them, immediate memory dimension is calculated from word learning and story memory test, which shows the memory ability of the subjects for the current things in a short time; visual space/structure dimension is calculated from graphic copying and line positioning test items, which reflects the cognitive ability of the subjects to spatial relations and positioning; the attention dimension is calculated from the item scores of digit breadth and coding test, which reflects the memory of the subjects and the rapid expression of the memorized information in a short time; the language dimension is calculated from the test items of picture naming and semantic fluency, reflecting the language expression and response ability of the subjects; and the delayed memory dimension is calculated from the word recall, word recognition, story recall and

Table 1 Demographic characteristic of two groups

Features	BD	HC	t/x^2	p
Number of cases (male/female)	30 (15/15)	31 (18/13)	1.314^{α}	0.252
Age (year), X ± SD	36.30 ± 11.015	33.61 ± 8.086	1.089^{b}	0.281
Educational years (years), X ± SD	13.43 ± 3.048	14.00 ± 2.436	-0.804^{b}	0.425
Right-handed (right/left)	30/0	31/0	–	–
HAMD Gauge, X ± SD	23.621 ± 5.570	–	–	–
RBANS Gauge	24/30	28/31	–	–

Note: SD: standard deviation; BD: biphasic disorder; HC: control group; a: chi-square test; b: double sample t test

picture recall tests to reflect the subjects' anterograde memory ability. Psychiatric professionals assess patients' cognitive abilities and input them into computer-specific databases.

Data acquisition

The subjects' magnetic resonance imaging (MRI) is scanned at the hospital's magnetic resonance center. The nuclear magnetic resonance machine used is made by Siemens Magnetom Trio 3 T in Germany [10]. Firstly, the professional nuclear magnetic resonance scanner will make an appointment about nuclear magnetic resonance scan time with the subjects in advance, inform them that they will scan the MRI and inform them of the relevant taboo rules. In order to avoid disturbing the subjects in the strange environment, it is necessary to familiarize with the surrounding environment before the scanning, avoid the interference of psychological factors, and inform the attention points during the scanning, such as keeping the whole body lying on the scanning table, keeping the state of relaxation, closing the eyes, and using the foam pad to fix head to avoid head movement, and wearing sound-proof headphones to reduce the interference of instrument noise. At the end of the scan, the subjects are asked whether they are asleep during the scanning process. At the same time, the magnetic resonance data are recorded in the CD prepared in advance according to the rules and returned to the research unit for input. The scanning sequence and parameters are shown in Table 2.

Data preprocessing

The whole preprocessing process of functional magnetic resonance data is carried out in DPABI software, including:

Convert the DICOM format of the original EPI image to NIFTI format; remove the first 10 time points; conduct time layer correction; carry out head movement correction; reorient functional phase; remove covariates; use DARTEL algorithm for (3*3*3) mm resampling, make space standardization to MNI template; use 6 mm full width and half height Gaussian kernel smoothing; remove linear drift (detrend) and Filter.

Quality control in DPABI is carried out. The subjects whose translation in X, Y and Z direction is greater than 2 mm and rotation angle is greater than 1 degree are excluded. The power spectrum of filtered time series is obtained by fast Fourier algorithm. ALFF is measured by obtaining the square root of voxel signal from 0.01 to 0.08 Hz, and then the ratio low frequency fluctuation amplitude (fALFF) is obtained by dividing the ALFF of each voxel by the mean of the whole frequency band amplitude.

VBM8 (http://dbm.neuro.uni-jena.de/vbm8/) plug-in is needed to process all the structural magnetic resonance data in SPM8. Specific steps include:

Transform the DICOM format of original T1 image to NIFTI format; relocate the structure phase; standardize to MNI space, divide white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF); make quality control; smooth-en GM with 8 mm full width and half height Gaussian kernel to get the volume of grey matter based on voxel morphology (VBM-GMV).

Data analysis

Functional phase data are analyzed by two-sample t-test in DPABI. Age and gender are used as covariates to analyze the difference of fALFF between bipolar group and control group. Multiple comparisons are corrected by GRF (General Regulatory Factor), and the threshold is set to $P < 0.05$.

