Neural Plasticity and Neuroimaging in Suicide and Self-harm

Lead Guest Editor: Wenbin Guo
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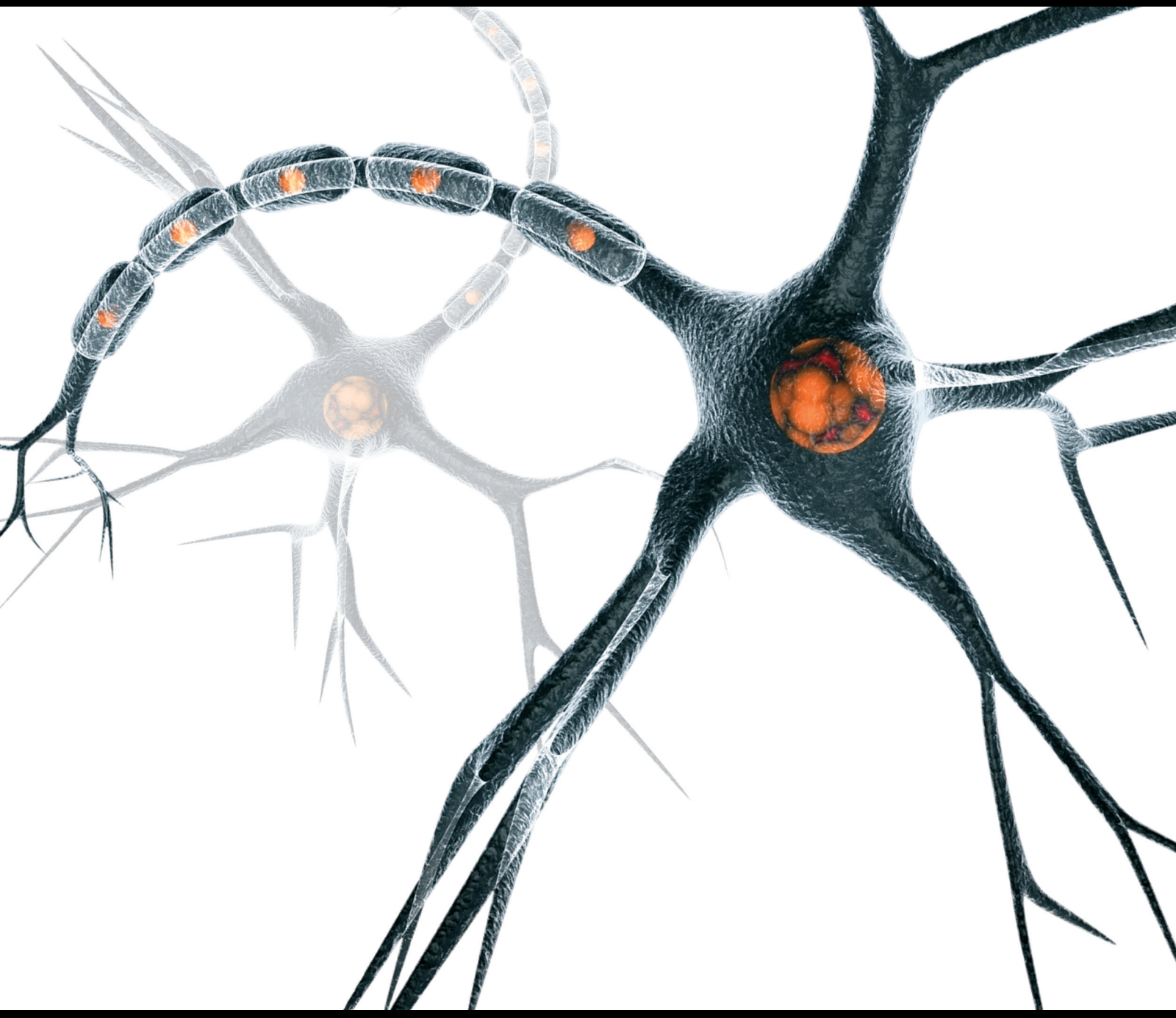

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Hindawi
Neural Plasticity
Volume 2021, Article ID 3741104, 9 pages
https://doi.org/10.1155/2021/3741104

Research Article

Altered Functional Connectivity Strength at Rest in Medication-Free Obsessive-Compulsive Disorder

Dan Lv,[1] Yangpan Ou,[2] Yuhua Wang,[1] Jidong Ma,[3] Chuang Zhan,[3] Ru Yang,[4] Yunhui Chen,[1] Tinghuizi Shang,[1] Cuicui Jia,[1] Lei Sun,[1] Guangfeng Zhang,[5] Zhenghai Sun,[1] Jinyang Li,[1] Xiaoping Wang,[2] Wenbin Guo ,[2] and Ping Li [1]

[1]*Department of Psychiatry, Qiqihar Medical University, Qiqihar, China*
[2]*National Clinical Research Center for Mental Disorders and Department of Psychiatry, The Second Xiangya Hospital of Central South University, Changsha, China*
[3]*Department of Psychiatry, Baiyupao Psychiatric Hospital of Harbin, Harbin, China*
[4]*Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha, China*
[5]*Department of Radiology, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, China*

Correspondence should be addressed to Wenbin Guo; guowenbin76@csu.edu.cn and Ping Li; lipingchxyy@163.com

Received 10 April 2021; Revised 25 July 2021; Accepted 17 August 2021; Published 8 September 2021

Academic Editor: Sergio Bagnato

Background. Previous studies explored the whole-brain functional connectome using the degree approach in patients with obsessive-compulsive disorder (OCD). However, whether the altered degree values can be used to discriminate OCD from healthy controls (HCs) remains unclear. *Methods*. A total of 40 medication-free patients with OCD and 38 HCs underwent a resting-state functional magnetic resonance imaging (rs-fMRI) scan. Data were analyzed with the degree approach and a support vector machine (SVM) classifier. *Results*. Patients with OCD showed increased degree values in the left thalamus and left cerebellum Crus I and decreased degree values in the left dorsolateral prefrontal cortex, right precuneus, and left postcentral gyrus. SVM classification analysis indicated that the increased degree value in the left thalamus is a marker of OCD, with an acceptable accuracy of 88.46%, sensitivity of 87.50%, and specificity of 89.47%. *Conclusion*. Altered degree values within and outside the cortical-striatal-thalamic-cortical (CSTC) circuit may cocontribute to the pathophysiology of OCD. Increased degree values of the left thalamus can be used as a future marker for OCD understanding-classification.

1. Introduction

Obsessive-compulsive disorder (OCD) is defined as a combination of intrusive thoughts (obsessions) and repetitive behaviors (compulsions), which affects social and occupational functions and imposes an economic burden on patients and their families [1, 2]. Although the pathophysiological mechanism of OCD remains unclear, neuroimaging studies have highlighted abnormalities in the cortical-striatal-thalamic-cortical (CSTC) circuit, including the anterior cingulate cortex, orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), thalamus, and striatum [3–6]. For example, increased and decreased levels of gray matter volumes in the left OFC and striatum and increased regional homogeneity (ReHo) and global brain functional connectivity (FC) in the lateral OFC and DLPFC were discovered at rest in OCD [7, 8]. Moreover, abnormal white matter within the CSTC circuit is associated with the clinical symptoms of OCD [9].

FC patterns at a resting state display a temporal correlation and provide the communication and interaction between spatially separated brain regions [10]. Previous studies applied a region-of-interest (ROI) approach to investigate the FC alterations in given brain regions at rest in OCD with inconsistent results [11–13]. The ROI analysis estimates the strength and significant series of correlations between a given brain region and all other brain regions. However, it may miss the crucial brain regions related to the pathophysiological mechanism of OCD [14]. The

voxel-wise degree analysis which is data-driven and high-resolution can be used to explore the pathophysiology of OCD to remedy this shortage. Degree analysis calculates the number of instantaneous FC of each voxel with other voxels in the whole brain rather than the given ROIs [15]. Compared to other FC methods, the advantage of degree analysis is obtaining FC throughout the whole brain in an unbiased way. Therefore, it can be used as an important index for evaluating the FC strength [15]. For this background, the degree analysis approach was used to investigate the pathophysiological mechanism of OCD from the FC alterations throughout the whole brain at rest in the present study. Previous studies have delineated the degree values from FC in schizophrenia [16] and Alzheimer's disease [17] to physical connectivity in patients with major depression [18], alcohol dependence [19], and schizophrenia [20]. In addition, increased degree values in the OFC and basal ganglia were found at rest in OCD [21], and changes in the degree of the right ventral frontal cortex were related to the alleviation of OCD symptoms. Furthermore, a decreased degree of the bilateral superficial amygdala can be used in predicting the effect of cognitive behavior therapy in OCD [22]. Although these studies used the degree approach to explore the whole-brain functional connectome in patients with OCD, whether the altered degree values can be used in discriminating OCD from healthy controls (HCs) remains unclear.

A support vector machine (SVM) is the most commonly used pattern of recognition algorithm in neuroimaging research, providing optimally distinguished categories by establishing a decision function or hyperplane based on well-defined datasets. Then, it utilizes the generated decision function or hyperplane to forecast a new observation belonging to the predefined group [23]. In the SVM analysis, feature selection is the key step to reduce the redundancy and to select meaningful features from the original feature sets [24]. The remaining meaningful features are integrated into a specific classifier via an embedded manner for SVM training [24]. Classification is the approach of classifying the given input by training with an appropriate classifier [25]. Many researchers suggested that SVM is an effective method to construct classifiers [25, 26]. Therefore, our present research applied the SVM method to detect whether abnormal degree values can be used in classifying patients with OCD from HCs.

In the current study, we compared the whole-brain functional connectome at rest in OCD and HCs with the degree approach. Moreover, SVM was used in determining whether abnormal degree values could be used in discriminating OCD from HCs. Based on previous studies, we hypothesized that patients with OCD would show altered degree values in the CSTC circuit at rest, and the altered degree values would be correlated with the clinical symptoms of OCD and could be used in differentiating OCD from HCs.

2. Materials and Methods

2.1. Subjects. We enrolled 40 medication-free patients with OCD from the Fourth Affiliated Hospital of Qiqihar Medical University and Qiqihar Mental Health Center, China, and 38 HCs from the community. The two groups were matched for gender, age, and education level. Diagnoses of OCD were confirmed with the Structured Clinical Interview for DMS-IV (SCID) (patient version). HCs were screened with the nonpatient version of SCID. The severity of OCD, anxiety, and depressive symptoms was evaluated using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Anxiety Rating Scale (HAMA), and 17-item Hamilton Rating Scale for Depression (HAMD), respectively. OCD patients with Y-BOCS total scores of greater than 16 and HAMD scores of less than 18 were considered eligible for the study. All the patients were free of any medication for at least 4 weeks before the brain image acquisition (18 patients were drug naïve, whereas 22 had a history of antiobsessive, antidepressant, or antipsychotic medication). The inclusion criteria were as follows: (1) 16-50 years of age; (2) Han Chinese, right-handed; (3) no acute physical disease and psychiatric or neurological illness; (4) no alcohol or drug dependence; (5) no contraindications for the MRI scan; and (6) no movement distance of more than 2 mm nor rotation angle of more than 2°. HCs with first-degree relatives suffering from any psychiatric disorder were excluded.

The current study was approved by the Medical Ethics Committee of Qiqihar Medical University. The subjects signed written informed consent forms after being informed of the study procedures.

2.2. Image Acquisition and Preprocessing. All imaging data were acquired using a 3.0-Tesla GE 750 Signa-HDX scanner at the Third Affiliated Hospital of Qiqihar Medical University, China. None of the subjects had clinically significant brain structural damage. The resting-state functional scans were acquired using an echo-planar imaging sequence with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 200 mm × 200 mm, FA = 90°, 33 axial slices, thickness/gap = 3.5 mm/0.6 mm, 64 × 64 matrix, and 240 volumes collected for 480 s.

All fMRI data were preprocessed using the Data Processing & Analysis for Brain Imaging (DPABI) software [27]. The following main steps were performed. First, the first 10 volumes were removed. The remaining 230 volumes were collected, and slice timing was corrected. Second, the head motion was corrected, and subjects with more than 2 mm of maximal translation and 2° of maximal rotation were excluded. Two HCs were excluded from further analysis due to excessive head motion. Third, the motion-corrected functional volumes were spatially normalized to the MNI space and resampled to an isotropic voxel size of 3 mm. Fourth, the processed images were smoothed with a 4 mm full width at half maximum (FWHM) Gaussian kernel, linearly detrended, and band-pass filtered (0.01-0.08 Hz). Fifth, the nuisance covariates, including white matter, 24 head motion parameters, and cerebrospinal fluid time course, were regressed out. Global signal regression (GSR) is a controversial issue in the resting-state fMRI preprocessing. Many researches clarified that the global signal contains some physiological signals, which are important and cannot be regressed out in the resting-state fMRI preprocessing [28,

Table 1: Demographic and clinical characteristics of participants.

	OCD patients ($n = 40$)	HCs ($n = 38$)	X^2/t	p
Age (years)	27.28 ± 8.16	27.18 ± 8.33	0.05	0.71
Sex (male/female)	27/13	25/13	0.026	0.87∗
Education (years)	13.40 ± 2.87	13.74 ± 3.03	-0.50	0.83
Illness duration (months)	66.68 ± 75.54			
Y-BOCS total score	24.90 ± 5.73	1.13 ± 0.88	25.27	<0.001
Y-BOCS obsessive thinking	12.85 ± 4.25	0.37 ± 0.49	17.98	<0.001
Y-BOCS compulsive behavior	12.05 ± 4.62	0.74 ± 0.72	14.92	<0.001
HAMD	8.05 ± 4.40	1.45 ± 0.95	9.04	<0.001
HAMA	10.83 ± 6.55	1.16 ± 1.00	9.00	<0.001
FD	0.04 ± 0.02	0.03 ± 0.01	1.25	0.13
Time points scrubbed out	1.13 ± 2.256	1.00 ± 2.418	0.25	0.95

OCD = obsessive-compulsive disorder; HCs = health controls; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; HAMD = 17-item Hamilton Depression Rating Scale; HAMA = Hamilton Anxiety Rating Scale; FD = framewise displacement. Variables of age, education, Y-BOCS total score, subscale score, HAMD score, HAMA score, and FD were tested by two-sample t-tests, and the results were indicated by t values. Categorical data such as gender was tested using the chi-square test, and the result was indicated by X^2.

29]. For this reason, we did not regress out the global signal in the current research. To verify whether the global signal has an impact on the current results, we reanalyzed the data with GSR. Finally, we scrubbed with a framewise displacement (FD) measure using a threshold of 0.2 together with one preceding and two subsequent volumes [30]. The mean FD for each participant was calculated, and no difference was observed between patients with OCD and HCs (Table 1).

2.3. Degree Analysis. Degree values represent the number of direct functional connections of a node with other nodes within the entire brain connectivity matrix. A correlation matrix is constructed by calculating the Pearson correlation coefficients of each voxel's time series to all other voxels' time series within a predefined gray matter mask. A threshold of 0.2 was used to remove the weak correlations when we constructed the voxel-voxel connectivity matrix [31]. Given the ambiguous explanation of negative correlations and detrimental effects of negative correlations on test-retest reliability, the present analyses were restricted to positive correlations by setting the negative correlations to 0 as described in the previous studies [17, 32, 33]. The degree value of a voxel was further computed as the sum of the connections at the individual level. Finally, the degree values were transformed into a Z-score map with the Fisher Z transformation in the whole brain voxel-wise for the improvement of normality.

2.4. SVM Analysis. SVM was conducted with the LIBSVM software (http://www.csie.ntu.edu.tw/cjlin/libsvm/). A "leave-one-out" cross-validation approach was used in verifying the performance of the SVM [34, 35]. One sample in each group was designated as the test sample, and the remaining samples were used as the training classifier. Then, the excluded subject pairs were used in testing the classifier's ability to reliably distinguish the groups (OCD/HCs). The step was repeated until the highest values for specificity and sensitivity were obtained [34, 35]. The global classification accuracy was obtained through the permutation testing, which was run 10,000 times for each sample (OCD/HCs).

Table 2: Regions with abnormal degree values in the patients with OCD.

Cluster location	Peak (MNI)			Number of voxels	t value
	x	y	z		
Left thalamus	-12	-12	9	198	5.3545
Left cerebellum Crus I	-30	-72	-27	64	4.7578
Left DLPFC	-18	42	45	25	-4.7994
Right precuneus	6	-51	21	57	-4.7865
Left postcentral gyrus	-66	-15	21	25	-5.2707

All effects survived a voxel-wise statistical threshold ($p < 0.05$) after Gaussian random field (GRF) correction for multiple comparisons (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$). OCD = obsessive-compulsive disorder; MNI = Montreal Neurological Institute; DLPFC = dorsolateral prefrontal cortex.

2.5. Statistical Analysis. The clinical and demographic data of OCD and HCs were compared using two-sample t-tests and the chi-square test with SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA).

Two-sample t-tests were conducted using the DPABI software for the identification of difference in degree values between OCD and HCs. The potential influences of the mean framewise displacement (FD), age, gender, and HAMD and HAMA scores were reduced by using them as covariates. The threshold was set at $p < 0.05$ corrected by the Gaussian random field (GRF) theory for multiple comparisons.

Partial correlation analyses were performed between degree values showing between-group differences and clinical variables (i.e., Y-BOCS total score, obsessive thinking score, compulsive behavior score, HAMD, and HAMA

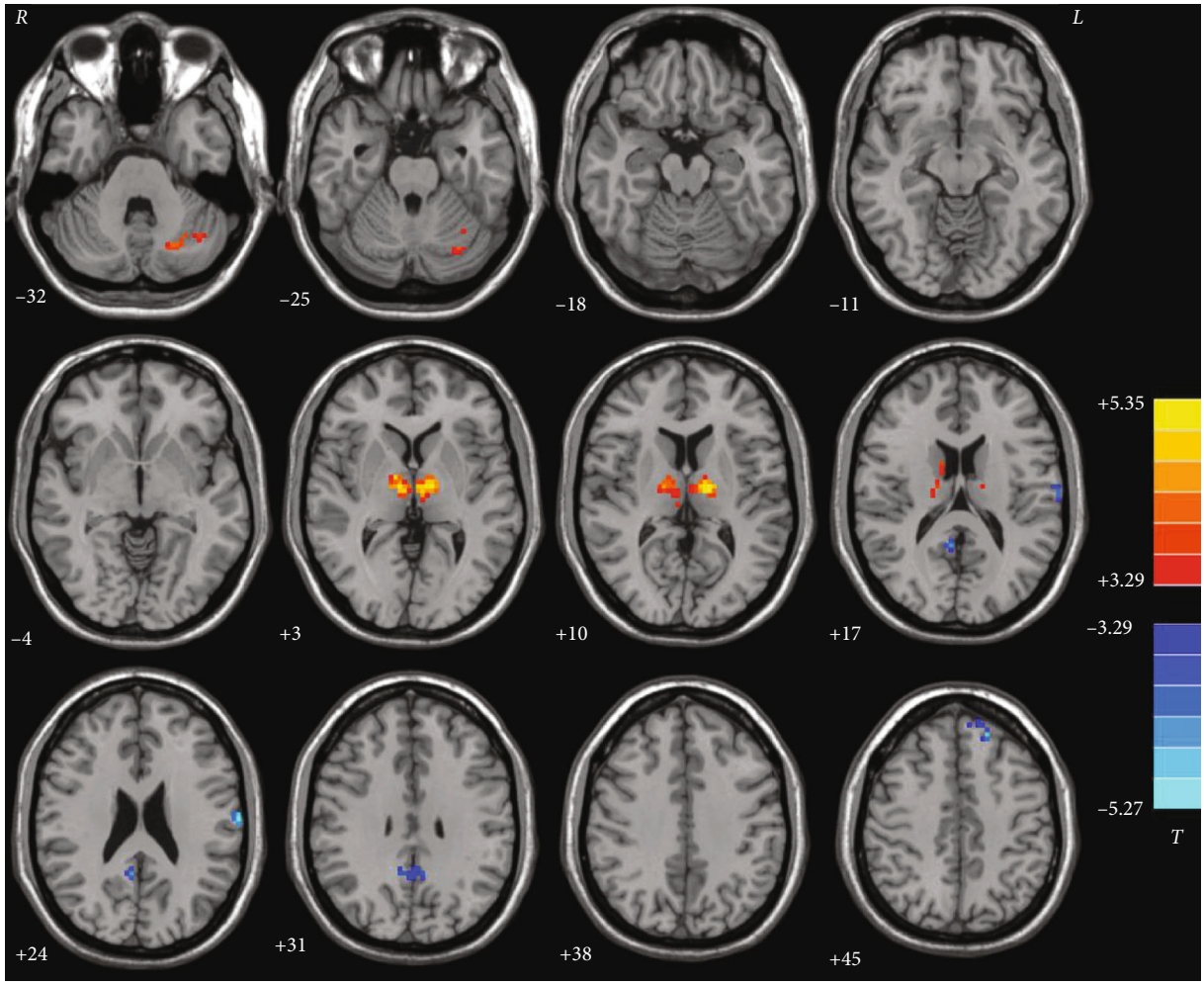

Figure 1: Brain regions with abnormal degree values in patients with OCD. t values from two-sample t tests with $p < 0.05$ (GRF corrected). Red denotes increased degree values; blue denotes decreased degree values. OCD = obsessive-compulsive disorder; GRF = Gaussian random field; L = left; R = right.

scores). Gender, age, illness duration, and education were used as covariates in OCD. The significance level was $p < 0.05$ (Bonferroni corrected). Moreover, we conducted the whole-brain voxel-based correlations between degree values in the whole brain and clinical variables with gender, age, illness duration, and education as covariates in OCD.