Table 2 Detailed parameters of magnetic resonance scanning

Parameter	Three-dimensional high resolution of whole brain T1 Weighted image Three-dimensional T1-weighted imaging T1-FL3D MP-RAGE	Resting state f MRI Echo plane imaging sequence EPI
Scan bits	Sagittal	Transverse dislocation
Repeat time TR (ms)	2300	2000
Echo time TE (ms)	2.95	30
Layer thickness (mm)	1.2	3
Layer number (layer)	160	32
Layer spacing (mm)	0.6	1
Point of time	160	212
Acquisition matrix	240 × 256	64*64
Reversal angle FA	9°	90°
Collect visual field (mm^3)	226 × 240	240 × 240
Scanning time	9 min 14 s	7 min 10s

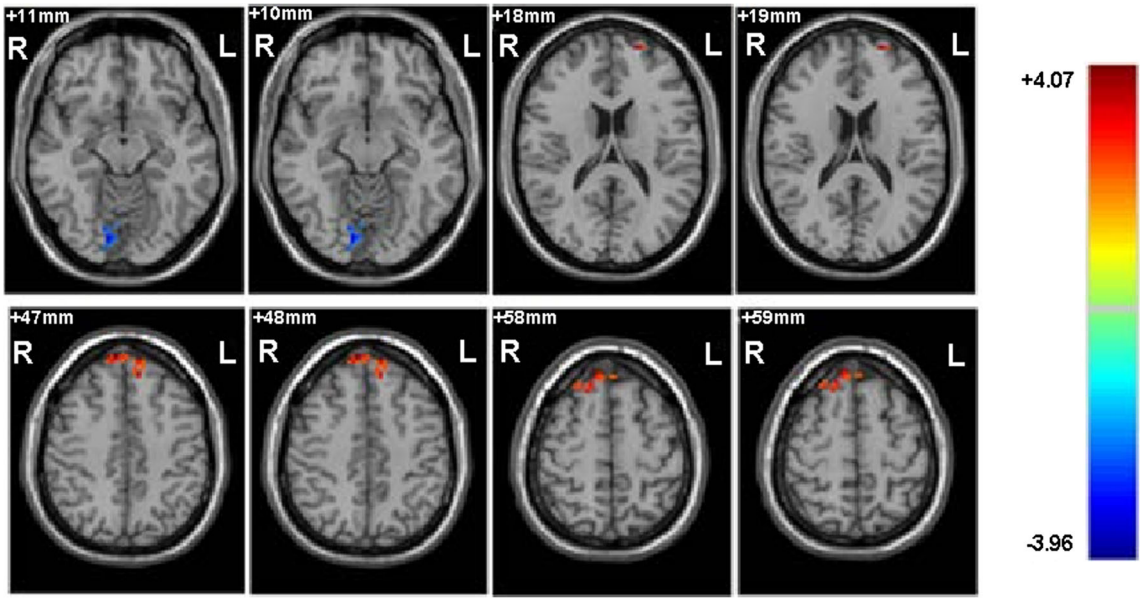

Fig. 1 Abnormal brain areas of f-ALFF in bipolar disorder depression group and control group

MASK is used to extract the mean fALFF of each abnormal brain area by DPABI. SPSS22.0 is used to correlate with clinical symptoms and cognitive symptoms of bipolar group, and $P < 0.05$ shows that there is statistical significance.

Structural phase data are analyzed by two-sample t-test in SPM 8. Age and gender are used as covariates to analyze the differences of GMV brain areas between bipolar group and control group. Multiple comparisons are corrected by GRF, and the threshold is set to $P < 0.05$. MASK is used to extract the mean GMV of abnormal brain areas by DPABI. SPSS22.0 is used to correlate with clinical symptoms and cognitive symptoms of bipolar group, and $P < 0.05$ shows that there is statistical significance.

To verify the coincidence between fALFF and GMV results, fALFF brain area difference map and GMV brain area difference map are superimposed on the same template (DPABI viewer is used to operate and set voxel >40). Meanwhile, in SPSS 22.0, Pearson correlation ($P < 0.05$, double tails) is carried out for fALFF and GMV difference brain areas, and the age, gender and education level of all subjects are well controlled (Figs. 1, 2 and 3).