3. Results

3.1. Demographics and Clinical Variables of Subjects. The demographics and clinical characteristics are presented in Table 1. Patients with OCD and HCs showed no significant difference in FD values, gender, age, or education. However, significant group differences in Y-BOCS, HAMD, and HAMA scores were found.

3.2. Group Differences in Degree Values. In comparison with HCs, patients with OCD had increased degree values in the left thalamus and left cerebellum Crus I and decreased degree values in the left DLPFC, right precuneus, and left postcentral gyrus (Table 2 and Figure 1). Furthermore, the results with GSR showed that patients with OCD had higher degree values in the left thalamus and lower degree values in the right precuneus (Table S1 and Figure S1 in Supplementary Materials).

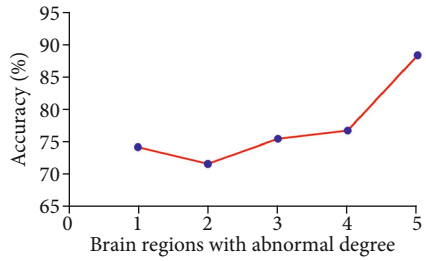

Figure 2: Accuracy of SVM using the five brain regions with abnormal degree values to separate OCD from HCs. The SVM result showed that the highest accuracy is 5. 1 = left cerebellum Crus I, 2 = right precuneus, 3 = left dorsolateral prefrontal cortex, 4 = left postcentral gyrus, and 5 = left thalamus. SVM = support vector machine; OCD = obsessive-compulsive disorder; HCs = health controls.

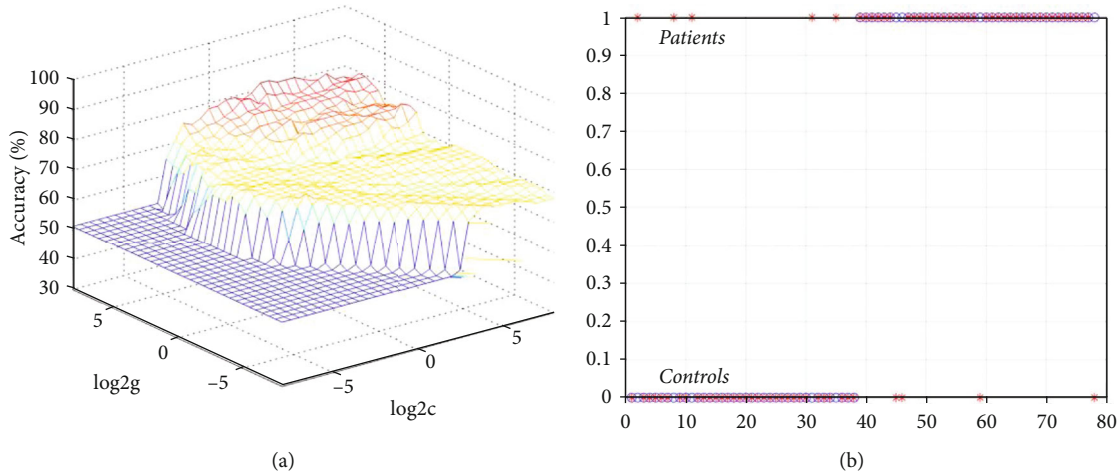

FIGURE 3: Visualization of SVM results for discriminating patients from controls using the degree values of the left thalamus. (a) 3D view of the classified accuracy with the best parameters. (b) Classified map of the degree values of the left thalamus. log 2c and log 2g mean the range and step size of the given parameters c and g (c and g are the parameters of the kernel functions in SVM training). The figure in (b) means the sensitivity and specificity of the SVM model. The horizontal axis conveys the predicted classification of each subject, and the vertical axis conveys the correct classification of each subject. SVM = support vector machine.

3.3. Correlation Analysis. No relationship was observed between degree values showing between-group differences and clinical variables and dimensions in each clinical trait (i.e., Y-BOCS, HAMD, or HAMA) in OCD. There was also no correlation between any clusters and clinical variables in the patients with the whole-brain voxel-based correlation analyses.

3.4. SVM Results. We used the altered degree values of the five brain regions for SVM classification. SVM results revealed that the accuracy of the left thalamus was the highest (Figure 2). Thus, the degree values in the left thalamus can be used in distinguishing OCD with an accuracy of 88.46% (69/78), a sensitivity of 87.50% (35/40), and a specificity of 89.47% (34/38) (Figure 3).

4. Discussion

The current study examined the whole-brain functional connectome in medication-free OCD at rest. Consistent with our hypothesis, patients with OCD showed altered degree values within the CSTC circuit (i.e., left DLPFC and left thalamus). In addition, the increased degree values in the left thalamus can be used in differentiating OCD from HCs. Moreover, OCD showed altered degree values outside the CSTC circuit (i.e., left cerebellum Crus I, right precuneus, and left postcentral gyrus).

The thalamus is a key region within the CSTC circuit, and thalamic-cortical dysconnectivity has been reported in OCD [36]. Increased gray matter volume and FC in the thalamus have been observed in OCD [8, 37–40]. Degree values of weighted networks are more resilient to FC disturbances, which are referred to as FC strength [15]. Previous studies have suggested that increased degree values are linked with increased FC strength by using the degree analysis to calculate the FC strength [31, 32]. In the current study, increased degree values in the left thalamus indicate increased functional strength between the thalamus and other brain regions at rest in OCD. Within the CSTC circuit, the thalamus is a gateway between the striatum and cortex, plays an important role in the integration of executive function and motor function, and controls the input and output of sensory information between the cortical motor areas and the basal ganglia [5, 36]. Increased functional strength in the thalamus is commonly explained as the compensatory reallocation of the thalamus for the activation of the connected brain areas [41, 42]. Therefore, increased functional strength in the thalamus may lead to excessive cortical information integration by activating the thalamic-cortical connectivity and may distort the subsequent behavioral selection process in OCD. Furthermore, the SVM classification is a binary classification algorithm that maximizes the boundary between classes in a high-dimensional space [43]. The current SVM results manifested that the increased degree in the left thalamus could be used as a future marker for OCD understanding-classification.

Within the CSTC circuit, we also observed decreased degree values in the left DLPFC, which is consistent with our previous findings in another independent OCD sample [44]. As an important brain region within the CSTC circuit, the DLPFC has been considered to be involved in the OCD pathophysiology [4, 44, 45]. Meanwhile, the DLPFC is the major component of the execution control network, which is related to executive functions during behavioral inhibition [46]. The decreased degree values of the left DLPFC indicate that the number of voxels located in the whole brain closely related to the left DLPFC decreased. Therefore, the ability of controlling intrusive thinking and repetitive behavior of OCD may reduce.

Apart from the CSTC circuit, the current study revealed increased degree values in the left cerebellum Crus I and decreased degree values in the right precuneus and the left postcentral gyrus at rest in OCD. The cerebellum is involved in the cognitive and affective process, which correlates with

obsessive and ruminative behaviors [47]. Previous studies found increased FC in the cerebellum in OCD [48, 49], and our previous research reported increased cerebellar and default-mode network connectivity at rest in OCD [50]. Moreover, Sha et al. discovered that patients with OCD showed increased FC in the cerebello-thalamo-cortical networks [51]. Increased functional strength in the cerebellum may be involved in the compensatory response in the cognitive and affective process at rest in OCD [41, 42]. The precuneus is associated with self-awareness processing [52]. Reduced degree values may disrupt the balance of the precuneus and other brain regions and may result in difficulty in integrating inner thought and external events in OCD [53, 54]. As a key brain area of the somatosensory network, the postcentral gyrus plays an important role in sensory-motor integration and transmission [55]. Compared with HCs, the degree values of the left postcentral gyrus are reduced in patients with OCD in the current study. Previous researches also reported decreased ReHo and voxel-mirrored homotopic connectivity in the postcentral gyrus at rest in OCD [56, 57]. The decreased degree values of the left postcentral gyrus may reduce the efficiency of information transmission within the sensory-motor pathway, therefore contributing to the repetitive and intrusive thoughts and behaviors in patients with OCD [58].

Previous studies revealed that altered degree values were mainly observed in the CSTC circuit (i.e., OFC and basal ganglia) and emotional modulation network (i.e., ventral frontal cortex and amygdala) in OCD [21, 22, 59]. Consistent with the previous research, the present study discovered altered degree values within the CSTC circuit (i.e., left DLPFC and left thalamus) but failed to discover altered degree values in the emotional modulation network at rest in OCD. Different sample sizes, clinical symptoms, medication status, data analysis, and different OCD subtypes may account for these inconsistencies [59–62]. Moreover, inconsistent with our hypothesis, the current study did not find any relationship between degree values showing between-group differences and clinical variables in OCD. We speculated that the abnormal degree values were possibly trait changes for OCD [63].

GSR is a controversial issue in the resting-state fMRI preprocessing. Many researches clarified that the global signal contains some physiological signals, which are important and cannot be regressed out in the resting-state fMRI preprocessing [28, 29]. For this reason, we did not regress out the global signal in the current research. Furthermore, different from the results without GSR, the results with GSR showed that patients with OCD had higher degree values in the left thalamus and lower degree values in the right precuneus, suggesting that GSR has an impact on the resting-state fMRI results [64].

Several limitations must be considered. First, 22 patients had a history of psychotropic medication, and the current results may be affected by psychotropic medication. Second, we only discovered some brain regions showing altered degree values at baseline in OCD. The effects of medication, psychotherapy, and physical therapy on changes in degree values in OCD should be investigated in future studies. Third, the present study did not collect cognitive and behavioral information. Fourth, the SVM results were not tested in another independent sample, presumably leading to overfitting and optimistic results. The leave-one-out approach was used to construct the model and to perform the SVM analysis due to the small sample size, which again could cause the overfitting issue. Fifth, a previous study has found that the SVM analysis needs at least 200 subjects to observe the reliable results [65]. The sample size of the current research was relatively small, and the power of SVM classification was limited, which was insufficient to draw strong conclusions based on the identified anomalies. Therefore, further researches are needed to use an alternate atlas for parcellation in order to make wiser conclusions in a small dataset [66]. Sixth, like degree analysis, the network homogeneity (NH) method can be used as an important index for evaluating the FC strength [67]. In a previous research, we used the NH method to investigate the FC strength within the default-mode network (DMN) in the same OCD sample [68]. Some similar results (i.e., decreased FC strength in the right PCC/PCu) were found between these two researches, suggesting that the current results can be reproduced to a certain extent. However, due to small sample size, the results (degree classifying neural areas) should be taken with caution. Finally, we did not divide OCD into different subtypes according to clinical symptoms. Future researches should strictly control the heterogeneity of OCD samples.

In conclusion, the current study discovered altered degree values within and outside the CSTC circuit at rest in OCD. The increased degree values of the left thalamus could be used as a future marker for OCD understanding-classification.

Data Availability

Our data may be available upon reasonable request. Please contact lipingchxyy@163.com for details.

Conflicts of Interest

All authors declare no conflict of interest.

Authors' Contributions

Dan Lv, Yangpan Ou, and Yuhua Wang engaged in data analysis and wrote the paper. Ping Li and Wenbin Guo conducted and designed the study. Jidong Ma, Chuang Zhan, Ru Yang, Yunhui Chen, Tinghuizi Shang, Cuicui Jia, Lei Sun, Guangfeng Zhang, Zhenghai Sun, Jinyang Li, and Xiaoping Wang participated in patient assessment and imaging data collection. Dan Lv, Yangpan Ou and Yuhua Wang have contributed equally to this work.

Acknowledgments

This work was supported by the Project of Education Department of Heilongjiang Province, China (2019-KYYWF-1215); Natural Science Foundation of Heilongjiang Province, China (LH2019H064); Training Program of Innovation and

Entrepreneurship for Undergraduates of Heilongjiang Province, China (201711230065); and Open Project of Shanghai Key Laboratory of Major Psychiatry (20-K04).

Supplementary Materials

Table S1: abnormal degree values in the patients with OCD (GSR removed). Figure S1: abnormal degree values in the patients with OCD (GSR removed). t values from two-sample t-tests with $p < 0.05$ (GRF corrected). Red denotes increased degree values; blue denotes decreased degree values. OCD = obsessive-compulsive disorder; GSR = global signal regression; L = left; R = right. *(Supplementary Materials)*

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Hindawi
Neural Plasticity
Volume 2021, Article ID 2348072, 7 pages
https://doi.org/10.1155/2021/2348072

Research Article

Injuries in Left Corticospinal Tracts, Forceps Major, and Left Superior Longitudinal Fasciculus (Temporal) as the Quality Indicators for Major Depressive Disorder

Ziwei Liu,[1,2] **Lijun Kang**,[1] **Aixia Zhang**,[1] **Chunxia Yang**,[1] **Min Liu**,[1,2] **Jizhi Wang**,[1] **Penghong Liu**,[1] **Kerang Zhang**,[1] **and Ning Sun**[1,3]

[1]*Department of Psychiatry, First Hospital of Shanxi Medical University, Taiyuan, China*
[2]*School of Humanities and Social Sciences, Shanxi Medical University, Taiyuan, China*
[3]*Department of Mental Health, Shanxi Medical University, Taiyuan, China*

Correspondence should be addressed to Kerang Zhang; atomsxmu@vip.163.com and Ning Sun; sunning@sxmu.edu.cn

Received 26 April 2021; Revised 10 July 2021; Accepted 2 August 2021; Published 21 August 2021

Academic Editor: Wenbin Guo

At present, the etiology and pathogenesis of major depressive disorder (MDD) are still not clear. Studies have found that the risk of first-degree relatives of MDD is 2–3 times that of the general population. Diffusion tensor imaging (DTI) has been previously used to explore the pathogenesis of MDD. The purpose of this study is to explore the etiology of MDD by DTI and further to explore the correlation between its clinical characteristics and the structural changes of white matter in the brain. The study included 27 first-episode, drug-naive patients with MDD, 16 first-degree relatives without MDD, and 28 healthy control subjects with no family history of MDD (HC). Results showed that the fractional anisotropy (FA) differences among the three groups were mainly in the left anterior thalamic radiation (LATR), right anterior thalamic radiation (RATR), left corticospinal tracts (LCST), forceps major (FMa), right inferior longitudinal fasciculus (RILF), and left superior longitudinal fasciculus (temporal) (LSLF(T)). Among the 6 sites, LCST, FMa, and LSLF(T) showed significant differences between MDD and First-degree relatives compared to HC. MDD patients had significant emotional symptoms, somatic symptoms, and cognitive impairment. FMa FA was significantly positively correlated with delayed memory score ($r = 0.43$, $P = 0.031$), and RILF FA was significantly negatively correlated with the FSS score ($r = -0.42$, $P = 0.028$). These results revealed that the white matter characteristics of MDD-susceptible patients were LCST, FMa, and LSLF(T) lesions, all of which may be quality indicators of MDD.

1. Introduction

Major depressive disorder (MDD) is characterized by cognitive impairments, functional disability, and mortality. In 2019, the prevalence of MDD in the Chinese population reached 6.8% [1, 2], and 15% of patients had suicidal behavior [3]. However, the pathogenesis of MDD is still unclear.

Genetic studies have shown that depression has familial clustering, and the prevalence of first-degree relatives is 2–3 times that of the general population. Having first-degree relatives with early/repeated episodes may increase the risk of MDD up to 6 times [4]. In the twin study, the heritability of MDD in males and females was 0.41 and 0.49, respectively, and it was found that the age of onset, number of relapses, comorbidities, anxiety, and clinical severity could predict the risk in relatives [5]. According to the high heritability, there are some diathologic changes in first-degree relatives that make them more susceptible to MDD. Meta-analysis of first-degree relatives of MDD patients showed significant differences in cognitive function. We proposed that cognitive impairment is a characteristic marker of familial aggregation of MDD [6]. It can be inferred that first-degree relatives of MDD may have similar characteristics, which may be related to the quality changes of the onset. Therefore, the task of exploring the clinical characteristics of the genetic rules of MDD is one of great significance.

Magnetic resonance imaging (MRI) is a safe and reliable neuroimaging technique. The commonly used MRI mainly

includes functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), and diffusion tensor imaging (DTI) [7]. The important principle of DTI is dispersion. The white matter of the brain has a fixed structure, which makes the dispersion of water molecules in each direction different, thereby resulting in an index called fractional anisotropy (FA). FA refers to the proportion of anisotropic components of water molecules in the whole dispersion tensor, and its value is between 0 and 1. Previous studies have shown that numerous changes in white matter fiber integrity are indicative of poor antidepressant efficacy [8]. These studies all showed abnormalities of corpus callosum (CC), capsula interna (CI), and superior longitudinal fasciculus (SLF) in MDD; however, without the ability to distinguish the quality change and the state change, the role they play is still unclear. Therefore, we hypothesized that MDD patients have white matter changes, some of which are quality indicators of MDD. We also hypothesized that the other parts are specific state changes that promote the occurrence of disease, and these white matter changes are closely related to clinical symptoms.

2. Materials and Methods

2.1. Participants

2.1.1. MDD. Inclusion criteria are the following: (1) first-episode, drug-naive patients with MDD admitted to the First Hospital of Shanxi Medical University; (2) $18 \leq \text{age} \leq 60$; (3) conformance to the Diagnostic and Statistical Manual of Disorders Fourth Edition (DSM-IV) MDD diagnostic criteria and through a Structured Clinical Interview for DSM-IV TR Axis I Disorders Patient Edition (SCID-I/P) screening [9]; (4) Hamilton Depression Scale 24 (HAMD-24) ≥ 20; (5) no regular use of antipsychotics, antidepressants, or sedative and hypnotic drugs in the two weeks before enrollment; and (6) right-handedness. Exclusion criteria are the following: (1) a history of diseases of the nervous system, major physical diseases, or endocrine diseases; (2) a history of brain injury, coma, and other diseases that may interfere with the study; (3) other medical conditions diagnosed by the DSM-IV, including a history of alcohol or drug abuse or dependence; (4) implanted metal materials, pacemakers, etc.; (5) pregnant or lactating women; and (6) a family history of manic episodes or bipolar disorder. A total of 27 cases were enrolled.

2.1.2. First-Degree Relatives. Inclusion criteria are the following: (1) biological parents, children, or siblings of above patients; (2) $18 \leq \text{age} \leq 60$; (3) HAMD-24 < 8; and (4) right-handedness. Exclusion criteria are the following: (1) meeting the inclusion or exclusion criteria for "MDD"; (2) severe head trauma or neonatal diseases; and (3) having a high fever convulsion in childhood or infancy. A total of 16 cases were enrolled.

2.1.3. HC. Inclusion criteria are the following: (1) $18 \leq \text{age} \leq 60$; (2) age, gender, and education level match the above two groups; (3) HAMD-24 < 8; and (4) right-handedness. Exclusion criteria are the following: (1) meeting the inclusion or exclusion criteria for "MDD"; (2) a clear family history of mental or neurological diseases; (3) severe head trauma or neonatal diseases; and (4) having a high fever convulsion in childhood or infancy. A total of 28 cases were enrolled.

This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University.

2.2. Methods

2.2.1. Diagnosis and Scale Evaluation. The general demographic data of the patients were collected: gender, age, education, family history, history of tobacco/alcohol use, and substance abuse. All of the scales were evaluated by the same experienced psychological evaluator. MDD should not be observed from a single perspective but must be observed from multiple perspectives of emotional experience, physical experience, and cognition [10]. We collected the following data from MDD and HC: the HAMD-24 for the patient's condition, the Snaith-Hamilton Pleasure Scale (SHAPS) for affective symptoms, the Fatigue Severity Scale (FSS) for somatic symptoms, and the Assessment of Neuropsychological Status (RBANS) for cognitive function.

2.2.2. fMRI Scanning. The data were collected by Siemens 3.0 T MRI scanner and 12-channel phased array surface head coil in Shanxi Provincial People's Hospital. During the scan, subjects were asked to remain awake, lie flat at rest, breathe calmly, and keep their heads in a fixed position. First, an MRI plain scan of conventional structural images was performed to exclude subjects with brain organic lesions. The DTI was collected with a single spin echo planar imaging sequence, axial scanning, scanning a total of 45 continuous level, 12 diffusion sensitive gradient direction, the diffusion sensitive coefficient $b = 1000$, while at the same time getting an axis a scan for the best tonsure diffusion weighted imaging $b = 0$, repetition time/echo time (TR/TE) $= 3600/90$ ms, matrix $= 128 * 128$, field of view (FOV) $= 24 * 24$ cm, flip angle=90°, thickness = 0 mm. The scanning time was 4 minutes and 14 seconds.

2.2.3. DTI Data Processing. The original image was converted from DICOM to NIFTI by the MRIconvert software. Based on the Matlab platform, using the PANDA to process the NIFTI data, the nonbrain tissues 3 mm away from the upper and lower, front and rear, and left and right directions of the scalp were all cut. FSL software was used for scalp stripping. The head movement correction and eddy current correction were performed on the subjects' head movements to obtain the brain template and calculate FA, based on the JHU white matter tractography atlas templates and to calculate the average 20 white matters in the region of interest (ROI) FA [11]. The raw DTI data were observed by the naked eye, and no obvious artifacts were found. The average FA in 20 ROI was extracted and placed in SPSS 23.0 for statistical analysis.

2.2.4. Statistical Analysis. This study used SPSS 23.0 ANOVA was performed for age, years of education, and HAMD-24 among the three groups, and the chi-squared test was used for gender. Measurement data were expressed as mean ± SD. The test level was set at $\alpha = 0.05$. $P < 0.05$ indicated that the

Table 1: General demographic data of each group.

Items	MDD ($n = 27$)	First-degree relatives ($n = 16$)	HC ($n = 28$)	F/χ^2	P
Sex (female/male)	19/8	11/5	17/11	0.306	0.738
Age	28.92 ± 8.72	30.93 ± 4.15	26.78 ± 6.91	1.643	0.201
Education (year)	13.77 ± 2.48	13.56 ± 2.12	14.85 ± 2.42	2.038	0.138
HAMD-24	26.92 ± 4.15	4.56 ± 1.71	5.39 ± 1.68	475.877	<0.01

Table 2: White matter fiber values and differences of MDD, First-degree relatives, and HC.

Fiber	MDD FA	First-degree relatives FA	HC FA	F	t
Left anterior thalamic radiation	0.39 ± 0.01	0.40 ± 0.02	0.41 ± 0.01	6.089	0.004*
Right anterior thalamic radiation	0.38 ± 0.02	0.39 ± 0.02	0.40 ± 0.01	8.754	0.000*
Left corticospinal tracts	0.56 ± 0.02	0.55 ± 0.02	0.58 ± 0.02	8.436	0.001*
Right corticospinal tracts	0.57 ± 0.02	0.57 ± 0.03	0.58 ± 0.02	3.358	0.041
Left cingulated	0.52 ± 0.02	0.53 ± 0.03	0.54 ± 0.03	1.468	0.238
Right cingulated	0.48 ± 0.04	0.49 ± 0.04	0.48 ± 0.03	0.399	0.673
Left hippocampus	0.40 ± 0.03	0.41 ± 0.03	0.41 ± 0.03	0.495	0.611
Right hippocampus	0.37 ± 0.02	0.43 ± 0.05	0.42 ± 0.04	0.604	0.549
Forceps major	0.57 ± 0.02	0.57 ± 0.02	0.59 ± 0.01	7.621	0.001*
Forceps minor	0.44 ± 0.02	0.44 ± 0.02	0.45 ± 0.01	2.494	0.090
Left inferior frontal occipital tract	0.42 ± 0.02	0.43 ± 0.02	0.44 ± 0.02	3.363	0.040
Right inferior frontal occipital tract	0.44 ± 0.02	0.44 ± 0.02	0.45 ± 0.02	4.820	0.011
Left inferior longitudinal fasciculus	0.44 ± 0.02	0.43 ± 0.03	0.44 ± 0.02	4.327	0.017
Right inferior longitudinal fasciculus	0.44 ± 0.02	0.45 ± 0.03	0.47 ± 0.02	6.675	0.002*
Left superior longitudinal fasciculus	0.37 ± 0.02	0.38 ± 0.01	0.38 ± 0.01	5.235	0.008
Right superior longitudinal fasciculus	0.39 ± 0.02	0.40 ± 0.03	0.40 ± 0.01	4.813	0.011
Left uncinate fasciculus	0.41 ± 0.02	0.40 ± 0.03	0.41 ± 0.01	0.178	0.838
Right uncinate fasciculus	0.41 ± 0.02	0.41 ± 0.02	0.42 ± 0.02	2.429	0.096
Left superior longitudinal fasciculus (temporal)	0.47 ± 0.03	0.47 ± 0.03	0.50 ± 0.04	5.996	0.004*
Right superior longitudinal fasciculus (temporal)	0.52 ± 0.04	0.53 ± 0.05	0.56 ± 0.05	4.345	0.017

*$P < 0.01$.

difference was statistically significant. The FA extracted from PANDA was placed in SPSS 23.0 and analyzed by ANOVA, and the regions with significant differences were compared in pairs under the Least—Significant Difference (LSD). The results were considered statistically significant when $P < 0.01$. Through SPSS 23.0, a Two-sample T-test was used to compare the differences of SHAPS/FSS/RBANS between MDD and HC. Pearson correlation analysis was used to analyze the correlation between abnormal FA with statistical differences and clinical characteristics in MDD. The results in $P < 0.05$ were considered statistically significant.

3. Results

3.1. General Demographic Data. There was no statistically significant difference in gender, age, or years of education among the three groups ($P < 0.05$), but there was a statistically significant difference in the HAMD-24 score ($P < 0.05$) (see Table 1).

Table 3: Comparison between MDD, First-degree relatives, and HC.

Fiber	MDD/HC	MDD/first-degree relatives	First-degree relatives/HC
LATR	0.001*	0.190	0.100
RATR	0.000*	0.234	0.022
LCST	0.003*	0.262	0.000*
FMa	0.001*	0.813	0.005*
RILF	0.001*	0.363	0.033
LSLF(T)	0.003*	0.878	0.007*

*$P < 0.01$.

3.2. White Matter FA

3.2.1. Overall White Matters FA. There were six differences in white matter in MDD, First-degree relatives, and HC, and

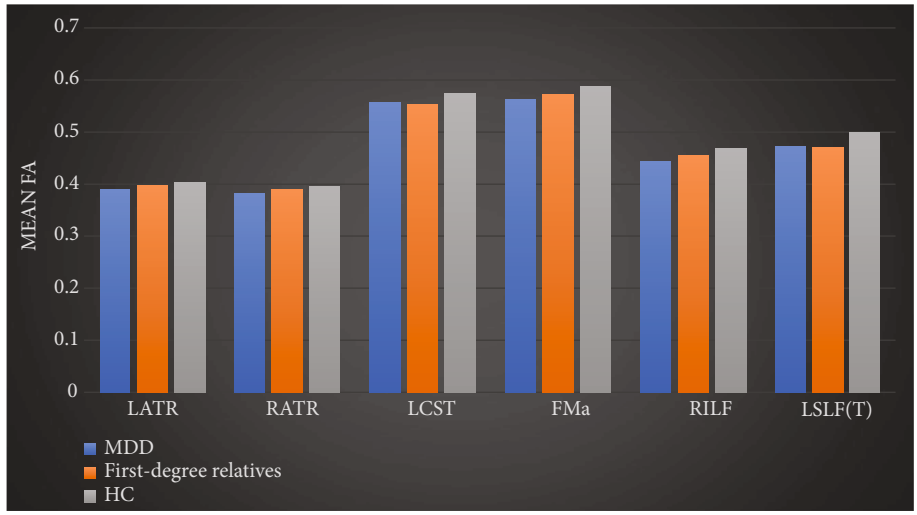

Figure 1: Differences in MDD, First-degree relatives and HC white matter. The bar graph represents the FA mean ± 2SD. $^{*}P < 0.01$.

these included LATR, RATR, LCST, FMa, RILF, and LSLF(T) ($P < 0.01$) (see Table 2).

3.2.2. MDD, First-Degree Relatives, and HC Were Compared Pair-Wise. Multiple comparisons and corrections of brain regions showed that there were significant differences between MDD/HC and First-degree relatives/HC in three regions: LCST, FMa, and LSLF(T); however, there were no significant differences between MDD/First-degree relatives. The values of MDD and First-degree relatives FA were both lower than that of the HC (see Table 3 and Figure 1).

3.3. Correlation Analysis of White Matter Changes and Clinical Manifestations

3.3.1. Differences in Clinical Manifestations between MDD and HC. MDD was significantly increased in SHAPS and FSS when compared to HC. The scores of immediate memory, visual span, speech function, attention, and delayed memory in the RBANS test of MDD were significantly lower than those of HC, and the difference was statistically significant ($P < 0.05$) (see Table 4).

3.3.2. Correlation between Abnormal White Matter FA and Clinical Manifestations. There was a significant positive correlation between FMa FA and delayed memory score ($r = 0.43$, $P = 0.031$), as well as a significant negative correlation between RILF FA and FSS total score ($r = -0.42$, $P = 0.028$). No significant correlation was found for the rest (see Table 5 and Figures 2 and 3).

Table 4: MDD and HC clinical symptoms difference.

Items	MDD	HC	t
Affective symptoms	23.15 ± 6.304	4.59 ± 4.29	0.000*
Physical symptom	46.185 ± 13.12	25.84 ± 5.79	0.000*
Spatial span	74.20 ± 15.16	96.19 ± 14.85	0.038*
Visual span	90.88 ± 20.10	103.42 ± 13.03	0.033*
Speech function	88.20 ± 17.88	97.27 ± 11.41	0.000*
Attentional function	99.76 ± 16.01	119.38 ± 13.29	0.004*
Delayed memory	84.12 ± 16.47	95.19 ± 6.87	0.000*

$^{*}P < 0.05$.

4. Discussion

4.1. About the DTI. This study used the JHU white matter tractography atlas, based on the parameters of ROI. The JHU white matter tractography atlas divides white matter fiber tracts into 20 regions. Although this method is less sensitive than voxel-based and white matter skeleton-based, the obtained results are reliable. At the same time, rather than just carrying out correlation analysis on a certain lump of differences, our study used a ROI-based analysis method to ascertain that each brain region had clear anatomical significance [12].

4.2. About the Results. These results indicated that while LCST ($P = 0.262$), FMA ($P = 0.813$), and LSLF(T) ($P = 0.878$) had the same white matter characteristics in patients with MDD as in first-degree relatives, they were not found in healthy controls. Therefore, we speculate that the impairment of LCST, FMA, and LSLF(T) is a quality indicator of MDD and that the first-degree relatives of MDD patients need more state changes to develop the disease. We also found that FMa was associated with cognitive function and that RILF was associated with physical symptom.

ATR is an important component of the cortical-thalamic-cortical circuit and is mainly involved in the execution and planning of complex behaviors, which can explain why ATR changes lead to the onset of MDD [13]. Our study showed the presence of bilateral ATR damage in MDD. Previous studies showed that the FA decrease of ATR was also found in bipolar disorder (BD), indicating that ATR plays an important role in the onset of affective disorders [14], though this may be related to the different participants. The FA reduction in LCST has been widely reported in previous studies on BD, which is similar to the findings located in

Table 5: Differences in clinical symptoms between MDD and HC.

Tests	Correlation between white matter and test scores					
	LATR	RATR	LCST	FMa	RILF	LSLF(T)
Affective symptoms	0.17	0.06	0.22	0.22	-0.13	0.03
Physical symptom	-0.03	-0.10	-0.12	-0.20	-0.42*	0.01
Spatial span	0.13	0.05	0.06	-0.37	0.18	-0.16
Visual span	-0.22	-0.15	-0.20	0.09	0.17	-0.04
Speech function	-0.11	-0.20	-0.03	0.22	0.21	-0.17
Attentional function	-0.79	-0.34	-0.03	0.13	0.21	-0.17
Delayed memory	0.24	0.35	0.15	0.43*	0.34	-0.05
Severity	0.22	0.15	0.36	0.21	0.27	-0.03

*$P < 0.05$.

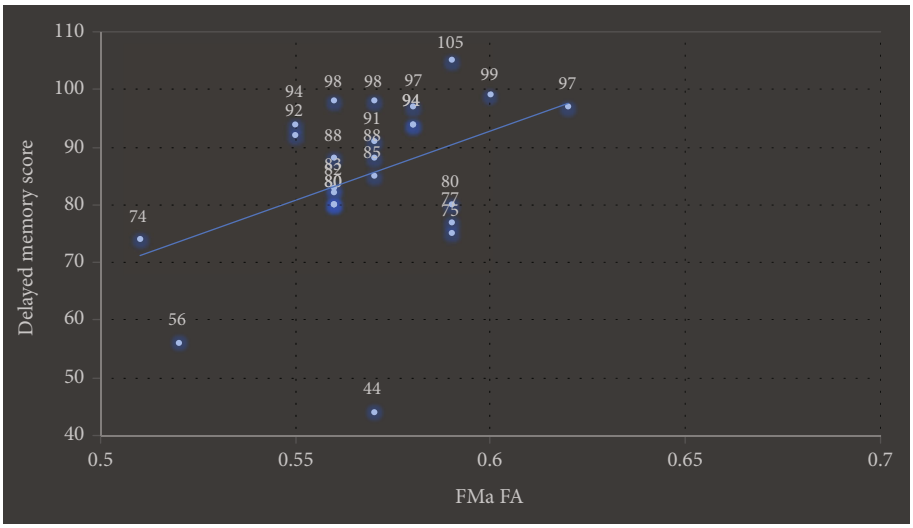

Figure 2: Dispersion of FMa FA and delayed memory score. FMa FA was positively correlated with a delayed memory score ($r = 0.43$, $P = 0.031$).

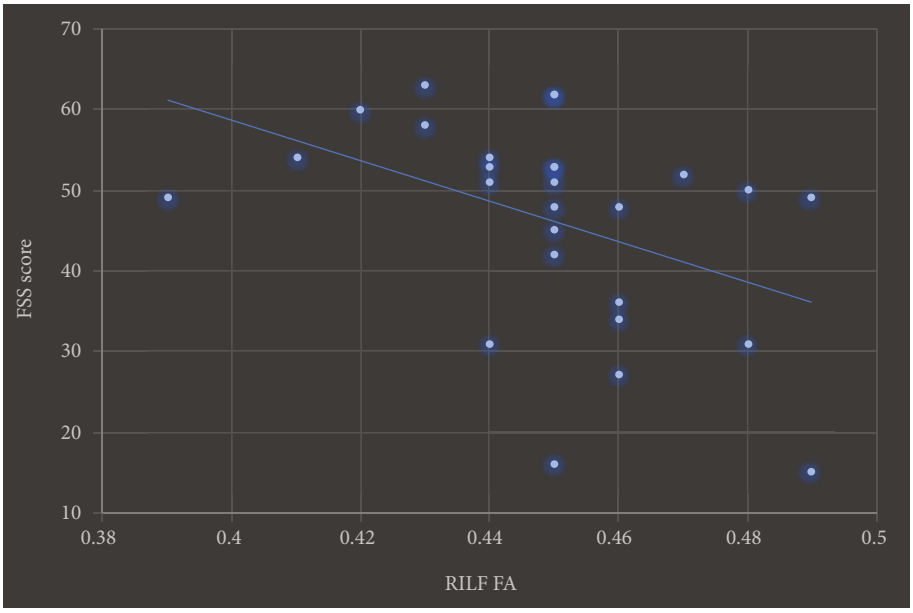

Figure 3: Dispersion of RILF FA and FSS. RILF FA was negatively correlated with total FSS score ($r = -0.42$, $P = 0.028$).

MDD in our study [15]. Chhetry et al. found that MDD remisses were associated with increased LCST FA [16]. Decreased FA of CST were also found in studies of patients with schizophrenia [17, 18]. There were also studies inconsistent with our results. Sacchet Matthew et al. obtained the MDD bilateral CST with a higher FA [19]. Meta-analysis showed that FMa reduction was a common feature of affective disorders [20]. Studies on MDD have also found that FA of FMa may be related to anhedonia [21], but our study did not find that, and this may be related to the heterogeneity of samples and different data processing methods. Previous studies have found ILF changes in MDD. Maurizio et al. found that ILF was significantly abnormal in MDD [22, 23]. FA abnormalities in LILF also exist in adolescent depression [24]. Reduced FA in LILF was found in all psychiatric disorders without distinguishing the disease types, and this change was related to the severity of the disease [25]. Our research also shows that first-degree relatives as high-risk groups have LILF anomaly, this may be related to the MDD recurrence. Studies have shown that the FA value of LSLF in MDD decreases, which is similar to our results [26]. FA changes in SLF may be related to the NETRIN1 signaling pathway [27]. Reduced FA in RSLF was found in individuals with a family history of BD [28], thereby suggesting a degree of heritability in RSLF changes. A previous review indicated that a lower FA value of ILF in Parkinson's disease patients leads to poor cognitive function, but our study did not show similar results [29].

There are many shortcomings in this study: the sample size should be expanded, and multiple methods were not used to verify the results. Of course, we did find brain imaging changes associated with the onset of MDD, and this provides the foundation for further research work.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ziwei Liu and Lijun Kang are co-first authors.

Acknowledgments

This study was supported by the National Natural Science Youth Fund Project (81601192 and 81701345), National Natural Science Foundation of China (81471379), National Key Research and Development Program of China (2016YFC1307103), Program for the Outstanding Innovative Teams of Higher Learning Institutions of Shanxi, and 136 Medical Rejuvenation Project of Shanxi Province.

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Hindawi
Neural Plasticity
Volume 2021, Article ID 7088856, 10 pages
https://doi.org/10.1155/2021/7088856

Research Article

The Interaction Effects of Suicidal Ideation and Childhood Abuse on Brain Structure and Function in Major Depressive Disorder Patients

Wei Wang,[1] Lijun Kang,[1] Nan Zhang,[1] Xin Guo,[1] Peilin Wang,[1] Xiaofen Zong,[1] Lihua Yao,[1] Hanping Bai,[1] Jing Cheng,[1] Ning Tu,[2] Hongyan Feng,[2] Gaohua Wang,[1] Lihong Bu,[2] Fei Wang,[3,4] and Zhongchun Liu[1]

[1]*Department of Psychiatry, Renmin Hospital of Wuhan University, Wuhan, Hubei, China*
[2]*PET/CT/MRI and Molecular Imaging Center, Renmin Hospital of Wuhan University, Wuhan, Hubei, China*
[3]*Early Intervention Unit, Department of Psychiatry, Affiliated Nanjing Brain Hospital, Nanjing Medical University, Nanjing, China*
[4]*Functional Brain Imaging Institute of Nanjing Medical University, Nanjing, China*

Correspondence should be addressed to Zhongchun Liu; zcliu6@whu.edu.cn

Received 16 April 2021; Accepted 17 June 2021; Published 22 July 2021

Academic Editor: Zhifen Liu

Suicidal ideation (SI) is a direct risk factor for suicide in patients with depression. Regarding the emergence of SI, previous studies have discovered many risk factors, including childhood abuse as the major public problem. Previous imaging studies have demonstrated that SI or childhood abuse has effects on brain structure and function, respectively, but the interaction effects between them have not been fully studied. To explore the interaction effect between SI and childhood abuse, 215 patients with major depressive disorder completed the Childhood Trauma Questionnaire to evaluate childhood abuse and Beck's Scale for Suicidal Ideation to evaluate SI. Then, they completed magnetic resonance imaging (MRI) within one week after completing questionnaires. Respectively, we preprocessed the structural and functional images and analyzed gray matter volumes (GMV) and mean fractional amplitude of low-frequency fluctuation (mfALFF) values. Results showed that the changes of GMV in the cuneus, precuneus, paracentric lobule, inferior frontal gyrus, and caudate nucleus and local activity in cuneal and middle temporal gyrus are in relation with SI and childhood abuse. And in left caudate, SI and childhood abuse interact with each other on the influence of GMV. That is, the influence of SI in GMV was related to childhood abuse, and the influence of childhood abuse in GMV was also related to SI. Therefore, the combination of SI and childhood abuse based on imaging should help us better understand the suicide ideation developing mechanism and propose more effective targeted prevention strategies for suicide prevention.

1. Introduction

According to the published statistics, up to 90% of those who commit suicide may have mental disorders. In addition, 50–70% of them may suffer from the major depressive disorder (MDD) [1]. Repeatedly thinking about death or self-injury and suicide prompts severe depression. Past studies have shown that persistent SI is a high-risk factor leading to suicide [2]. SI is affected by several other factors, such as age, gender, the severity of depression, impairment of social function, and family history of suicide [3, 4]. Meanwhile, past studies have reported that childhood abuse is significantly associated with an increased risk of SI. There is a greater likelihood for a person to think about suicide if he or she had suffered from severe trauma in childhood [5]. Childhood abuse includes physical and emotional abuse, neglect, and sexual abuse before the age of 16 years, which often leads to the development of serious consequences, including not only an increased risk of SI but also a huge socioeconomic burden [6–8]. The Interpersonal–Psychological Theory of Suicide

believes that childhood abuse is a risk factor for SI in adulthood [9]. Angst et al. and Björkenstam et al. also confirmed this view from their research [10, 11]. Therefore, childhood abuse can be considered to be a predictor of SI [12]. Another study of patients with depression demonstrated that patients with SI scored significantly high on emotional abuse and neglect [13]. Smith et al. [14] suggested that childhood abuse can be a powerful predictor of SI because the trauma caused by all forms of childhood abuse is associated with the lack of a sense of belonging and responsibility. At present, most studies conducted across the world focus on the impact of a single type of childhood abuse, but only a few studies have assessed the various forms of childhood abuse [15].

Previous studies have reported that the biological basis of SI in patients with MDD involves changes in the brain structure and function [16]. One clinical study has revealed that MDD patients with SI possess different functional collections in the middle frontal gyrus compared to MDD patients without SI [17, 18]. The middle frontal gyrus is involved in the acquired ability of suicide networks in men [19]. Past studies based on voxel-based morphometry (VBM) have shown that people with SI have a decreased cortical volume in the left middle frontal gyrus relative to that in healthy people [20]. Therefore, the changes in the middle frontal gyrus are believed to be an important biological marker of SI [16]. Various psychological abnormalities associated with the development of suicide indicate potential interference in the fields of cognition, execution, inhibition, and emotion. The two key brain regions responsible for processing emotional and cognitive information, especially emotional stimulation and executive function, are the amygdala and the prefrontal cortex [21, 22]. Another study reported that, when compared with healthy controls and MDD patients without SI, the gray matter volume (GMV) of MDD patients with SI was decreased in the left and right dorsolateral prefrontal cortex and in the right ventral prefrontal cortex, which further adds to the supportive evidence reported by Wang et al.'s study [23, 24]. In addition, the posterior cingulate cortex and the parahippocampal region can be considered to be interactive interfaces for emotion, cognitive assessment, and memory [25–29]. In clinical cases, reduced GMV of the frontoparietal cerebellar network was recorded in depressed patients with SI as well as decreased executive function, cognitive inflexibility, and impaired decision-making and problem-solving abilities [30–36].