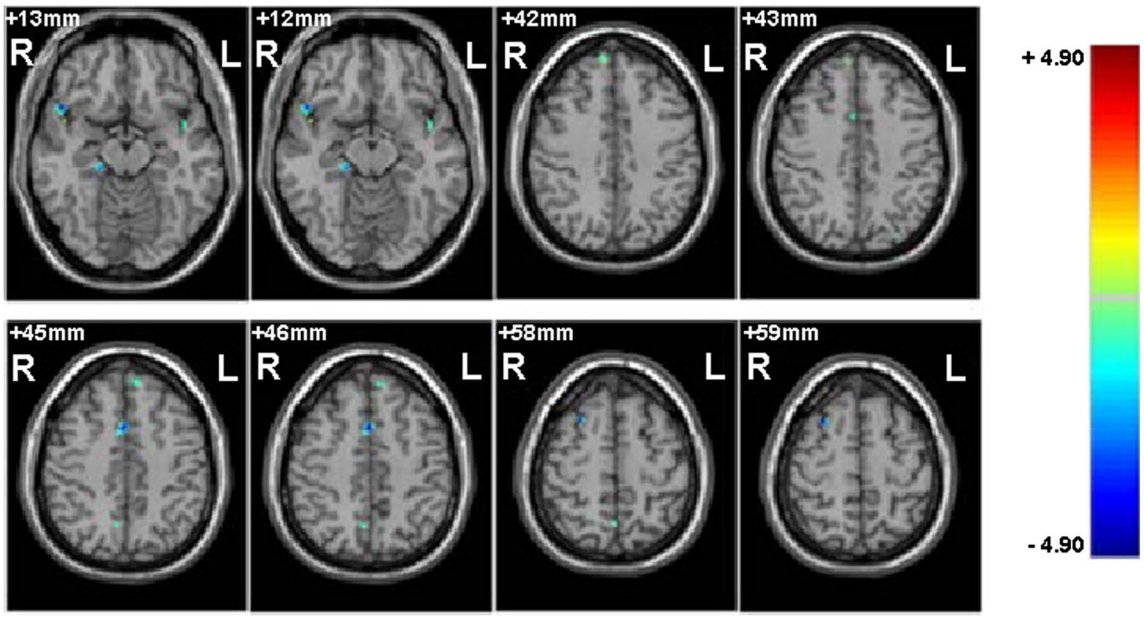

Fig. 2 Abnormal brain areas of GMV in bipolar disorder depression group and control group

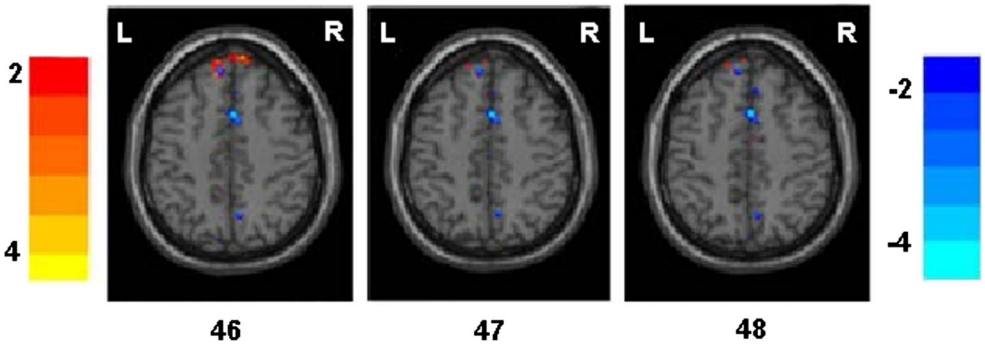

Fig. 3 Integration results of different brain areas in bipolar disorder depression group

Results and discussion

Differential results of fALFF in bipolar disorder and depressive episodes

Compared with the normal control group, the f-ALFF values in the right lingual gyrus decreases significantly in bipolar disorder and depressive episode group, but the f-ALFF values in the bilateral superior frontal gyrus and left superior frontal gyrus increase significantly (Table 3).