Some other studies have reported that childhood abuse is associated with abnormal brain structure and function. Marshall et al. [37] found that exposure to childhood abuse can have a negative impact on brain development, often increasing the risk for the development of psychopathological symptoms. A meta-analysis based mainly on adult participants revealed that abuse is linked to reduced GMV in the prefrontal cortex and ventral superior temporal gyrus [38]. Another meta-analysis reported differences in GMV of the amygdala, but not in the hippocampus region. It was also reported that adults previously exposed to childhood abuse displayed an increase in the size of the right amygdala when compared with other adults without such an experience [39]. Overall, the most consistent findings were concentrated in the ventromedial and dorsal prefrontal cortex as well as the lateral temporal lobe cortex [40, 41]. The decrease in the cortical thickness in these areas may be related to the various forms of interruption of emotional regulation [42]. In a study based on functional magnetic resonance imaging (fMRI), the activation of the dorsolateral and dorsomedial prefrontal cortex was observed with an increase in abused adolescents during cognitive reassessment when compared with that in nonabused adolescents [43]. It can thus be inferred that childhood abuse is associated with structural and functional changes in the lateral and ventromedial frontal lobes, which may lead to behavioral and emotional control issues [44].

In the past, concerns and changes related to suicide prevention did not effectively reduce the suicide rates [45]. Identifying the risk factors and protective factors that can better predict the risk of suicide is of critical significance. Because SI occurs before a person makes suicidal attempts, identifying SI is essential to prevent the risk of suicide [46]. Meanwhile, childhood abuse is believed to be a risk factor for SI. Therefore, the combination of childhood abuse and SI based on imaging is expected to facilitate the comprehension of the mechanism of SI development and propose better-targeted successful prevention strategies for suicide prevention. We thus hypothesized that the development of SI and childhood abuse is related to the changes in the structure and function of certain brain areas, involving interaction effects between SI and childhood abuse in certain brain areas.

2. Methods and Materials

2.1. Participants and Design. All patients included in this study visited the outpatient clinic of the Renmin Hospital of Wuhan University from July 2020 to January 2021. Two experienced psychiatrists diagnosed the MDD patients based on the DSM-5 criteria. After their enrollment, the patients were explained about the study in detail and their consent was obtained. The MDD patients who signed the informed consent forms were included in the "Early warning system and comprehensive intervention for depression" (ESCID), a website employed to enroll patients with depression and to evaluate the severity of their presenting symptoms. The exclusion criteria included the following: (1) psychiatric diseases, except MDD, diagnosed according to the DSM-5; (2) history of severe head trauma or intracranial disease; (3) severe stiffness or other symptoms that could interfere with the study; (4) transcranial magnetic stimulation (TMS) or MECT treatment within 6 months; (5) pregnancy; and (6) being left-handed. Next, the patients filled the basic information in the questionnaire and underwent the following tests: Digit Symbol Substitution Test (DSST) [47], Childhood Trauma Questionnaire (CTQ) [48], and Beck's Scale for Suicidal Ideation (BSS) [49], and completed MRI within 1 week.

All the patients participating in our study were categorized into 2 groups according to their BSS test results: MDD patients without SI (MDD) and MDD patients with SI (MDD-SI). Similarly, the groups MDD1, MDD2, MDD3, MDD4, MDD5, and MDD6 were created, which included MDD patients without any childhood abuse, without emotional abuse, without physical abuse, without sexual abuse,

without emotional neglect, or physical neglect, respectively. The groups of MDD-CTQ, MDD-EA, MDD-PA, MDD-SA, MDD-EN, and MDD-PN included MDD patients with at least one type of childhood abuse, emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, respectively.

This study protocol was approved by the Ethics Committee of Renmin Hospital of Wuhan University, Wuhan, Hubei, China.

2.2. Research Instruments

2.2.1. General Information Questionnaire. The general information questionnaire asked for demographic data such as gender, age, somatic diseases, and past diagnosis and treatment.

2.2.2. DSST. The subjects were asked to fill the corresponding symbols in order within 90 s. The final score reflected the subjects' processing speed, executive functions, learning abilities, memory capacity, and attention capacity [47].

2.2.3. CTQ. A questionnaire is designed to evaluate the experience of individuals before the age of 16 years concerning emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. When the value of emotional abuse ≥ 13 or physical abuse ≥ 10 or sexual abuse ≥ 8 or emotional neglect ≥ 15 or physical neglect ≥ 10, the patient was considered to have a history of childhood abuse. When the above criteria were not met, the patient was considered to have no history of childhood abuse [48].

2.2.4. BSS. Beck et al. compiled this scale in 1979 to quantify and evaluate SI. This scale is divided into 2 parts; the first 5 questions were used to determine the presence of SI and the last 14 questions to assess the severity of SI. When the answers to questions 4 and 5 were "no," we believed that the patient had no SI within nearly 1 week. Otherwise, the patient was believed to have SI and was expected to complete the next 14 questions [49].

2.3. MRI Acquisition. MRI data was acquired at the PET center of Renmin Hospital of Wuhan University using a 3.0 T scanner (General Electric, Milwaukee, USA). Spin echo-planar imaging (EPI) sequence was used in structural imaging, with the following parameters: repetition time (TR) = 8.5 ms, echo time (TE) = 3.2 ms, preparation time = 450 ms, flip angle (FA) = 120, visual field (FOV) = 256 mm, acquisition matrix = 256 mm, slice thickness = 1 mm, slice gap = 0 mm, and locs per slab = 180. The scanning time was 4 minutes and 41 seconds. Resting-state fMRI requires subjects to be quiet, close their eyes, breathe smoothly, in a more comfortable position, without any physical movement, and do not carry out any thinking activities. EPI sequence was used, axial scanning was performed for 212 times, 32 slices, slice thickness = 3.0 mm, slice gap = 0 mm, interval = 1 mm, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, acquisition matrix = 64×64, and visual field (FOV) = $240 \times 240\ m^3$. The scanning time was 16 minutes.

2.4. Data Processing. The structural imaging data were preprocessed based on the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/) in Statistical Parametric Mapping 8 (SPM 8; https://www.fil.ion.ucl.ac.uk/spm/software/) to perform data conversion, test quality, segment and normalize, extract index, retest the quality, and smooth. The original imaging data collected were in the DICOM format and required conversion into the NIFTI format for processing. The purpose of segment and normalization was to separate the gray matter, white matter, and cerebrospinal fluid and to ensure that the images of all subjects were in the same space, and the anatomical positions corresponding to the same coordinates were consistent. The normalization process was conducted by the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm to the Montreal Neurological Institute (MNI) template. We then extracted the GMV of all the subjects. All structural images were smoothed with an 8 mm full-width at the half-maximum (FWHM) Gaussian filter.

The Restplus V1.2 toolbox in SPM 12 was used to preprocess the resting-state fMRI data. After data conversion, the first 10 volumes were discarded to reach the steady state. In addition, we conducted slice timing to complete the time-level correction. The spatial-level correction includes realignment and normalization. The subjects with excessive head movement (>3 mm or >30) according to the realignment parameter were excluded. Normalization was performed using the DARTEL algorithm to the MNI template. All functional images were smoothed with a 6 mm full-width at a half-maximum (FWHM) Gaussian filter. Then, we performed detrend, nuisance covariate regression, and filtering (0.01–0.08 Hz). The values of mALFF could be extracted using the above processes.

The abovementioned operations were conducted in the MATLAB R2013b platform (MathWorks, Sherborn, MA, USA).

2.5. Statistical Analyses. The difference in the gender and the results of CTQ between the MDD group and the MDD-SI group was calculated by Chi-square analysis. The Mann–Whitney U-test was applied to measure the differences in age between the 2 groups. The difference between the 2 groups regarding the DSST results was explored by 2 independent sample t-test. The abovementioned analysis was completed using the IBM SPSS Statistics (Version 26.0). The analysis of GMV and mfALFF was executed in SPM 12 by a two-sample t-test and full factorial. Post hoc analysis of the region of interest (ROI) was conducted in Restplus V1.2 based on the MATLAB R2013b and IBM SPSS Statistics (Version 26.0) by analysis of variance (ANOVA) and pairwise comparison. Imaging findings were considered to be significant at $P < 0.001$, corrected by the Gaussian random field (GRF) correction, while the other findings were considered to be significant at $P < 0.05$.

3. Results

3.1. Differences in Demographics and Clinical Characteristics. A total of 215 patients were enrolled in the study, of which 18 did not complete the BSS questionnaire, 2 did not complete the CTQ questionnaire, and 30 could not undergo MRI due

Table 1: Differences in demographics and clinical characteristics.

		MDD		MDD-SI		$\chi^2/Z/t$	P
		n	%	n	%		
Gender	Female	30	20.83	114	79.17	0.696	0.404
	Male	14	26.42	39	73.58		
First episode	No	25	29.41	60	70.59	4.316	0.038*
	Yes	19	16.96	93	83.04		
Head motion (>3 mm or > 3 degree)	No	27	22.13	95	77.87	0.461	0.734[a]
	Yes	2	14.29	12	85.71		
CTQ	No	20	25.97	57	74.03	1.139	0.286
	Yes	23	19.49	95	80.51		
Emotional abuse	No	34	24.29	106	75.71	1.442	0.230
	Yes	9	16.36	46	83.64		
Physical abuse	No	34	21.52	124	78.48	0.137	0.711
	Yes	9	24.32	28	75.68		
Sexual abuse	No	39	23.49	127	76.51	1.352	0.245
	Yes	4	13.79	25	86.21		
Emotional neglect	No	25	25.0	75	75.00	1.038	0.308
	Yes	18	18.95	77	81.05		
Physical neglect	No	27	24.32	84	75.68	0.775	0.379
	Yes	16	19.05	68	80.95		
Age (median) ($P_{25} \sim P_{75}$)		23 (22~31)		23 (21~26)		-1.791[b]	0.073
HAMD-17 (median) ($P_{25} \sim P_{75}$)		14 (7~20)		21 (16~25)		-4.530[b]	<0.001*
DSST (mean ± SD)		69.67 ± 2.42		60.42 ± 1.68		2.531[c]	0.013*

*$P < 0.05$ means significant difference. [a]Fisher's exact test; [b]Z score of age; [c]t score of DSST.

to scheduling issues. Of the 185 patients who underwent MRI, 16 showed obvious abnormalities in the brain structure, such as the transparent septum, and 19 failed to obtain their fMRI images. The reasons for the same included the patient's inability to complete the entire examination process and the loss of data during data transfer. According to the BSS results, there were 44 individuals in the MDD group (22.34%) and 153 in the MDD-SI group (77.66%). According to the CTQ outcomes, there were 130 (61.03%) participants who had experienced abuse in their childhood and 83 (38.97%) who had not experienced any type of abuse. Specifically, 55 (28.21%) individuals experienced emotional abuse, 37 (18.97%) physical abuse, 29 (14.87%) sexual abuse, 95 (48.72%) emotional neglect, and 84 (43.08%) physical neglect. The results revealed no significant difference with respect to age, gender distribution, head motion, and exposure rates of various types of childhood abuse cases ($P > 0.05$) between the MDD group and the MDD-SI group. The proportion of SI in first-onset patients was higher ($\chi^2 = 4.316$, $P = 0.038$). When compared with patients with low scores, those with high HAMD-17 scores included a higher proportion of patients with SI ($Z = -4.530$, $P < 0.001$). In addition, in patients with SI, the DSST score was lower ($t = 2.531$, $P = 0.013$) (Table 1).

3.2. Differences in GMV. We noted differences in GMV among the groups MDD1 and MDD-CTQ, MDD5 and MDD-EN, and MDD6 and MDD-PN in the left cuneus ($T = -3.899$, $P < 0.001$; $T = -4.053$, $P < 0.001$; $T = -3.536$, $P < 0.001$). In the left paracentral lobule, the GMV of the MDD-PA group was significantly larger than that of the MDD3 group ($T = -3.955$, $P < 0.001$). In terms of MDD patients with sexual abuse, the GMV of MDD patients without sexual abuse was larger in the left triangular portion of the left inferior frontal gyrus ($T = 4.1578$, $P < 0.001$). Moreover, a difference of GMV was also noted in the left precuneus between the MDD5 and MDD-EN groups ($T = 4.558$, $P < 0.001$). The GMV of patients with SI was significantly smaller than that of patients without SI in the right lingual gyrus ($T = 3.777$, $P < 0.001$). The results of full factorial between SI and childhood abuse suggested differences in the left caudate ($T = 13.589$, $P < 0.001$). Post hoc analysis revealed that, in the left caudate, the GMV of nonSI-nonCTQ was larger than that of nonSI-CTQ ($I - J = 0.173$, $P = 0.003$) and SI-nonCTQ ($I - J = 0.104$, $P = 0.040$), while that of nonSI-CTQ was smaller than that of SI-CTQ ($I - J = -0.122$, $P = 0.006$) (Tables 2 and 3; Figures 1 and 2).

3.3. Differences in mfALFF. The mfALFF value of the MDD-PA group was significantly lower than that of the MDD3 group in the left cuneus ($T = 4.514$, $P < 0.001$), while that of the MDD-SA group was lower than that of the MDD4 group in the left middle temporal gyrus ($T = 4.238$, $P < 0.001$). However, there were no significant results based on the full factorial experiment ($P > 0.001$; Table 4).

Table 2: Differences in GMV.

Group 1 : Group 2	Region	Voxel	MNI coordinates			T/F values
			X	Y	Z	
MDD1 : MDD-CTQ	Cuneus (L)	407	-10.5	-79.5	39.0	-3.8990
MDD3 : MDD-PA	Paracentral lobule (L)	534	-9.0	-37.5	66.0	-3.9553
MDD4 : MDD-SA	Frontal-Inf-Tri (L)	642	-46.5	28.5	7.5	4.1578
MDD5 : MDD-EN	Cuneus (L)	201	-10.5	-79.5	28.5	-4.0525
	Precuneus (L)	628	-4.5	-52.5	52.5	4.5582
MDD6 : MDD-PN	Cuneus (L)	225	-18.0	-70.5	22.5	-3.5359
MDD : MDD-SI	Lingual (R)	184	13.5	-48.0	-3.0	3.7768
SI∗CTQ[a]	Caudate (L)	77	-16.5	21.0	10.5	13.5885

[a]Interaction effect of SI and childhood abuse. Notes: MDD patients without any kind of childhood abuse (MDD1); MDD patients with any kind of childhood abuse (MDD-CTQ); MDD patients without physical abuse (MDD3); MDD patients with physical abuse (MDD-PA); MDD patients without sexual abuse (MDD4); MDD patients with sexual abuse (MDD-SA); MDD patients without emotional neglect (MDD5); MDD patients with emotional neglect (MDD-EN); MDD patients without physical neglect (MDD6); MDD patients with physical neglect (MDD-PN); MDD patients without suicidal ideation (MDD); MDD patients with suicidal ideation (MDD-SI).

Table 3: Post hoc analysis of interaction between SI and childhood abuse.

	$I - J$	P	CI (95%)
nonSI-nonCTQ vs. nonSI-CTQ	0.173	0.003*	0.0579~0.2876
nonSI-nonCTQ vs. SI-nonCTQ	0.104	0.040*	0.0051~0.2039
nonSI-nonCTQ vs. SI-CTQ	0.050	0.286	-0.0424~0.1429
nonSI-CTQ vs. SI-nonCTQ	-0.068	0.150	-0.1615~0.0250
nonSI-CTQ vs. SI-CTQ	-0.122	0.006*	-0.2085~-0.0365
SI-nonCTQ vs. SI-CTQ	-0.054	0.096	-0.1182~0.0098

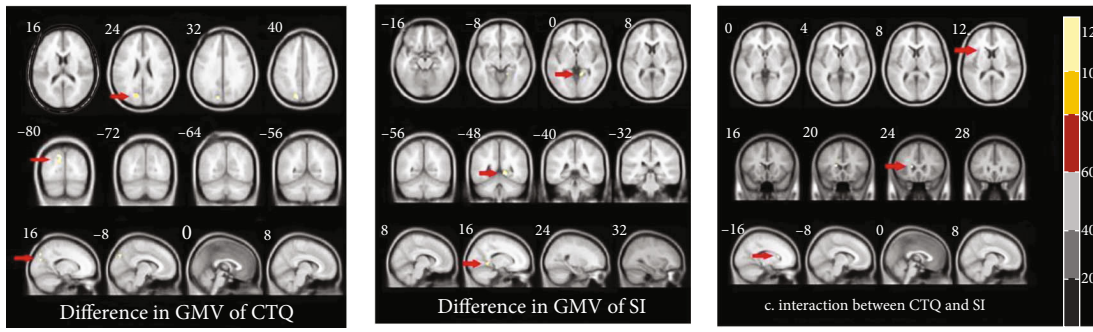
*$P < 0.05$ means significant difference.

4. Discussion

Our demographic analyses revealed no significant difference in the distribution of sex, age, head motion, and incidence of childhood abuse between the MDD and MDD-SI groups. As such, our results conform to those of previous studies partially. A clinical study revealed that age was not significantly associated with SI within the past 4 weeks, although it was negatively correlated with SI within the past 1 year; however, there was no significant correlation with respect the gender and SI [50]. Another study by Eswatini revealed that women of age 25–34 years were more likely to develop SI [51]. Some past studies have also suggested that the impact of gender on SI is related to puberty, as this gender difference was not observed in prepubertal youth; on the other hand, the incidence of SI in women (15.7%) was higher than that in men (12.4%) after puberty [52]. However, with regard to the incidence of childhood abuse, our results were not completely consistent with those of previous studies. A large-sized clinical study on pregnant women revealed that pregnant women with a history of childhood abuse had a high risk of developing SI, especially when they had been subjected to emotional abuse, physical abuse, and sexual abuse [53]. A meta-analysis reported that childhood abuse was associated with an increase in SI occurrence, but a higher heterogeneity was reported by only a few studies [54]. The difference in the inferences reported by different studies may be related to the difference in the cultural backgrounds, economic development levels, sample size, and research standards across the studies.

The DSST score of the MDD patients with SI was significantly lower than that of MDD patients without SI. This observation was generally consistent with that reported by previous studies, many of which suggested that SI is associated with neurocognitive impairment, especially inattention, memory loss, and executive function, such as response inhibition and impaired decision-making [55–58]. Therefore, the early identification of defects of attention, memory, and executive functions may provide an opportunity for early intervention to prevent SI occurrence. People with SI respond to real events in a desperate cognitive schema, with the belief that the difficulties encountered will not be resolved in the future and will not tolerate pain [50]. In other words, cognitive intervention is of great significance toward reducing SI. Specific interventions in cognition such as attention, impulse, problem-solving, and decision-making can maximize the advantages of existing SI-intervention methods [59].

The results of the VBM-based study revealed that the GMV in the left cuneus of MDD patients with prior experience of childhood abuse was larger than that of those who had not experienced any childhood abuse. Previous studies have also indicated that childhood abuse can lead to changes in the brain structure, although the specific structural changes recorded vary from a study to another. Past studies have also shown that childhood abuse is associated with decreased GMV in the hippocampus, corpus callosum, and prefrontal cortex [60–62]. Other scholars believe that different types of abuses may have common neurobiological consequences and that the affected children may feel reduced pain because of the weakening of the development of the sensory system and pathways that transmit disgust and traumatic experiences [63, 64]. However, the analysis of the interaction effects between SI and childhood abuse based on VBM revealed that the influence of SI on the GMV of left caudate changes with whether there is childhood abuse or not.



(a) (b) (c)

Figure 1: Differences in GMV. (a) Difference in GMV between MDD1 and MDD-CTQ in left cuneus. (b) Difference in GMV between MDD and MDD-SI in right lingual. (c) Interaction between CTQ and SI in left caudate.

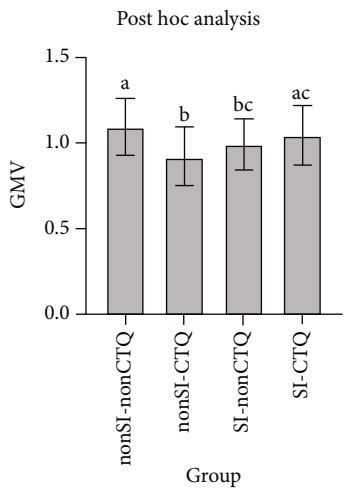


Figure 2: GMV of ROI extracted according to interaction effect. Notes: nonSI-nonCTQ: MDD patients without suicidal ideation and childhood abuse; nonSI-CTQ: MDD patients without suicidal ideation but with childhood abuse; SI-nonCTQ: MDD patients with suicidal ideation but without childhood abuse; SI-CTQ: MDD patients with suicidal ideation and childhood abuse.

Previous studies have also demonstrated that the caudate nucleus is related to reward-processing and decision-making abilities, while childhood abuse and suicide are related to reward processing alone, which is consistent with our present results to a certain extent [65–67]. From the perspective of imaging, this finding indicates an evident correlation between childhood abuse and SI. This finding also reminds us that taking effective measures to reduce the incidence of childhood abuse may reduce the overall risk of suicide in the future.

Although there was no significant difference in the brain structure between MDD patients with emotional abuse and those without that experience, we noted that GMV in the left cuneus and precuneus of MDD patients with emotional neglect was significantly lower than that in MDD patients without emotional neglect. The results of the fMRI-based study showed that the local activity in the left cuneus of MDD patients with the experience of physical abuse was lower than that of MDD patients without this experience. The precuneus is a part of the default mode network (DMN) that participates in the processing of introspection and emotions [68]. The precuneus plays an important role in visuospatial imagery, episodic memory retrieval, and self-processing operations [69]. Previous studies have revealed that the structural and functional changes of the cuneus and precuneus are related to the differences in memory-related metacognitive abilities among different individuals [70]. This effect was also confirmed through a noninvasive low-frequency TMS study conducted in the precuneus [71]. When compared with MDD patients without the experience of physical abuse and physical neglect, those MDD patients with these experiences had greater GMV in the paracentric lobule and cuneus, respectively. The paracentric lobule is related to the movement and sensation of the lower limbs. At present, no direct relationship between this brain region and childhood abuse has been reported, although it may provide a new direction for further research. A large sample-sized study conducted in the community suggested the most significant reduction in the GMV of the right medial frontal gyrus in individuals with early exposure to severe corporal punishment [72]. Past studies on the brain regions mentioned earlier have reported that these areas are involved in addiction, suicide-related behavior (include SI), depression, and posttraumatic stress disorder (PTSD) [73–75]. However, these studies did not determine whether the observed differences in the GMV of the brain regions can be attributed to the cause or consequence of physical abuse.

The MDD patients with sexual abuse showed smaller GMV in the triangular portion of the left inferior frontal gyrus than in MDD patients without sexual abuse. The function of the prefrontal cortex is related to cognitive, emotional, pain, and behavioral management. Meanwhile, when compared with MDD patients without sexual abuse, patients with sexual abuse demonstrated lower local activity in the middle temporal gyrus. However, the results of previous studies are not completely consistent with our present studies. This difference can be possibly attributed to the fact that the decrease in the GMV of the abovementioned brain regions may precede the existence of sexual abuse and may exist as a risk factor. However, there exists no favorable evidence to support this conjecture [76].

The GMV in the lingual gyrus of MDD patients without SI was significantly higher than in those with SI, albeit no significant results were noted in their respective fMRI.

Table 4: Differences in mfALFF.

Group 1 : Group 2	Region	Voxel	MNI coordinates			T values
			X	Y	Z	
MDD3 : MDD-PA	Cuneus (L)	132	12.0	-90.0	24.0	4.5144
MDD4 : MDD-SA	Temporal-Mid (L)	39	-48.0	-60.0	0	4.2377

Notes: MDD patients without physical abuse (MDD3); MDD patients with physical abuse (MDD-PA); MDD patients without sexual abuse (MDD4); MDD patients with sexual abuse (MDD-SA).

Past studies support that changes in the brain structure and function are associated with an increased risk of SI, although there exist some inconsistent results for these specific areas with changes [77]. The lingual gyrus is mainly responsible for vision, especially with the processing of letters, and may be involved in logical analysis and visual memory processing. A clinical study revealed that MDD patients without SI have stronger functional connectivity in the lingual gyrus than MDD patients with SI [78]. Although our results are consistent with the findings of some past studies, there exists no evidence strong enough to support the results. However, our result suggests that the lingual gyrus demands more attention, which should be covered in future studies on SI. The results of another ROI-based study are partly consistent with these previous studies, in that the GMV in the left dorsolateral prefrontal cortex of MDD patients with SI is smaller than that of patients without SI [23]. Several past studies have suggested that the dorsal striatum plays a unique role in reflecting SI and have emphasized the importance of imaging methods to detect SI in adolescents [79]. Although the imaging changes in MDD patients with SI are not particularly clear, further technological developments and studies should be able to provide a more convenient and accurate method for the evaluation of SI.

5. Conclusion

MDD patients with SI have reduced GMV in the lingual gyrus, while the GMV and mfALFF value of patients who had experienced childhood abuse in the cuneus, precuneus, paracentral lobule, and inferior frontal gyrus also changed. In MDD patients, the influence of SI on the GMV of the caudate varies with whether there is childhood abuse or not. These findings cumulatively reflect on the association between childhood abuse and SI from the perspective of imaging. However, further research is warranted to determine the biomarkers that produce SI as well as to ascertain the complete pathway connecting childhood abuse with SI.

6. Limitation

First and foremost, compared with previous imaging studies, our sample size is sufficient, but due to the large incidence of SI and small incidence of various types of childhood abuse, the proportion of the case group and the control group is not perfectly balanced, and the sample size can be expanded in further study. Second, because the clinical study involves the changes of the patient's condition, we ask only for no TMS and MECT treatment in the past 6 months but do not limit their use of drugs. So, the effects of drugs cannot be ruled out. Third, the patients' SI and childhood abuse are evaluated by the self-rating scale, and there may be deviations when recalling, which is inevitable. Fourth, although we rule out other mental disorders that meet the DSM-5 criteria, MDD patients are often accompanied by other symptoms, such as anxiety, obsessive-compulsive, and other symptoms. It is impossible to completely rule out all these. Fifth, our study is conducted only in patients with MDD, so our results are only applicable to patients with MDD and cannot be extended to the community population.

Data Availability

The data used in this study to support our findings are questionnaires and DICOM statistics, and they are available from the corresponding authors on reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

We thank all participants of this study. We are also grateful to professor Zhongchun Liu for his contribution to the construction of ESCID, we thank Lijun Kang for her suggestion on data analysis methods, and we thank Yake Xu, Nan Zhang, Simeng Ma, Peilin Wang, and Shuxian Xv for their help in the research process.

Acknowledgments

This work was supported by the National Key R&D Program of China (grant number: 2018YFC1314600), the National Natural Science Foundation of China (grant number: 81771472), the National Science Fund for Distinguished Young Scholars (81725005 to Fei Wang), and the National Natural Science Foundation Regional Innovation and Development Joint Fund (U20A600012 to Fei Wang).

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Hindawi
Neural Plasticity
Volume 2021, Article ID 6619515, 8 pages
https://doi.org/10.1155/2021/6619515

Review Article

Role of BDNF-mTORC1 Signaling Pathway in Female Depression

Xianquan An,[1] Xiaoxiao Yao,[1] Bingjin Li,[1] Wei Yang,[1] Ranji Cui,[1] Guoqing Zhao,[2] and Yang Jin[1]

[1]*Jilin Provincial Key Laboratory on Molecular and Chemical Genetic, Second Hospital of Jilin University, Changchun 130041, China*
[2]*China-Japan Union Hospital of Jilin University, China*

Correspondence should be addressed to Guoqing Zhao; guoqingzhao1965@163.com and Yang Jin; jy18@mails.jlu.edu.cn

Received 23 November 2020; Accepted 22 January 2021; Published 9 February 2021

Academic Editor: Roberto Esposito

Depression is a common psychological and mental disorder, characterized by low mood, slow thinking and low will, and even suicidal tendencies in severe cases. It imposes a huge mental and economic burden on patients and their families, and its prevention and treatment have become an urgent public health problem. It is worth noting that there is a significant gender difference in the incidence of depression. Studies have shown that females are far more likely to suffer from depression than males, confirming a close relationship between estrogen and the onset of depression. Moreover, recent studies suggest that the brain-derived neurotrophic factor- (BDNF-) mammalian target of rapamycin complex-1 (mTORC1) signaling pathway is a crucial target pathway for improving depression and mediates the rapid antidepressant-like effects of various antidepressants. However, it is not clear whether the BDNF-mTORC1 signaling pathway mediates the regulation of female depression and how to regulate female depression. Hence, we focused on the modulation of estrogen-BDNF-mTORC1 signaling in depression and its possible mechanisms in recent years.

1. Introduction

Depression is a kind of mood disorder characterized by persistent depression, slow thinking, and decreased will activity. It is worth noting that the incidence of depression has significant gender differences. Because of the physical and social characteristics, the number of women suffering from depression worldwide is about twice that of men [1]. After puberty, females are more likely to suffer from depression than males, and the prevalence rate of females is significantly higher than men [2]. Other studies have shown that females exhibit depressive-like behaviors during periods of rapid estrogen decline, such as premenstrual, prenatal, postpartum, and perimenopausal periods [3–5]. Therefore, the function and regulation of estrogen are inevitably closely involved in the incidence of depression.

There is convincing scientific evidence that estrogen has neuroregulatory and neuroprotective effects, which are directly related to emotion. Studies have shown that estrogen levels in depressed females are lower than those in normal females, and persistently low levels of estrogen are closely related to the occurrence of depression. Estrogen can directly act on related brain regions and regulate the expression of target genes related to emotional and cognitive functions through classical nuclear receptor pathways. Preclinical studies have shown that bilaterally ovariectomized mice can be used as an effective estrogen deficiency-induced depression animal model and show a significant increase in depressive-like behaviors in the forced swimming test [6, 7]. 17β-Estradiol increased the expression of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex (PFC), alleviated despair, and enhanced pleasure in ovariectomized female mice [8]. Depressive behaviors in females during the rapid decline of estrogen levels are closely related to the widespread distribution of estrogen receptors in emotionally related brain areas such as the hippocampus, PFC, and amygdala [9, 10]. At the same time, the antidepressant-like effects induced by 17-estradiol were absent in estrogen receptor β knockout mice but did not show significant changes in α-receptor knockout mice [11]. The increase of depression-like behavior in mice induced by estrogen deficiency was mainly related to the estrogen receptor. Clinically, the susceptibility to depression

increases during the transitional period of menopause and early after the last menstruation [12]. Moreover, the quality of life of postmenopausal depression patients is significantly lower [13]. But evidence from clinical studies suggests that hormone treatment, especially estradiol, has successfully alleviated depression [14, 15]. Depressive symptoms in young men were also involved with elevated estradiol levels [16]. These data further support the view that estrogen levels are critical in the pathobiology of affective disorders.

2. BDNF-mTORC1 Signaling Pathway

BDNF is a member of neurotrophic factors, a family of proteins that are essential for the growth and survival of neurons. It is playing an increasingly pivotal part in the pathophysiology of depression and the therapeutic mechanism of related antidepressants. Preclinical studies have shown that bilateral ovariectomy as an effective depression model induced by estrogen deficiency significantly decreased BDNF levels in the hippocampus and PFC [9, 10]. This suggested that increased depressive-like behaviors in mice induced by estrogen deficiency are primarily related to ERβ. Further studies found that the BDNF level in the brain of estrogen receptor β knockout mice was remarkably reduced, while that in the brain of estrogen receptor α knockout mice was little changed [17]. Therefore, the estrogen receptor β-BDNF signaling pathway may mediate the regulation of depressive-like behaviors in female mice.

mTORC1 is a major growth regulator, whose signal pathway is closely related to synaptic plasticity; that is, it affects dendrites and dendritic spines by controlling the synthesis of proteins related to synaptic formation [18]. Hence, the mTORC1 signaling pathway is closely related to the synaptic structure and function plasticity. Researchers found that inhibition of the mTOR signal delayed the onset of puberty in female rats to some extent [19]. Moreover, expression decrease of mTORC1 and its upstream or downstream proteins, as well as inhibition of 1synaptic growth and regulation, in brain regions such as the hypothalamus, PFC, and hippocampus of ovariectomized murine, was reversed by estrogen administration [20–22]. These mean that the mTOR signaling pathway is indeed related to the regulation of estrogen, particularly in the central nervous system (CNS). Beyond that, downregulation of the mTORC1 pathway and synaptic changes have also been found in a variety of other models of depression in murine [23–25]. Likewise, clinical studies have also found decreased levels of mTORC1 expression and decreased synaptic formation in the PFC of depressed patients [26]. All of these indicate that the antidepressant effects mediated by the mTORC1 signaling pathway may also be closely related to the classical neural circuit.

Although there is no evidence to suggest a specific mechanism by which estrogen regulates mTORC1, BDNF is a key regulator. Recent researches have led to discoveries that the considerable upstream pathways of mTOR in the brain are PI3K/Akt/mTORC1 [27], MEK/ERK/mTORC1 [28], and LKB1/AMPK/mTORC1 [29]. As the upstream of LKB1 activation, the role of extracellular BDNF is realized by the upregulation of intracellular cAMP [30]. Meanwhile, chronic restraint stress reduced levels of mTORC1 and its downstream effectors such as 4E-BP-1 and p70S6K in the rat hippocampus, which is antagonized by antidepressants, escitalopram and paroxetine [31].

BDNF has been shown to affect the nervous system through the BDNF-mTORC1 pathway. In several reports, ketamine and scopolamine enhance the number and maturity of synapses by activating the BDNF-mTOR pathway to upregulate the expression of various synapse-related proteins, while blocking mTOR signals can completely interrupt the occurrence and behavioral response of these synapses [32–35]. It may be a unique fast-acting antidepressant mechanism. Studies have also manifested that hypidone hydrochloride activates pyramidal neurons by relieving the inhibitory effect of 5-HT_{1A} receptors on GABAergic neurons and then acts on the BDNF-mTORC1 pathway to exert an antidepressant role [36, 37]. These findings make mTORC1 an attractive therapeutic target for depression. For example, NV-5138, a novel antidepressant (a mTORC1 activator), enhances mTORC1 signaling and increased the number, function, and protein levels of synapses in the PFC, in which BDNF is required to participate [38]. In turn, the fast-acting antidepressant effects of ketamine and its active metabolite (2R,6R)-hydroxyketamine were blocked by BDNF function-blocking antibody or rapamycin [39, 40], a classical inhibitor of the mTORC1 [41], suggesting that researches on mTORC1 will help in the further development of antidepressants.

3. Role of BDNF-mTOR1 Signaling Pathway in Depression

3.1. BDNF-mTORC1 Signaling Pathway and Rapid Antidepressant Effects. Briefly, the potential mechanism of rapid antidepressant action of the BDNF-mTORC1 signaling pathway may be as follows: first, glutaminergic neurons release glutamate by inhibiting the activity of GABA interneurons; then, the AMPA receptor and VDCC were further activated to promote the release of BDNF; finally, the release of BDNF activates TrkB, Akt, ERK, AMPK, etc., and then activates the mTORC1 pathway, which promotes increases in proteins involved in synaptic formation (e.g., GluA1 and PSD95) and further increases the frequency and amplitude of the excitatory postsynaptic current (EPSC), thus promoting the growth of neurons and synapses to play an antidepressant-like role [34, 42, 43]. Although the mTORC1 pathway is considered to be an effective therapy for depression at present, there is still a separate report in which mTORC2, but not mTORC1, is required for hippocampal mGluR-LTD and associated behaviors [44], and further research is needed to investigate the role of mTORC2.

3.2. BDNF-mTORC1 Signaling Pathway and Autophagy. Autophagy is a conservative process of maintaining cellular energy and protein homeostasis [45]. It can effectively eliminate damaged proteins and organelles associated with certain diseases [46], but overactivated autophagy can also damage cells. Therefore, whether autophagy plays a positive or negative role in regulating neurological diseases is still a matter of debate [47]. What is certain is that autophagy dysfunction may lead to a variety of neurological disorders, such as

depression, epilepsy, and Alzheimer's disease [48–50]. mTORC1 is a key molecule in autophagy, which can inhibit autophagy by competitively occupying ULK1 [51]. Its activated pathways such as Akt and MAPK signaling pathways inhibit autophagy, while negatively regulated pathways such as AMPK and P53 signaling pathways promote autophagy [52–54]. This indicates that mTOR is a key regulatory component in the relationship between depression and autophagy. And the mTOR signaling pathway indeed exerts neuroprotective effects by regulating autophagy and inducing nerve regeneration by promoting protein synthesis [55].

According to studies, autophagy regulates depression bidirectionally. On the one hand, obvious excessive autophagy activation during some depression results in the decline of the survival rate of neurons and glial cells and neuronal apoptosis [56]. Some antidepressants effectively function by improving this activated autophagy through the mTOR pathway [57]. Patchouli alcohol can inhibit excessive autophagy, repair synapses, and restore hippocampal autophagy flux by activating the mTOR signaling pathway, thus preventing depressant-like behaviors induced by CUMS [58]. Interestingly, BDNF promotes neuron survival by activating mTOR signaling to improve excess autophagy flux [59]. Besides, the BDNF-TrkB pathway also participates in the regulation of autophagy. For instance, the BDNF-TrkB pathway regulates antidepressant-like actions of H2S and fluoxetine by enhancing hippocampal autophagy [49, 60]. The neuroprotection of BDNF in vitro is also performed by inhibiting autophagy through the PI3K-Akt-mTOR pathway [53]. The regulation of autophagy by local BDNF-mTOR may also affect synaptic plasticity since the suppression of mTOR in stimulated neurons causes AMPA receptor degradation in spines through autophagy [52].

On the other hand, it has also been proved that autophagy between neurons is impaired in depression, which can be alleviated by pharmacologic enhancement of autophagy [61]. The majority of antidepressants may kick in through the upregulation of autophagy [62]. Ketamine, a quick-acting antidepressant, is an example [63], although its enhancement of mTOR activity has been confirmed. As one of the most abundant and bioactive constituents in vitamin E, α-tocopherol showed antidepressant-like effects on mice through the upregulation of autophagy mediated by the mTOR-AMPK pathway [54]. Trehalose may work on depression due to its ability to enhance autophagy as well [64]. Therefore, the BDNF-mTORC1 pathway can indeed regulate depression through autophagy, but its specific mechanism remains to be studied.

3.3. BDNF-mTORC1 Signaling Pathway and Monoamine Neurotransmitters. According to the monoaminergic hypothesis, lack of monoamine neurotransmitters such as 5-HT, DA, and NE in the brain may cause depression [65]. Estrogen deficiency has been shown to have significant effects on monoaminergic systems, including 5-HT, DA, and NE [66]. As an instance, the anxiety-like behavior caused by food restriction may be mediated by the decreased activation of estrogen receptor β in the serotonergic dorsal raphe nucleus neurons, which may be due to the decrease of the estrogen level [67]. It has been found that the disturbance of estrogen balance during menopause results in the imbalance of the BDNF-5-HT_{2A} signal and the decrease of synaptic plasticity, which puts the brain in a depressed state [17]. Furthermore, 17β-estradiol preferentially acts as an antidepressant by regulating levels of multiple neurotransmitters, dopaminergic receptors, serotonergic receptors, and the sigma-1 receptors expressed in the CNS to regulate neurotransmitter systems [68–70]. Thus, the monoaminergic system exerts the vital regulatory part in female depression.

Studies have shown that the rapid activation of the mTOR pathway is a significant medium for the rapid antidepressant action of ketamine and scopolamine [34]. Other studies have revealed that selective stimulation of the 5-HT_{1A} receptor in the medial PFC has also been shown to alleviate depressant-like behaviors [71, 72]. This may be through the activation of the AMPA receptor-BDNF-mTOR signal, thereby enhancing the synaptic function of mPFC [73]. In another study, scopolamine can increase the concentration of 5-HT and dopamine neurotransmitter system in the brain and cause delirium symptoms, while selective 5-HT_{1A} antagonist reverses it to some extent through the induction of PI3K-Akt-mTORC1 [74]. Besides, the inhibition of rapamycin on the Akt-mTOR pathway blocked the change of 5-HT_{2AR} signal transduction mode [75]. 20(S)-Protopanaxadiol and liquiritigenin may also have antidepressant effects through normalization of monoamine neurotransmitter and corticosterone (CORT) levels and enhancement of the BDNF-mTOR pathway [76, 77]. The interaction between the 5-HT_6 receptor and mTOR pathway was also found; that is, 5-HT_6 receptor activation can increase mTOR signal in rodent PFC. In connection with cognitive impairment, rapamycin, an mTOR inhibitor, can reverse the increase of mTOR activity in PFC like a 5-HT_6 antagonist, thus improving cognitive disorder induced by 5-HT_6 agonists [78]. All these demonstrated the interaction between the BDNF-mTORC1 pathway and the monoaminergic system in the occurrence and treatment of depression.

3.4. BDNF-mTORC1 Signaling Pathway and Neuroendocrine System. Hyperactivity and stress feedback disorder of the HPA axis is particularly considerable in the pathogenesis of depression, which may be improved by regulating the homeostasis of the HPA axis. On the one hand, there is a close relationship between the activities of the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonad (HPG) axis, and they interact in estrogen-mediated affective disorders. CNS regulates the synthesis and secretion of estrogen through the HPG axis, while estrogen regulates the functions of the pituitary and hypothalamus through the HPA axis in a feedback way, thus affecting the levels of stress hormones like corticotropin- (ACTH-) releasing hormone, ACTH and CORT [79], and thereby relieving the emotional stress of postmenopausal women [80].