Differential results of GMV in bipolar disorder and depressive episodes

Compared with the normal group, GMV in bilateral superior temporal gyrus, bilateral superior frontal gyrus, right middle frontal gyrus, right parahippocampal gyrus, and anterior cuneiform lobe decrease significantly in the bipolar disorder depression group (Table 4).

Integration of the results of fALFF and GMV differentiated brain regions

The difference maps of fALFF and GMV brain areas in the disease group are superimposed on the same template. The functional and structural differences of brain areas overlap partially in the left superior frontal gyrus, but there is no statistical significance in the correlation analysis of functional and structural differences of brain areas (Table 5).

Relevant research results of HAMD scale and function and structure

No correlation is found between clinical symptoms and functional or structural differences in the brain areas of the disease group (Table 5).

Relevant research results of RBANS scale and function and structure

There is no correlation between functional phase differential brain areas and RBANS scale in the patients with bipolar disorder and depressive episode. However, parts of the differential brain areas in GMV structure in the disease group are correlated with the RBANS scale, which is statistically significant. Specifically, GMV values in the left superior frontal gyrus are negatively correlated with vocabulary memory in the RBANS scale, GMV values in the anterior cuneiform lobe are negatively correlated with delayed memory, while GMV values in the right superior frontal gyrus are positively correlated with speech function. No correlation is found among other items of the RBANS scale (Table 6).

Discussion on depressive episodes of bipolar disorder

Previous studies have found that the fALFF value of lingual gyrus in bipolar patients is lower than that in healthy controls, which is consistent with the results of this study. The lingual gyrus is located between the talus groove and the lateral groove. It is posterior to the occipital lobe and anterior to the

Table 3 Abnormal brain areas of f-ALFF in bipolar group and control group

Brain area	Brodmann Zoning (BA)	Voxel number	Hemisphere	MNI coordinate			Peak value t
				X	Y	Z	
Lingual gyrus	BA18	148	Right	6	−87	−12	−3.7409
Frontal gyrus	BA9	105	Right	8	42	46	3.9197
Frontal frontal gyrus	BA10	70	Left	−18	60	18	3.7625
Frontal gyrus	BA9	79	Left	−10	41	44	3.9741

Table 4 Abnormal brain areas of GMV in bipolar group and control group

Brain area	Brodmann area (BA)	Voxel number	Hemisphere	MNI coordinate			Peak value t
				X	Y	Z	
Superior temporal gyrus	BA38	89	Right	48	10	−11	−4.855
Superior temporal gyrus	BA48	73	Left	−43	3	−13	−4.2548
Parahippocampal gyrus	BA30	96	Right	21	−30	−12	−4.8403
Frontal gyrus	BA9	63	Right	10	51	42	−4.1053
Median frontal gyrus	BA8	64	Right	27	16	58	−4.8626
Frontal gyrus	BA9	44	Left	−7	43	48	−4.3115
Anterior lobe of wedge	BA7	54	Right	3	−61	54	−4.2864

temporal lobe, and partially constitutes the parahippocampal gyrus. The lingual gyrus is a structure in the visual cortex and plays an important role in word recognition. Studies have shown that the lingual gyrus is associated with the regulation of visual stimuli, especially letters [11, 12]. In addition to the recognition of letters, the lingual gyrus is also associated with semantic processing. The subjects with aphasia undergo fMRI measurement to determine which areas are affected. Repeated stimulation does not affect the tongue regulation of the subjects, while the regulatory activities of the aphasics are significantly less than those of the control group. It is also thought to play a role in analyzing logical conditions (i.e. the logical order of events) and coding visual memory. This may explain to some extent the difference between positive and negative facial emotional stimulation in depressive patients and normal people.

Structural analysis shows that GMV in bilateral superior temporal gyrus, bilateral superior frontal gyrus, right middle frontal gyrus, right parahippocampal gyrus, and anterior cuneiform lobe decrease in bipolar patients. These brain regions are obviously related to the default mode network, which is currently recognized commonly.