On the other hand, studies have confirmed that neurotrophins such as BDNF are involved in neuroendocrine regulation [81]. An early study in adult rats found that continuous BDNF administration into the ventricle affected activity and biological rhythm of the HPA axis [82]. In a later study, knockdown of BDNF by siRNA in rats inhibited the expression

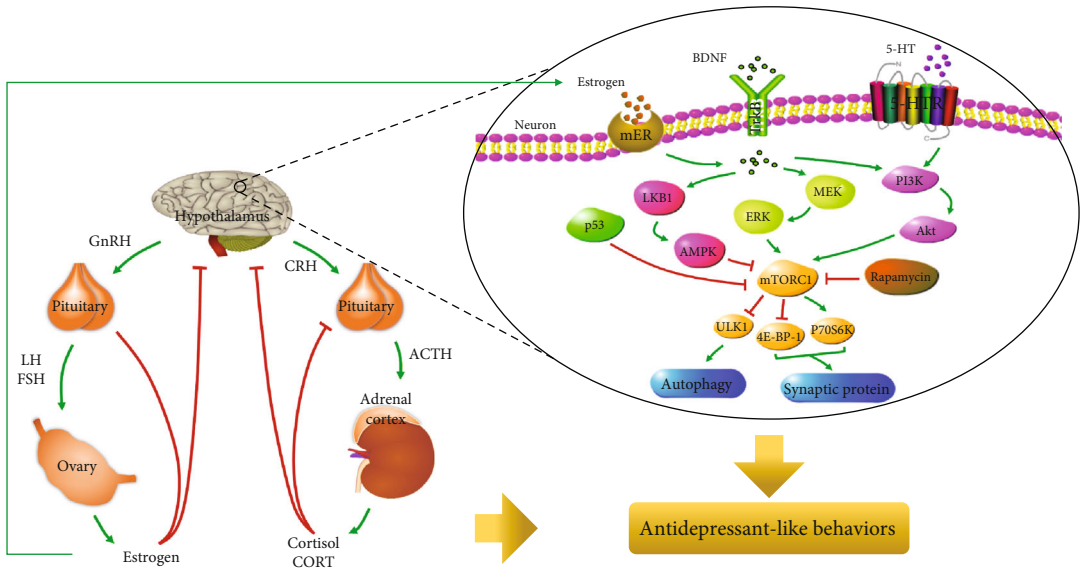

Figure 1: The regulatory effects of the estrogen-BDNF-mTORC1 signaling pathway in depression. Green arrows indicate activation; T-shaped red arrows indicate inhibition. Abbreviations: 5-HTR: 5-hydroxytryptamine receptor; ACTH: corticotropin; AMPK: AMP-activated protein kinase; Akt: serine/threonine protein kinase; BDNF: brain-derived neurotrophic factor; CRH: corticotropin-releasing hormone; ERK: extracellular signal-regulated kinase; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; LKB1: liver kinase B1; MEK: mitogen-activated extracellular signal-regulated kinase; mER: membrane estrogen receptor; mTORC1: mammalian target of rapamycin complex-1; PI3K: PI-3 kinase; TrkB: tyrosine kinase B.

of endogenous BDNF in different brain areas as well as weakened the growing level of ACTH and CORT caused by normal stress [83]. A recent study found that patients with two separate BDNF single nucleotide polymorphism alleles (rs2049046 and rs11030094), beneficial alleles associated with antidepressant responses, had significantly lower cortisol responses to dexamethasone suppression/CRH tests at discharge [84]. These prove the vital function of BDNF in regulating the HPA axis. Furthermore, some drugs exert antidepressant-like and neuroprotective effects in this way. The improvement of Apelin-13 in chronic stress depressive-like behaviors was achieved through upregulation of BDNF by improving the HPA axis and hippocampal glucocorticoid receptor disorder [85]. The reduction of depressive-like behavior in mice treated with CSDS can be alleviated by dammarane saponin through the restoration of monoamine neurotransmitter levels and HPA axis, which is achieved in part by increasing the BDNF-mTOR pathway [86]. Similarly, water extract of Vaccinium bracteatum leaf showed neuroprotective effects by increasing phosphorylation of CREB in CORT-induced cell damage mediated by the mTOR signaling pathway [87]. Cortisol induces PC12 cell injury by blocking autophagy mediated by the AMPK-mTOR pathway [88, 89]. Autophagy activated AMPK activator metformin and mTOR inhibitor rapamycin, and chlorogenic acid significantly reduced CORT-induced PC12 cytotoxicity by activating autophagy [88, 89]. The potential regulatory role of the estrogen-BDNF-mTORC1 signaling pathway in depression is shown in Figure 1.

4. Conclusion

Overall, there are more and more innovative researches on the pathogenesis of depression, which offers hope for the quality of life for patients. The BDNF-mTORC1 signaling pathway is considered to be an important target pathway for rapid antidepressant therapy, which plays a beneficial role in female depression. Next, further search for drugs acting on the BDNF-mTORC1 pathway or allosteric modulators of mTORC1 is of great significance to improve its role in the pathology of depression, which will greatly improve the situation of female patients.

Data Availability

Data are available upon request.

Conflicts of Interest

The authors claim that there are no conflicts of interest.

Authors' Contributions

RJC, BJL, and WY contributed to the conception and design of the minireview and provided the critical revisions; YJ and XQA wrote the first draft of the manuscript. All authors revised the manuscript and approved the submitted version.

Acknowledgments

This work was supported by grants from the National Key R&D Program of China (Grant #2018YFC1311600), the Jilin Province Medical and Health Talents (2017F012, 2019SCZT007, and 2019SCZT013), the Jilin Science and Technology Agency (20170204049SF, 20190701078GH, 20200201465JC, and 20200301005RQ), and the Scientific

Research Foundation of the Education Department of Jilin Province (Grant No. JJKH20201107KJ).

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Hindawi
Neural Plasticity
Volume 2021, Article ID 6639739, 12 pages
https://doi.org/10.1155/2021/6639739

Research Article

Functional Decoupling of Emotion Coping Network Subsides Automatic Emotion Regulation by Implementation Intention

Shengdong Chen,[1] **Nanxiang Ding**,[2] **Fushun Wang**,[1] **Zhihao Li**,[3] **Shaozheng Qin**,[4] **Bharat B. Biswal**,[5] **and Jiajin Yuan**[1]

[1]*The Laboratory for Affect Cognition and Regulation (ACRLAB), Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu, China*
[2]*School of Psychology, Southwest University, Chongqing, China*
[3]*School of Psychology, Shenzhen University, Shenzhen, Guangdong, China*
[4]*State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China*
[5]*Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, USA*

Correspondence should be addressed to Jiajin Yuan; yuanjiajin168@126.com

Received 17 October 2020; Revised 1 December 2020; Accepted 18 December 2020; Published 5 January 2021

Academic Editor: Wenbin Guo

Automatic emotion regulation (AER) plays a vital role in the neuropathology underlying both suicide and self-harm via modifying emotional impact effortlessly. However, both the effortless account and the neural mechanisms of AER are undetermined. To investigate the neural changes at AER, we collected functional MRI (fMRI) in 31 participants who attended to neutral and disgust pictures in three conditions: watching, goal intention (GI), and reappraisal by implementation intention (RII). Results showed that RII (but not GI) decreased negative feelings and bilateral amygdala activity without increasing cognitive efforts, evidenced by the reduced effort rating and less prefrontal engagement during RII compared with during watching and GI. These emotion-regulatory effects of RII cannot be explained by emotional habituation, as the supplementary experiment ($N = 31$) showed no emotional habituation effects when the same disgust pictures were presented repeatedly three times for each watching and GI condition. Task-based network analysis showed both RII and GI relative to watching increased functional connectivities (FCs) of the ventral anterior cingulate cortex to the left insula and right precuneus during conditions, two FCs subserving goal setup. However, RII relative to GI exhibited weaker FCs in brain networks subserving effortful control, memory retrieval, aversive anticipation, and motor planning. In these FCs, the FC intensity of putamen-operculum/lingual and paracentral-superior temporal gyri positively predicted regulatory difficulty ratings. These findings suggest that the setup of implementation intention automatizes emotion regulation by reducing the online mobilization of emotion-coping neural systems.

1. Introduction

Emotion regulation, a process to modulate any components of emotional activity [1], plays a vital role in maintaining one's health and avoiding suicide or self-harm. Though it has been suggested that emotion regulation can be realized by either effortful or automatic process [2], most studies to date focus on the effortful forms of emotion regulation that is resource demanding. For instance, neuroimaging studies found that intentional reappraisal decreased emotional experience and emotion-related subcortical activation (e.g., amygdala) at the cost of increasing control-related prefrontal activation [3, 4]. The cognitive cost, in some instances, may lead to a failure of emotion regulation. For example, individuals with major depressive disorder are characterized by deficits in prefrontal cognitive control function, which consequently leads to disinhibition of negative emotion [5].

An increasing number of behavioral and electrophysiological studies have recently examined automatic or implicit forms of emotion regulation [6–8]. The recent two-

dimensional framework proposed that these different forms of emotion regulation can be organized along two orthogonal psychological dimensions: (a) the nature of emotion regulation goal, ranging from implicit/nonconscious to explicit/-conscious and (b) the nature of the emotion change process, ranging from more automatic to more controlled [9]. Across these different forms of emotion regulation, implementation intention, most broadly, tends to produce some of the largest effect size ($d_+ = 0.91$) relative to passive watching (control condition; [10]). More importantly, though the antecedent buildup of implementation intentions is cognitively demanding (i.e., conscious and explicit), the execution of emotion regulation process by implementation intentions is automatic, without involving intentional regulatory efforts upon emotional stimulation [11, 12].

Implementation intentions were proposed to promote the attainment rate of goal intentions [13]. Goal intention (GI) defines desired end states and has the general format of "I want to attain Z!" (e.g., "I will not get upset!"). However, people often struggle to regulate their emotional responses with only such a goal intention to regulate emotions [6, 14]. By specifying when, where, and how goal-directed behaviors should be initiated in the form of "if-then" plan (e.g., "If loss sign is encountered, then I will keep calm!"), implementation intention links a goal-relevant situational cue (e.g., loss sign) with a goal-directed behavior (e.g., "keep calm"), which reduces the intention–behavior gap between intended outcome and actual goal attainment [15]. Gallo and Gollwitzer [16] first reported that forming implementation intention for the control of spider phobia reduced the subjects' fearful experience for spider-related stimuli during a cognitive demanding task. Additionally, an event-related potential (ERP) study by Gallo et al. [11] reported that forming an implementation intention reduced occipital P1 amplitudes for threatening stimuli compared to GI or watching conditions. Recently, Gallo et al. [12] found that a reappraisal-based implementation intention (RII) allowed participants to rate disgusting pictures as being less unpleasant than participants in the watching or GI groups.

However, there were two limitations in these previous studies of implementation intention. First, these studies did not use objective indexes to measure cognitive costs between regulation and no-regulation conditions, which were unable to verify the effortless or automatic characteristics of implementation intention. Specifically, Gallo and colleagues [11, 12] only collected subjective measures of cognitive efforts during goal intention and implementation intention conditions, but not during the control condition (i.e., passive watching), leaving it unclear whether implementation intention or goal intention enhanced cognitive efforts compared to the control condition. Second, what these studies measured are self-reported or electrophysiological variables. Few studies have examined neural mechanisms of automatic emotion regulation by implementation intention using functional MRI (fMRI). The only exception was one fMRI study by Hallam et al. [17] that involved implementation intention and cognitive reappraisal. However, the RII was manipulated in a controlled (not automatic) way in this study, i.e., participants were reminded to use the RII strategy every time a reappraisal cue was presented. Though RII reduced self-reported affect and amygdala activity compared to goal intention, RII also led to cognitive control-related activation in dorsolateral prefrontal regions [17].

Therefore, we here performed one fMRI experiment to examine the automatic characteristic and neural mechanisms of negative emotion regulation by RII. In the fMRI experiment, cognitive reappraisal, which requires reformulating the meaning of the emotional situation, was chosen as the target strategy to be planted into implementation intention. Intentional cognitive reappraisal has been suggested to effectively reduce negative emotional outcomes, which, however, was commonly accompanied by increased cognitive efforts at both neural [3] and behavioral [18] levels. Disgust was chosen as the target emotion, as it has proven to elicit robust neural activation in both cognitive-control and emotion-generative regions (e.g., amygdala) [3, 19, 20].

Furthermore, the amygdala and insula have been suggested to be central regions underlying the generation of disgust [3, 19, 20]. Prefrontal regions like dorsolateral prefrontal cortex (dlPFC) and dorsal anterior cingulate cortex (dACC) are consistently involved in controlled reappraisal and play a critical role in top-down cognitive control [3, 4]. Therefore, neural activity in these two emotion-generative regions (amygdala and insula) and two cognitive control-related regions (dlPFC and dACC) were used to provide objective indexes of emotional responses and cognitive costs, respectively. We predicted that RII would reduce the subjective experience of disgust without increasing subjective reports of cognitive efforts. We also predicted that RII would reduce the disgust responses in emotion-generative regions without increasing the cognitive control regions' activity compared to GI or control condition (i.e., automatically). Furthermore, we conducted a voxel-wise whole-brain analysis and a task-related network analysis to explore the neural mechanisms subserving the automatic emotion regulation by RII.

2. Materials and Methods

2.1. Participants. Given our aim to compare the negative emotional responses among the two regulations (GI and RII) and one control (watching) condition, we determined the sample size based on a power analysis using the G-power software for repeated ANOVA [21]. We specified a medium effect size (0.25), 0.8 power, and a moderate correlation (0.5) among the repeated measurements (3), which yielded a recommended sample size of 28. We used a medium effect size ($f = 0.25$) [22] because the values found in previous studies (average $f = 0.45$) [12, 14] would yield a very small sample size (9). To avoid the possibility that some of the data cannot be used because of head movement or other uncontrollable reasons, we employed thirty-one healthy, right-handed college students (16 males, $M_{age} = 21.34$) from the Southwest University in China with the normal or corrected-to-normal vision to participant in this study. Written informed consent was obtained before the experiment, and the study was approved by the local ethical committee of the Institutional Human Participants Review Board of the Southwest University Imaging Center. Data of

5 participants were excluded due to excessive head movement (larger than 3 mm) during fMRI scanning.

2.2. Stimuli. The stimulus material consisted of two categories with 90 pictures in total: 45 disgust and 45 neutral pictures, taken from the International Affective Picture System (IAPS) [23] and the Chinese Affective Picture System (CAPS) [24]. Each picture's valence and arousal scores were assessed by 30 independent raters, independent of the experiment sample. The disgust pictures showed bloody burn victims and mutilated bodies. Within the bidimensional valence and arousal model, such contents are rated as negative and high arousal, while neutral pictures had medium standard emotional valence and low arousal ratings. The pictures were presented in a randomized order, and the raters blind to the experiment intention were asked to rate to what degree they felt sadness, fear, joy, disgust, and anger on scales ranging from 1 (little) to 7 (very). Results revealed a significant main effect for the unpleasant pictures, ($F(4, 40) = 1088.96$, $p < 0.001$, and $\eta^2 = 0.96$). Post hoc Bonferroni tests showed that disgust pictures were rated as being more likely to produce disgust ($M = 5.74$) when compared with fear ($M = 4.22$, $p < 0.001$), sadness ($M = 3.90$, $p < 0.001$), anger ($M = 2.85$, $p < 0.001$), and joy ($M = 1.41$, $p < 0.001$). These findings suggest that unpleasant pictures elicit disgust effectively.

2.3. Design and Procedure. The present study used a three × two factorial design with the regulation condition (watching, GI, and RII) and type of pictures (neutral/negative) as two repeated factors.

Prior to fMRI scanning, participants were trained to be familiar with the experimental task while viewing 15 practice pictures. Participants were told to estimate their negative emotional intensity after the presentation of 3 consecutive pictures using a five-point scale ranging from 0 (not at all) to 4 (very), "How negative did you feel?" After viewing all the pictures, participants received a questionnaire that assessed the consumption of cognitive resources: "How much did you try to cope with negative feelings?" and "How difficult was it to cope with negative feelings?" The two items were also accompanied by a five-point scale ranging from 0 (not at all) to 4 (very). The individual difference in the habitual use of reappraisal was measured before fMRI scanning using the Emotion Regulation Questionnaire (ERQ; [25]).

During fMRI, participants performed three tasks in turn: passive watching, GI, and RII (Figure 1). When performing each of the three tasks, participants first received the task instruction and reinforced it by rehearsal for one minute. Specifically, participants in the watching task were just required to pay close attention to the pictures without further instructions related to emotion regulation. Besides paying close attention to pictures, participants in the GI task were instructed to form a goal intention ("I will not get disgusted!"). In the RII task, participants were instructed first to form a goal intention and a goal-directed if-then plan ("I will not get disgusted! And if I see blood, then I will take the perspective of a physician!").

After the instruction stage, participants in each task only needed to attend to the pictures without any additional cues or instruction to avoid any further voluntary regulatory process. Each task consisted of 10 blocks (5 neutral and 5 negative blocks) that matched in valence and arousal, and each block consisted of 3 consecutive pictures (2 s each) of the same valence. Both neutral and negative pictures across the three tasks were not significantly different in valence and arousal (ps > 0.8). Each of the 10 blocks was presented for 6 s in a random order following a fixation of 6 to 10 s (average 8 s). Following each block, the scale to assess negative emotion intensity appeared on the screen for 4 s. At the end of each task, two scales to assess cognitive efforts in emotional coping were also presented for 4 s each. There was no missing data on any of the subjective measures.

2.4. Imaging Data Acquisition and Preprocessing. Data were acquired on a Siemens Trio 3.0 Tesla (Magnetom Trio, Siemens, Erlangen, Germany) scanner with a gradient echo planar imaging sequence (32 axial slices, TR/TE = 2 s/30 ms, FA = 900, matrix size = 64 × 64, FOV = 220 × 220 mm^2, voxel size = 3.4 × 3.4 × 3 mm^3, and 386 volume measures). High-resolution structural images were acquired for registration purposes using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR/TE = 1900 ms/2.52 ms, FA = 9°, FOV = 256 × 256 mm^2, slices = 176, thickness = 1.0 mm, and voxel size = 1 × 1 × 1 mm^3). SPM8 [26] was used for the fMRI data analysis with regular preprocessing steps of slice timing, realignment, volume registration, spatial normalization (resampled into 3 mm isotropic voxels), and spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum. Head movement estimates derived from the realignment step were included as nuisance regressors in subsequent general linear modeling (GLM) to diminish the impact of movement-related effects.

2.5. Imaging Data Analysis. For each participant, the voxel-wise whole-brain GLM included 6 regressors of interest (negative and neutral pictures in three scans of watching, GI, and RII). At the group level, a general linear contrast of watching-negative versus watching-neutral was applied to detect brain activation associated with disgust responses. Based on Random Field Theory, T-statistics for each voxel were thresholded at $p < 0.01$ and an extent of 10 voxels for multiple comparisons across the whole brain with a family-wise error rate (FWE).

Region of interest (ROI) analyses were next performed to test whether RII could decrease activation related to disgust responses in typical emotion-generative regions. The emotion-generative regions (bilateral amygdala and bilateral insula) were defined by the respective anatomical masks of the AAL atlas [27] by WFU_PickAtlas toolbox [28]. To examine whether RII increased activation in cognitive control-related regions, three ROIs in bilateral dlPFC and dACC were further defined as the Brodmann areas 9 and 46 combined (left and right), as well as a 10 mm radius sphere at Talairach coordinates ($X = 0$, $Y = 12$, and $Z = 42$) [29], respectively. For each of these ROIs, the mean percent signal

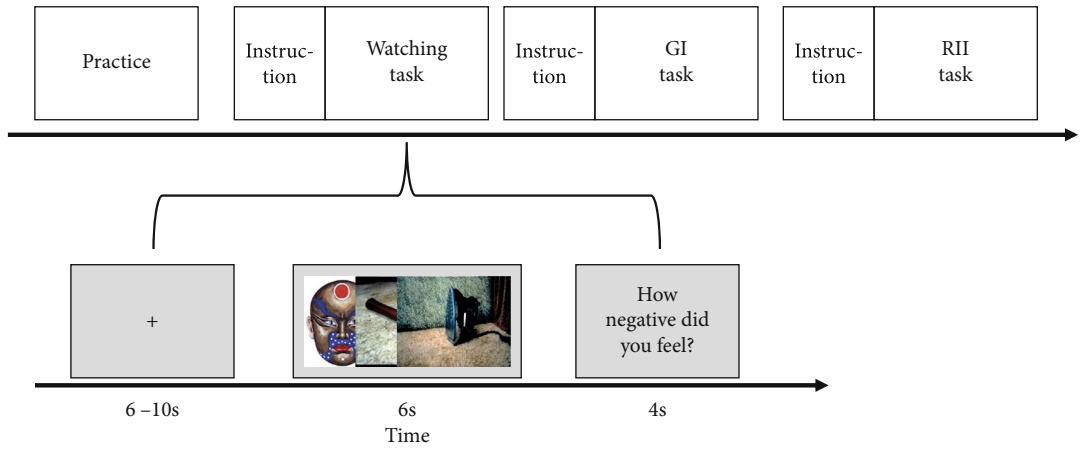

Figure 1: Experimental design for three tasks. The experiment consisted of three tasks, and each task consisted of five neutral and five negative blocks. "How negative did you feel?" rating (0 = not at all to 2 = moderately to 4 = extremely) appeared at the end of each block. GI: goal intention; RII: reappraisal-based implementation intention.

changes (PSCs) of each individual were extracted using the Marsbar toolbox [30]. The emotional intensity of negative affect during each condition was represented as the average contrast values (negative > neutral) for the four emotion-generative regions and three cognitive control-related regions.

2.6. Estimation of Task-Related FC. Using the CONN toolbox [31], we estimated the task-related FC between each pair of brain regions in a network of 229 spherical (radius = 3 mm) regions. Of these regions, 227 ROIs were selected from 264 coordinates reported by Power et al. [32]. Those coordinates are the centers of putative functional areas (and subcortical and cerebellar nuclei), which were defined by multiple-task fMRI meta-analyses [33] and by a resting-state FC MRI parcellation technique [34]. These 227 ROIs have also been assigned to 10 well-established functional networks, comprising low-level input and output networks (visual, auditory, and sensorimotor networks), subcortical nodes, the default mode network (DMN), ventral and dorsal attention networks (VAN and DAN), and cognitive control networks (frontal-parietal network, FPN; cingulo-opercular network, CON; salience network, SN; [35, 36]). Bilateral amygdala ROIs defined via the contrast of watching – negative > watching – neutral (S-Table 1) were also added in the connectivity analysis given their central role in the processing of disgust.

Regional time series within each of these 229 ROIs were extracted from the preprocessed fMRI data on individual level. The task onset times were modeled, and covariates of no interest (e.g., the realignment confound, white matter, and CSF signal) were regressed out using a component-based noise correction method (CompCor) [37]. Time series of voxels within 229 ROIs were averaged, and those average time series were correlated with each other. The resulting correlation coefficients were then Fisher z-transformed to normalize their distribution. These values represent the connectivity between the source and target regions during each task condition. The computed ROI-to-ROI connectivity matrices of each participant were finally entered into the second-level group analysis that treated participants as a random variable in a 3-by-2 ANOVA. In this network analysis, false positives were controlled by the false discovery rate (FDR) of $p < 0.05$.

2.7. Statistical Analysis. We conducted the null hypothesis significance test (NHST) analysis using SPSS 20.0. We also conducted Bayesian ANOVA to analyze cognitive efforts' subjective and neural measures, mainly because we expected that RII would not increase cognitive efforts relative to the watching condition. We computed Bayes factors (BF_{10}) using JASP with default prior width [38]. We interpreted BF_{10} of 1-3 as anecdotal, 3–10 as moderate, >10 as strong evidence for accepting H1, and BF_{10} of 1-1/3 as anecdotal, 1/3–1/10 as moderate, and <1/10 as strong evidence for accepting H0 [39].

3. Results

3.1. Manipulation Check of Emotion Induction. To check whether the disgusting pictures elicited the target emotion disgust, we contrasted watching-negative versus watching-neutral on both experience and neural measures of negative emotion during the passive watching. Results showed that the watching-negative versus watching-neutral contrast resulted in increased subjective ratings of negative affect ($t(25) = 28.49$ and $p < 0.01$) (S-Figure 1A) and increased responses in prefrontal cortex, bilateral temporal and occipital cortex, parietal cortex, and subcortical regions (S-Table 1). As expected, we confirmed that the typical emotion-generative regions, including the amygdala and insula, were bilaterally activated by this contrast (S-Figure 1B). There were no significant brain responses for watching-neutral versus watching-negative contrast. Both behavioral and neural findings supported that the disgusting pictures successfully elicited the target emotion of disgust.

3.2. Subjective and Neural Emotion Regulation Effects. The univariate ANOVAs of negative emotional ratings and the percent BOLD signal changes in the key emotion-generative regions (amygdala and insula) were conducted among the three conditions (watching, GI, and RII). At both the behavioral and neural levels, the intensity of negative affect during each condition was represented by the negative emotion index minus the neutral emotion index. Its higher values mean more negatively emotional intensity during the condition.

3.2.1. Negative Emotional Ratings. There were significant differences in negative emotional ratings across the three conditions (Figure 2(a)), at both before ($F(2, 50) = 29.82$, $p < 0.001$, and $\eta^2 = 0.54$) and after ($F(2, 49) = 6.62$, $p < 0.01$, and $\eta^2 = 0.22$) taking habitual reappraisal as a covariate. Bonferroni post hoc comparisons indicated that the RII condition ($M = 2.74$) had a significantly lower negative emotional level than the watching condition ($M = 3.98$, $p < 0.001$) and the GI condition ($M = 4.11$, $p < 0.001$). The watching condition and the GI condition showed no significant differences in negative emotion experience, ($p = 1.0$).

3.2.2. Neural Responses in Emotion-Generative ROIs. There were significant main effects in bilateral amygdala responses (left/right amygdala: $F(2, 50) = 6.43/3.62$, $p = 0.003/0.03$, and $\eta^2 = 0.20/0.13$; Figures 3(a)–3(c)). In Bonferroni post hoc comparisons that in the left amygdala, PSC ($M = 0.25$) was smaller during RII than in watching conditions ($M = 0.53$, $p = 0.008$). The watching and the GI (0.37) conditions showed no significant differences ($p = 0.10$). Similarly, in the right amygdala, PSC during the RII condition ($M = 0.20$) was also smaller than the watching condition ($M = 0.36$, $p = 0.02$). The watching condition and the GI ($M = 0.28$) condition showed no significant differences ($p = 0.68$). However, no significant main effects were found in the left insula ($F(2, 50) = 0.90$, $p = 0.42$, and $\eta^2 = 0.04$) or in the right insula responses ($F(2, 50) = 0.51$, $p = 0.60$, and $\eta^2 = 0.02$).

These findings showed that forming implementation intention effectively realized emotion-regulatory goals, reducing negative feelings and disgust-related neural activations (bilateral amygdala).

3.3. Subjective and Neural Cognitive Costs of Reappraisal-Based Implementation Intention. We conducted the univariate ANOVA analysis of both subjective cognitive efforts and the percent BOLD signal changes in the bilateral dlPFC and dACC among the three conditions (watching, GI, and RII).

3.3.1. Subjective Cognitive Efforts. No significant differences in the subjective effort of negative emotion regulation emerged among the watching ($M = 2.57$), the GI ($M = 2.69$), and the implementation intention conditions ($M = 2.27$, Figure 2(b)); $F(2, 50) = 1.82$; $p = 0.17$; $BF_{10} = 0.487$. The self-reported difficulties in coping with negative emotions were significantly different among the watching ($M = 2.42$), GI ($M = 2.35$), and RII conditions ($M = 1.73$, Figure 2(c)); $F(2, 50) = 7.64$; $p < 0.01$; $\eta^2 = 0.23$; $BF_{10} = 34.08$. The RII condition was linked with a significantly lower report of difficulties than the watching ($F(1, 25) = 14.46$, $p < 0.01$, $\eta^2 = 0.37$, and $BF_{10} = 40.95$) and GI conditions ($F(1, 25) = 7.66$, $p = 0.01$, $\eta^2 = 0.23$, and $BF_{10} = 4.53$), whereas GI and watching showed no significant differences ($F(1, 25) = 0.19$, $p = 0.66$, and $BF_{10} = 0.226$).

3.3.2. Neural Responses in Cognitive Control-Related ROIs. To check whether implementation intention engenders voluntary control in the neural level, we directly tested the BOLD signal changes of key nodes of the frontoparietal control network. The main effects of BOLD responses in the right ($BF_{10} = 0.196$) and left ($BF_{10} = 0.773$) dlPFC and dACC ($BF_{10} = 0.705$) ROIs were not significant ($ps > 0.10$) (Figure 4).

3.3.3. Whole-Brain Analyses. Moreover, to test whether, in addition to the regions of interest, other regions were affected by RII, a 3-by-2 repeated-measure ANOVA was run in a whole-brain analysis with picture type and strategy type as factors. The strongest interaction effect was found in the left mPFC, vmPFC, and postcentral regions (Table 1). Follow-up t-tests showed that the difference between negative and neutral block was significant during both GI (left mPFC: $t = 4.63$, $p < 0.001$; vmPFC: $t = 2.58$, $p < 0.02$) and watching conditions (left mPFC: $t = 6.05$, $p < 0.001$; vmPFC: $t = 8.85$, $p < 0.001$), but not during RII (left mPFC: $t = -1.86$, $p = 0.075$; vmPFC: $t = 1.18$, $p = 0.25$) in left mPFC and vmPFC. The difference between negative and neutral block at the postcentral region was only significant during the watching condition ($t = 7.22$, $p < 0.001$) but not during GI ($t = 1.28$, $p = 0.21$) and RII ($t = 0.14$, $p = 0.89$) (Figure 5). These findings indicate that RII did not increase disgust-related neural processing in the prefrontal regions.

Together, these behavioral and neuroimaging findings showed that RII facilitated downregulation of disgust responses without more cognitive resource costs compared to watching and GI conditions.

3.3.4. Task-Related FC Analyses. We applied task-related FC analysis to the 3-by-2 experimental datasets by considering ROIs as nodes and the block-by-block FC between each pair of ROIs as edge intensity. After computing the ROIs pairwise correlation matrix of each condition for each participant, we conducted a 3-by-2 repeated-measure ANOVA of FC with picture valence and type of strategies as factors at the group level.

The strongest interaction effect was found in 12 pairs of ROI-to-ROI FC (corrected for multiple comparisons via FDR) (see S-Table 2). Planned comparisons for each FC were then conducted by testing how the FC intensity difference between negative and neutral blocks varies across the regulation conditions. Specifically, we were mainly interested in the contrasts GI/RII versus watching and RII versus GI. According to cognitive subtraction principle, the contrasts GI and RII versus watching condition should reflect the FC underlying the intentional and automatic pursuit of emotion regulation goals (GI and RII), respectively. The contrast RII versus GI should reflect FC related to the differences of automation

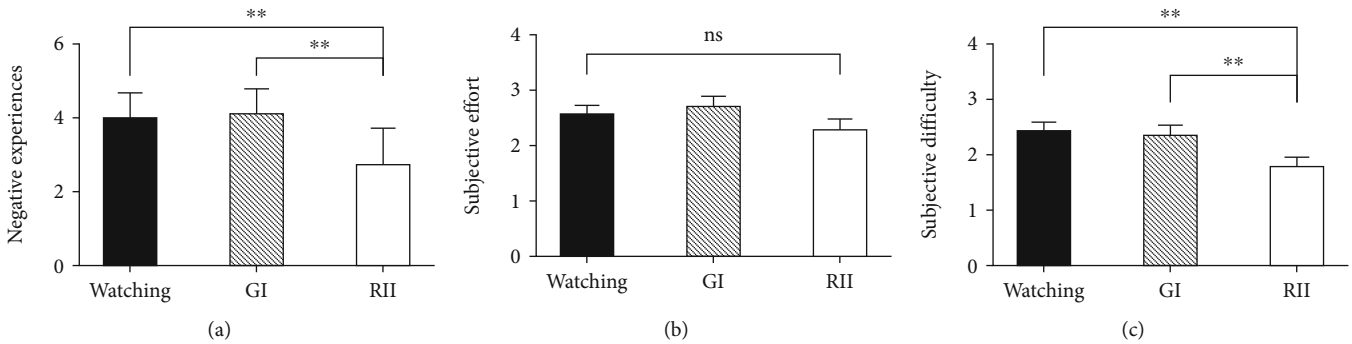

Figure 2: The subjective negative experience (a), subjective effort (b), and subjective difficulty (c) ratings of the watching, GI, and RII conditions. Error bars = SEM; ** means $p < 0.01$; ns stands for not significant.

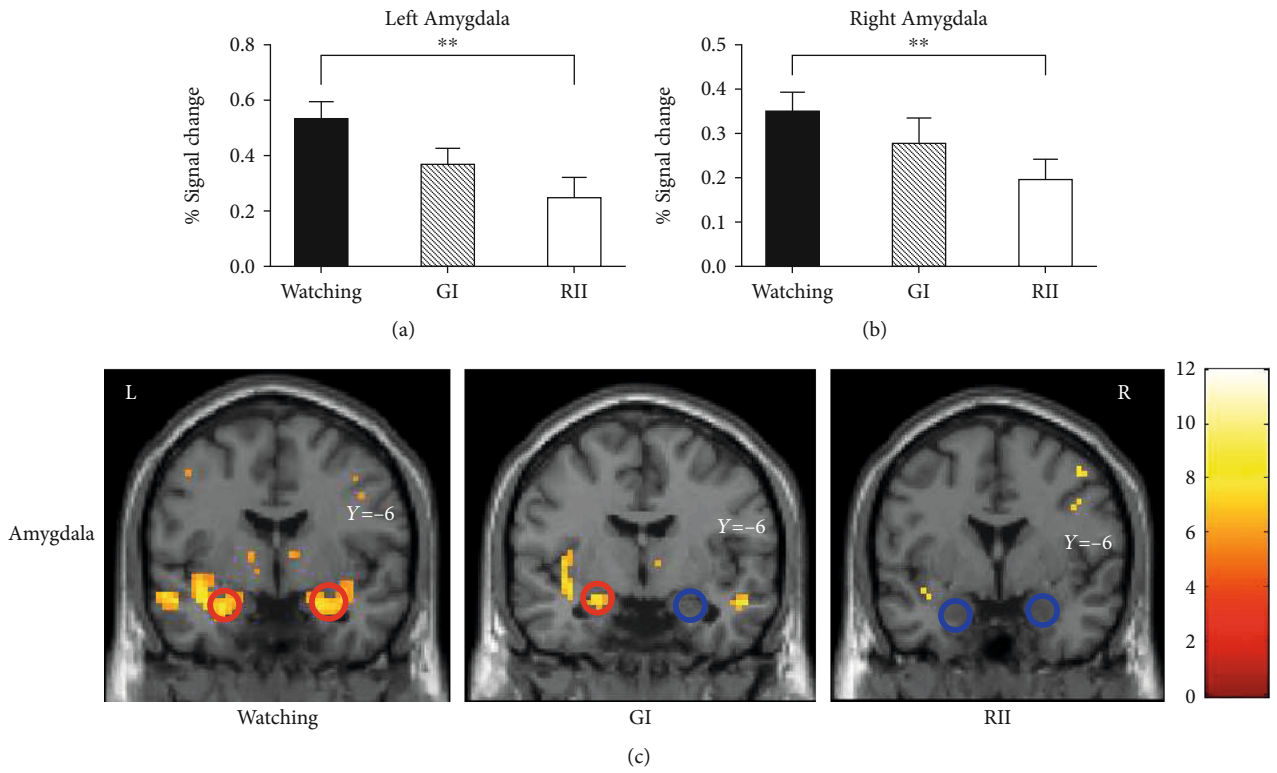

Figure 3: The emotion-regulatory effects of RII in the (a) left and (b) right amygdala ROIs. The intensity of negative affect during each condition was represented by the BOLD signal changes of the negative block versus the neutral block. (c) An illustration of amygdala activation among watching, GI, and RII conditions (FWE corrected $p = .01$ and an extent of 10 voxels). Error bars = SEM; ** means $p < 0.01$.

between the goal-directed GI and stimulus-driven RII. The results of contrasts GI and RII versus watching condition showed close similarities: four significant FCs for the contrast GI versus watching condition and two of these four FCs for the contrast RII versus watching condition (see Table 2 and Figures 6(a) and 6(b)). Further, seven FCs showed significant decreases in FC intensity during RII than GI (see Table 2 and Figure 6(c)). These seven FCs, as discussed later, may constitute an interactive neural system underpinning online emotion-related coping. Accordingly, we guess the reduced functional coupling in this system might reflect less mobilization of online processing resources for the attainment of emotion regulatory goal during RII.

Moreover, we conducted a correlation analysis between the FC intensity and the subjective difficulty index during RII relative to GI to investigate whether the survived FC could predict behavioral markers of cognitive efforts. Both FC and subjective indexes of regulatory difficulty were computed by using GI minus RII. We focused on the subjective difficulty index because it was related to negative experiences ($r = 0.39$ and $p = 0.024$) during GI relative to RII after a correction of FDR 0.05 (S-Figure 2), whereas the cognitive effort index was not ($r = 0.33$ and $p = 0.049$). The correlation analysis demonstrated that three of seven FC intensity were positively correlated with subjective difficulty: R putamen-L Rolandic operculum, $r = 0.54$ and $p = 0.002$; R lingual gyri-

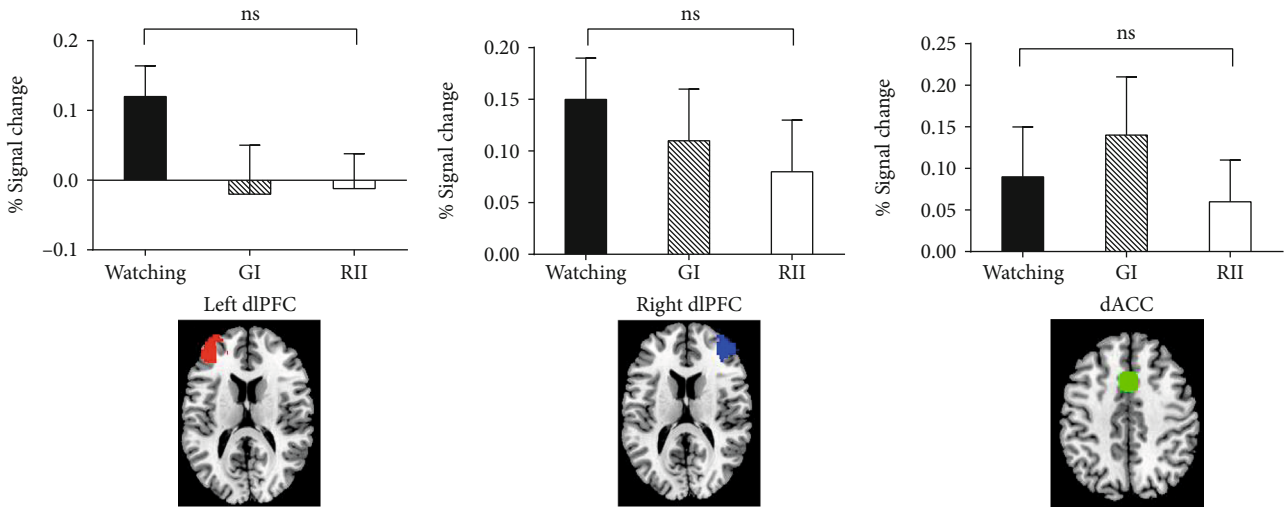

Figure 4: The neural responses of the left and right dlPFC and dACC in the watching, goal intention (GI), and reappraisal by implementation intention (RII) conditions. Error bars = SEM; ns stands for not significant.

Table 1: Voxel-wise group activations by 3-by-2 ANOVA with picture type and strategy type as repeated factors.

Brain regions	Brodmann	*X*	*Y*	*Z*	Voxels	*F* value
L mPFC	10	-6	51	9	104	21.78
	10	-9	54	27	23	17.79
L vmPFC	11	-12	45	-15	91	20.05
	11	-6	36	-18	16	19.58
L postcentral	6	-27	-33	66	13	18.77

Note: all clusters reached a significance level of $p = 0.05$ (FWE corrected). For each cluster, *X*, *Y*, and *Z*, MNI coordinates; L: left.

R putamen, $r = 0.35$ and $p = 0.04$; R paracentral lobule-R STG, $r = 0.41$ and $p = 0.02$ (S-Figure 2BCD). However, only the correlation of R putamen-L Rolandic operculum survived an FDR of 0.05 correction for multiple comparisons.

4. Discussions

The present study examined the automatic emotion-regulatory effects of RII at both behavioral and neural levels and its underlying functional connectivity mechanisms. Consistent with previous studies [6, 12, 14], our results revealed that RII effectively decreased both negative experiences and brain activity in emotion-generative regions. Importantly, these emotion-regulatory effects were not achieved at the cost of greater involvement of cognitive control resources, as the RII did not increase self-reported efforts and control-related prefrontal activations. Furthermore, FC analysis results demonstrated close similarities between the contrast GI versus watching condition and the contrast RII versus watching condition in vACC-based FCs, and the connectivity intensity was decreased during RII than GI in seven distributed FCs.

We found that the RII effectively reduced the emotional experiences and activation of the bilateral amygdala relative to the passive watching condition. In contrast, the GI and watching conditions showed no significant differences at both behavioral and neural indices. These findings coincided well with previous findings that forming an implementation intention effectively downregulated the subjective experience of negative emotions [12, 16], amygdala activation [17], and occipital P1 event-related potential amplitudes [11]. These findings confirmed the effectiveness of RII in reducing negative emotional outcomes at both the behavioral and neural levels. Importantly, it should be noted that the emotion-regulatory effects of RII cannot be explained by emotional habituation. In the supplementary experiment ($N = 31$), we observed no habituation effects when repeating to present disgust pictures (S-Figure 3).

Importantly, we observed no enhancement of subjective efforts but reduced control difficulty during RII compared with those under the other two conditions. There was also no activity increase in the cognitive control-related ROIs (bilateral dlPFC and dACC) during RII relative to watching and GI. The dlPFC and dACC have been suggested to be generally involved in cognitive-resource-demanding tasks, such as working memory [40, 41], decision-making [42], and voluntary emotion regulation [3]. The increased activation of these regions is considered to represent increased cognitive control [3, 41]. Moreover, the whole-brain analysis showed that RII, relative to the watching and GI conditions, did not increase the emotion-related activity of mPFC and vmPFC. The mPFC and vmPFC play essential roles in the appraisal, expression, and regulation of negative emotion, similar to the cognitive control functions of dlPFC and dlPFC described above [43, 44]. These findings consistently suggest that emotion regulation by RII did not involve cognitive control mechanisms and operated automatically.