Table 5 Relevant results of abnormal brain areas and clinical symptoms in bipolar disorder depression group

Brain area		HAMD	
		r	P
fALFF	Right superior frontal gyrus	0.328	0.082
	Left superior frontal gyrus	0.19	0.912
	Left frontal gyrus	0.16	0.407
	Right lingual gyrus	−0.246	0.166
GMV	Right superior temporal gyrus	0.085	0.662
	Left superior temporal gyrus	0.275	0.148
	Parahippocampal gyrus	−0.266	0.164
	Frontal gyrus	0.213	0.267
	Right median frontal gyrus	−0.082	0.74
	Frontal gyrus	0.166	0.39
	Right anterior cuneate lobe	0.271	0.155

Superior temporal gyrus is the key pathway structure of amygdala and prefrontal cortex, which contains the main auditory cortex. Wernicke region is located in this area. It participates in auditory processing, including language, and is responsible for processing voice, which is considered to be an important structure of social cognition. Some scholars have made a systematic meta-analysis of many previous studies using VBM. A total of 2407 bipolar patients, 4101 depressive patients and normal controls are studied. It is found that the large-scale brain regions of bipolar patients show bilateral insulas and the volume of gray matter in bilateral superior temporal gyrus decrease compared with the control group. The results of this study are consistent with those of the above studies, suggesting that abnormalities in the superior temporal gyrus may be closely related to bipolar disorder.

Consistent with the results of this study, most of the functional magnetic resonance studies and structural magnetic resonance studies have detected abnormalities in this brain area. In functional studies, researchers found that ALFF in the ventral prefrontal cortex and dorsolateral prefrontal cortex increased in bipolar disorder patients compared with control group. Similarly, abnormalities of f-ALFF in this brain region have been detected. The results of this study are also consistent with a large number of meta-analyses. In structural studies, the reduction of gray matter volume in the superior frontal gyrus has also been reported in many reports. It is worth mentioning that Hibar et al. have conducted the largest clinical study on brain structural imaging so far. They collected 6503 samples from 28 international teams of the ENIGMA Biphasic Working Group (including BD2447 cases) and analyzed them. The results showed that the gray matter in the frontal, temporal and parietal cortex of the biphasic group became thinner.

It is found that the left superior frontal gyrus is related to vocabulary memory, the anterior cuneiform lobe is related to delayed memory, and the right superior frontal gyrus is related to speech function. Previous studies have found that the

Table 6 Relevant results of abnormal brain areas and cognitive symptoms in bipolar group

Brain area		RBANS		
		Speech function	Vocabulary memory	Delayed memory
fALFF	Right superior frontal gyrus	0.067	−0.21	−0.15
	Left superior frontal gyrus	−0.173	−0.167	−0.133
	Left frontal gyrus	0.035	−0.09	−0.111
	Right lingual gyrus	0.015	0.026	0.221
GMV	Right superior temporal gyrus	0.354	0.03	−0.0571
	Left superior temporal gyrus	0.078	−0.312	−0.309
	Parahippocampal gyrus	0.23	−0.051	−0.204
	Right superior frontal gyrus	0.325*	−0.006	0.121
	Right median frontal gyrus	0.049	−0.178	−0.077
	Left superior frontal gyrus	0.13	−0.429*	−0.077
	Right anterior cuneate lobe	−0.371	0.069	−0.387*

Note: *P<0.05; **P<0.01

prefrontal-limbic system is an important regulatory system in depression, and its dysfunction is closely related to depression. In this regulatory network, anterior cingulate gyrus, amygdala and hippocampus are important parts. Functional connectivity studies have found that the activity of the dorsolateral, dorsolateral prefrontal cortex and dorsal cingulate gyrus of patients is weakened, while the activity of the ventral lateral prefrontal lobe, the hypogenic cingulate gyrus and the amygdala is enhanced. As mentioned above, bipolar patients often show cognitive impairment, such as lack of execution and emotional instability. It is speculated that the superior frontal gyrus plays an important regulatory role in the pathogenesis of bipolar disorder. Its disorder may hinder the exchange of information between the internal (DMN) and external (ECN) of the brain, and the transmission efficiency of information in the cerebral nerve circuits is low, leading to persistent abnormal emotional experience and resulting in a series of clinical symptoms such as cognitive imbalance.

Conclusion

The results of MRI in depression patients with bipolar disorder are correlated with their cognitive characteristics. Compared horizontally, from neuroimaging to neuropsychology, the disease status is more comprehensively reflected and detailed. The relationship between resting brain function, brain structure and cognitive characteristics is discussed, which is more beneficial to the understanding and treatment of bipolar disorder. Functional imaging and structural imaging are linked, and there are already research results on the functional joint structure of depressive disorders. This study provides some reference value for the brain imaging study of bipolar disorder patients with depressive episodes.

Based on the brain image analysis method of bipolar disorder, the abnormal brain areas related to LCSPT (limbic cortex striatum globus pallidus thalamic nerve circuit) emotional circuits are found from both functional and structural perspectives. More importantly, the superior frontal gyrus has significant abnormalities in functional analysis and structural analysis, which is the most stable and reliable, and has significant correlation with cognitive function, suggesting that this region plays an important role in the pathogenesis of bipolar disorder.

Compliance with Ethical Standards

Conflict of Interest Author Xiaohong Wang declares that he has no conflict of interest. Author Na Zhao declares that he has no conflict of interest. Author Jingjing Shi declares that he has no conflict of interest. Author Yuhua Wu declares that he has no conflict of interest. Author Jun Liu declares that he has no conflict of interest. Author Qiang Xiao declares that he has no conflict of interest. Author Jian Hu declares that he has no conflict of interest.

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

This article does not contain any studies with animals performed by any of the authors.

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

References

1. Savitz, J. B., Nugent, A. C., Bogers, W. et al., Habenula volume in bipolar disorder and major depressive disorder: a high-resolution magnetic resonance imaging study. *Biological Psychiatry* 18(5): 523–523, 2013.

2. Di Tommaso Morrison, M. C., Carinci, F., Lessiani, G., Spinas, E., Kritas, S. K., Ronconi, G., Caraffa, A., and Conti, P., Fibromyalgia and bipolar disorder: extent of comorbidity and therapeutic implications. *J Biol Regul Homeost Agents* 31(1):17–20, 2017.
3. Duff, B. J., Macritchie, K. A., Moorhead, T. W. et al., Human brain imaging studies of DISC1 in schizophrenia, bipolar disorder and depression: a systematic review. *Schizophrenia Research* 147(1):1–13, 2013.
4. Cerimele, J. M., Chwastiak, L. A., Dodson, S. et al., The Prevalence of Bipolar Disorder in Primary Care Patients With Depression or Other Psychiatric Complaints: A Systematic Review. *Psychosomatics* 54(6):515–524, 2013.
5. Okasha, T., Fikry, M., Kowailed, A. et al., Screening for bipolar disorder among patients undergoing a major depressive episode: Report from the BRIDGE study in Egypt. *Journal of Affective Disorders* 147(1–3):217–224, 2013.
6. Woo, Y. S., Shim, I. H., Wang, H. R. et al., A diagnosis of bipolar spectrum disorder predicts diagnostic conversion from unipolar depression to bipolar disorder: a 5-year retrospective study. *Journal of Affective Disorders* 174:83–88, 2015.
7. Su, J. P., Liu, H. F., Zhang, H. L., He, Y. J., and Nie, Y., Effects of different degrees of depression on inflammatory response and immune function in patients with ovarian cancer. *J Biol Regul Homeost Agents* 32(5):1225–1230, 2018.
8. Bartoli, F., Crocamo, C., Dakanalis, A. et al., Purinergic system dysfunctions in subjects with bipolar disorder: A comparative cross-sectional study. *Comprehensive Psychiatry* 73:1–6, 2017.
9. Rovera, C., Mauri, M. C., Di, P. C. et al., Effect of N-desalkylquetiapine/quetiapine plasma level ratio on anxiety and depression in Bipolar Disorder: a prospective observational study. *Therapeutic Drug Monitoring* 39(4):1, 2017.
10. Perugi, G., Angst, J., Azorin, J. M., Bowden, C. L., Mosolov, S., Reis, J. et al., Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *The Journal of clinical psychiatry* 76(3):e351–e358, 2015.
11. Vancampfort, D., Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B. et al., Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 14(3):339–347, 2015.
12. Hirschfeld, R. M., Differential diagnosis of bipolar disorder and major depressive disorder. *Journal of affective disorders* 169: S12–S16, 2014.