Moreover, FC analysis showed close similarities between the contrast GI versus watching condition and the contrast RII versus watching condition. Specifically, the FC intensity between left vACC and two nodes (right precuneus and left insula) was increased during both GI and RII than watching conditions. Given that RII builds upon the GI and the context-response association, it is reasonable to infer that

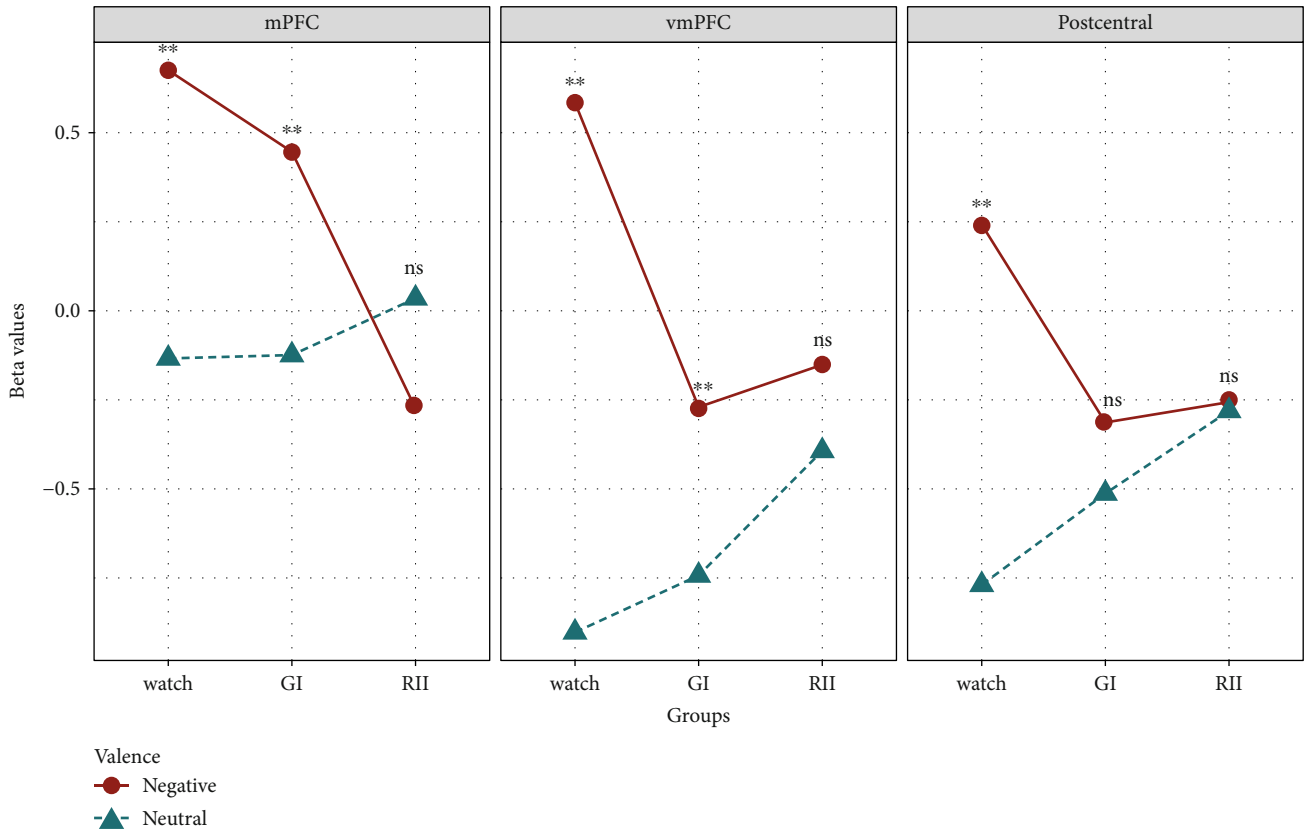

Figure 5: Changes of beta values of activation clusters for the interaction effects (picture type * strategy type). ** means $p < 0.01$; ns stands for not significant.

Table 2: Planned comparisons of functional connectivity intensity between watching, GI, and RII conditions.

FC	t value
GI vs. watching	
L vACC-R precuneus	4.78
L vACC-R SMG	4.77
L vACC-L insula	4.67
R ITG-L MTG	2.86
RII vs. watching	
L vACC-L insula	2.82
L vACC-R precuneus	2.53
RII vs. GI	
R lingual gyri-R putamen	-6.22
R ITG-L MTG	-6.13
R paracentral lobule-R STG	-4.66
R putamen-L Rolandic operculum	-5.98
R postcentral gyri-R paracentral lobule	-5.01
R IPL-R SPL	-4.70
L vACC-R SMG	-4.49

Note: all connections reached a significance level of two-tailed $p < 0.05$. FC: functional connectivity. For each connection, L: left; R: right. ITG: inferior temporal gyri; MTG: middle temporal gyri; STG: superior temporal gyri; IPL: inferior parietal lobule; SPL: superior parietal lobule; SMG: supramarginal gyri.

these two FCs may be necessary for self-related emotion-regulatory goal pursuit, regardless of the degree of task automation. The left insula has been suggested to be a key node of SN [32], critical for developing and updating motivational states with specific associated actions (i.e., goals) [45]. And the vACC and precuneus are hubs of DMN, involved in self-relevant information processing [32]. Given the close association between SN and DMN [46], these two networks may interact to mark the emotionally salient stimuli and then to process it directed by the self-relevant goals ("I will not get disgusted"; Figure 6(d)).

Beyond the similarities between GI and RII, the connectivity intensity was decreased during RII than GI in seven distributed FCs. Previous studies have pointed out that GI is a goal-directed process, whereas RII is a stimulus-driven one [10, 13]. Therefore, we guess the increased FC intensity during GI compared to RII may reflect a goal-directed (top-down) online emotion-related coping that underlies the gap between emotion-regulatory goals and emotion-regulatory success. These seven FCs can be summarized into three networks that may cooperate to perform this process. First, the connection IPL-SPL, as a part of FPN, is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses [47], and its activity increases with higher cognitive demand [48]. Second, the putamen-Rolandic operculum, vACC-SMG, postcentral-paracentral lobule, and paracentral lobule-STG connections are involved in aversive anticipation (postcentral-paracentral lobule and

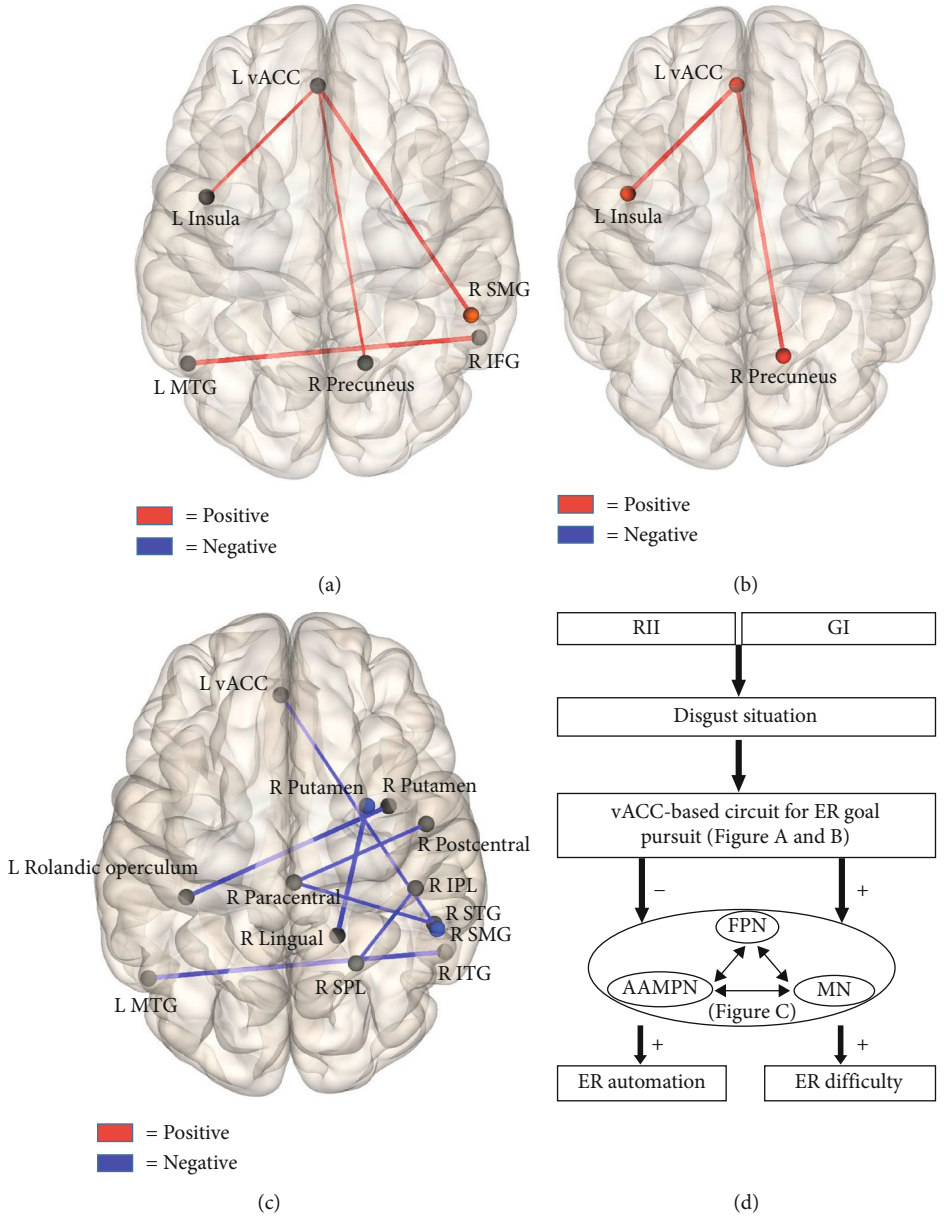

Figure 6: Functional connectivity patterns of the contrasts GI (a) and RII (b) versus watching condition and the contrast RII versus GI (c). The connections (edges) between ROIs marked in red mean that GI or RII relative to watching shows greater FC strength, and those marked in blue mean that RII relative to GI shows weaker FC intensity. ITG: inferior temporal gyri; MTG: middle temporal gyri; SMG: supramarginal gyri; STG: superior temporal gyri; IPL: inferior parietal lobule; SPL: superior parietal lobule; SMG: supramarginal gyri. (d) The dynamic architecture of the FC mechanisms underlying GI and RII. FPN: frontoparietal network; AAMPN: aversive anticipation and motor planning network; MN: memory network; ER: emotion regulation.

paracentral-STG) and emotion-related motor planning and preparation (putamen-Rolandic operculum and vACC-SMG). Specifically, anticipatory activity in the right postcentral gyrus and STG is associated with greater emotional responses and decreased regulation success [49]. Neural patterns of the postcentral gyrus and paracentral lobule are closely related to the averseness level [50]. Further, SMG is involved in planning goal-oriented actions [51]. Putamen and Rolandic operculum also play similar roles in motor planning [52] and execution [53]. Last, ITG, MTG, and lingual gyri are key nodes of memory systems, mediating interconnected memory functions, like establishing representations in long-term memory [54] and memory retrieval [55].

Together, these three networks may constitute a neural system subserving the goal-directed, online emotion coping mechanism, including components of cognitive control, memory reference, and retrieval, as well as aversive anticipation and motor planning. Without the antecedent formation of a situation-response association (e.g., if-then plan), participants may have mobilized this system upon receipt of stimulus to achieve their emotion-regulatory goals, leading to

greater experienced regulatory difficulty during GI than RII. We also observed positive correlations between the FC (of R putamen-L Rolandic operculum and paracentral lobule-STG) intensity and self-rating of emotion coping difficulty. These correlations suggest that increased difficulty of emotion coping is coupled with the higher online mobilization of the emotion-related coping network, which provides a possible explanation for the little emotion regulation effect during GI. On the other hand, given that task automatization is accompanied by decreasing activation of the putamen [56] and FPN [36], the decreased FC intensity during the RII may reflect a greater degree of goal-dependent automaticity.

Several limitations need to be acknowledged. First, only healthy participants were studied, and it is therefore unclear whether our results are generalizable to clinical samples. Given the cognitive control deficits in individuals with emotional disorders (e.g., anxiety and depression), implementation intention, as a way of automatic emotion regulation, may facilitate the clinical population compared to voluntary strategies. Second, this study only combined implementation intention with cognitive reappraisal. However, there are other emotion regulation strategies, like attentional deployment or expressive suppression. The neural mechanisms underlying different emotion regulation strategies by implementation intentions may be different. Third, this study focused on the downregulation of negative emotional outcomes without measuring neural substrates underlying the GI and RII formation. It is possible that participants paid cognitive resources during the formation of implementation intentions before stimulus presentation. Thus, future studies need to assess both the formation and application of implementation intention concerning control-related neural underpinnings.

In summary, we found that RII effectively decreased negative emotional responses at both behavioral and neural levels without enhancing cognitive control resource involvement. Functional decoupling of emotion coping network may subserve automatic emotion regulation by implementation intention.

Data Availability

All the data are available from the corresponding author on reasonable request.

Disclosure

This manuscript has been submitted as a preprint in the below link: https://www.biorxiv.org/content/10.1101/336800v3.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Shengdong Chen, Nanxiang Ding, and Fushun Wang contributed equally to this work.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant numbers 31971018 and 31671164). The authors would like to thank Wei Gao, Ruosong Yuan, Chen Changming, and Xie Chao for their help in data collection and analysis.

Supplementary Materials

S-Figure 1: the contrast of watching-negative versus watching-neutral on behavioral and neural indices. (a) Negative emotional ratings during passively viewing of disgust pictures (watching condition). Error bars = SEM. (b) From the one-sample t-test across all 26 participants for the contrast watching-negative versus watching-neutral. The display threshold was $p = .01$, FWE corrected and an extent of 10 voxels. $^{**}p \leq 0.01$, S-Figure 2: the correlation analysis showed that during GI relative to RII, subjective regulatory difficulty was related to greater (a) subjective cognitive efforts and (b) negative experiences, and that the changes of FC intensity were related to greater subjective regulatory difficulty. Results of (c) R putamen-L Rolandic operculum survived a FDR of 0.05 correction for multiple comparisons, whereas (d) R lingual gyri-R putamen and (e) R paracentral lobule-R STG did not. Contour line density in (a) and (b) means the extent of point overlap. S-Figure 3: mean subjective ratings of negative emotions for the watching and GI groups during three times. The negative affect during each condition was represented by the negative emotion rating minus the neutral emotion rating, and its higher values mean more negatively emotional experiences during the condition. Error bars = SEM; ns stands for not significant. S-Table 1: group activations for contrast watching-negative versus watching-neutral. S-Table 2: results of 3-by-2 ANOVA of functional connectivity analysis. *(Supplementary Materials)*

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Hindawi
Neural Plasticity
Volume 2020, Article ID 8859388, 9 pages
https://doi.org/10.1155/2020/8859388

Research Article

Distinct Associations of Cognitive Impairments and Reduced Gray Matter Volumes in Remitted Patients with Schizophrenia and Bipolar Disorder

Ting Sun,[1,2] **Pengfei Zhao**,[1,2] **Xiaowei Jiang**,[1,2,3] **Yifang Zhou**,[2,4] **Chao Li**,[1,3] **Linna Jia**,[1,2] **and Yanqing Tang**[2,4]

[1]*Brain Function Research Section, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China*
[2]*Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China*
[3]*Department of Radiology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China*
[4]*Department of Geriatric Medicine, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China*

Correspondence should be addressed to Yanqing Tang; tangyanqing@cmu.edu.cn

Received 11 September 2020; Revised 4 November 2020; Accepted 30 November 2020; Published 11 December 2020

Academic Editor: Zhifen Liu

Background. Cognitive impairments are documented in schizophrenia (SZ) and bipolar disorder (BD) and may be related to gray matter volumes (GMVs). Thus, this study is aimed at exploring whether the association between cognitive impairments and GMV alterations is similar in patients with SZ and BD and understanding the underlying neurobiological mechanisms. *Methods*. A total of 137 adult subjects (46 with SZ, 35 with BD, and 56 age-, sex-, and education-matched healthy controls (HC)) completed the MATRICS Consensus Cognitive Battery (MCCB) and structural magnetic resonance imaging scanning. We performed group comparisons of the cognitive impairments, the GMV alterations, and the association between them. *Results*. Compared with HC, the patients with SZ and BD showed shared deficits in 4 cognitive domains (i.e., processing speed, working memory, problem solving, and social cognition) and the composite. SZ and BD had commonly decreased GMVs, mainly in the insula, superior temporal pole, amygdala, anterior cingulate, and frontal cortices (superior, middle, opercular inferior, and orbital frontal gyrus). No correlation between MCCB scores and GMVs was detected in SZ. However, for BD, working memory was relevant to the right hemisphere (i.e., right insula, amygdala, superior temporal pole, and medial and dorsolateral superior frontal gyrus). *Limitations*. The major limitations were that not all patients were the first-episode status and no medication. *Conclusions*. The association was mainly limited to the BD group. Thus, the underlying pathophysiology of the cognitive deficits, in terms of GMV alterations, may be diverse between two disorders.

1. Introduction

Cognitive impairments are the characteristic of schizophrenia (SZ) [1], covering almost all main domains. Although not as severe as those with SZ [2–4], patients with bipolar disorder (BD) also suffer significantly and share considerable overlaps with SZ in several cognitive domains, especially processing speed, verbal learning, and working memory [5, 6]. Impairments persist even in the absence of affective and/or psychotic symptoms [6–8], thereby seriously affecting socio-occupational ability and causing these clinically stable people (remitted SZ and BD) to remain unable of having normal or relatively normal social life [1, 6, 7, 9].

A series of studies, such as neuroinflammation [10, 11] and neurotrophic factor [12, 13], has been conducted on the impaired cognitive function of SZ and BD, but the underlying neurobiological mechanism is still unclear. Neuroimaging techniques, applied universally in the study of neuropsychiatric disorders, infer alterations of brain structure may have an impact on cognitive function [14, 15]. Voxel-based morphometry is a useful method in investigating the whole-brain structural alterations [16].

Many findings on the altered gray matter volumes (GMVs) of subjects with SZ and BD have been reported. Although the results of these reports have slight differences, similar alterations were observed in patients with SZ and BD. For example, one study reported changed GMVs in multiple frontal-temporal cortices of the patients with SZ across two cultural backgrounds (Germany and Japan) [17]. Meanwhile, other authors used meta-analyses to summarize GMV alterations in BD and also informed the regions located in frontal-temporal cortices [18]. These common brain structural alterations were supported by the findings of other researchers [19, 20]. Other similarly altered GMVs in patients with SZ and BD, such as cingulate and insula, were also documented [19–22].

These GMV alterations reported above are associated with cognitive impairments in subjects with SZ and BD. For instance, small frontal GMVs are associated with low premorbid intelligence quotient in patients with SZ and BD [15, 23]. However, studies on the association are limited thus far, and differences were observed in the findings, which were mainly concentrated on the following aspects: (1) the same impaired domain is associated with different GMV reductions in two disorders, such as social cognition, which is linked to the medial prefrontal cortex in SZ [24], while it is connected to the right middle cingulate gyrus in BD [25]; and (2) the two fields do not correlate, as the results of a cross-sectional study in subjects with SZ, which revealed that metacognition ability is independent of GMV alterations [26], and as the findings in those with BD, which indicated that cognitive deficits and GMVs have no association [27, 28].

These contradictory findings should be further studied to advance the understanding of altered brain structure that is linked to cognitive deficits. Considering the effect of the mood state and/or psychotic symptoms on GMVs [29], we focused on remitted patients with SZ and BD. We supposed that shared cognitive deficits and common GMV alterations in subjects with SZ and BD had similar associations. Thus, this study is aimed at determining similarities between the two patient groups in the severity of cognitive deficits, the extent of GMV alterations, and the correlation between cognitive impairments and GMV changes and subsequently at understanding the underlying neurobiological mechanisms of cognitive impairments in psychiatric disorders.

2. Materials and Methods

2.1. Participants. The study was conducted in a single site and recruited 137 individuals (age range, 18–50 years old): 46 with SZ, 35 with BD, and 56 healthy controls (HC). After a detailed description of the present study, all participants provided written informed consent as approved by the Medical Science Research Ethics Committee of the First Affiliated Hospital of China Medical University. All participants were recruited from the inpatient and outpatient services at the Shenyang Mental Health Center and the Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang, China. HC was recruited from the surrounding community via advertisement. The presence or absence of Axis I psychiatric diagnoses in participants was determined by two trained psychiatrists via the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders. All patients met the DSM-IV diagnostic criteria for BD or SZ without any other Axis I disorders. HC had no current or lifetime, personal or familial history of DSM-IV Axis I disorders. Exclusion criteria for all participants included the following: (1) substance/alcohol abuse or dependence, (2) any concomitant major medical disorder, (3) any neurological illness, (4) a history of head trauma with loss of consciousness for $\geq$5 min, (5) any magnetic resonance imaging (MRI) contraindications, and (6) suboptimal imaging data quality.

Symptom severity was assessed by the Hamilton Depression Rating Scale (HAMD-17) [30], Young Mania Rating Scale (YMRS) [31], and Brief Psychiatric Rating Scale (BPRS) [32]. The clinically stable criteria for patients included the following: (1) for SZ: BPRS score < 35; and (2) for BD: YMRS score < 7 and HAMD − 17 score < 7.

2.2. Cognitive Assessment. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is a reliable tool in assessing cognitive function from multidomains, which was introduced to evaluate and promote cognition in SZ and validated subsequently in BD [33–36]. The MCCB contains 10 tasks across 7 cognitive domains, including (a) processing speed (Trail Making Test A, Symbol Coding, and Category Fluency), (b) verbal learning (Hopkins Verbal Learning Test-Revised), (c) working memory (Spatial Span, Letter Number Span), (d) visual learning (Brief Visuospatial Memory Test-Revised), (e) reasoning, problem solving (The Mazes), (f) attention-vigilance (Continuous Performance Test-Identical Pairs), and (g) social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test). A total of 10 subtest scores and a composite score are included in this instrument. All subjects were tested cognition on the same day as the MRI scan.

2.3. MRI Acquisition. MRI scans were performed on a GE Signa HD 3.0-T scanner (General Electric, Milwaukee, USA) at the Image Institute of the First Affiliated Hospital of China Medical University, Shenyang, China. T1-weighted, high-resolution, and 3D image data were collected using a 3D fast spoiled gradient-echo sequence (repetition time = 7.2 ms, echo time = 3.2 ms, field of view = $240 \times 240\ mm^2$, matrix = 240×240, flip angle = 13°, slice thickness = 1 mm, number of slices = 176, no gap, voxel size = $1.0\ mm^3$). A standard head coil was applied to transmit and receive the nuclear magnetic resonance signal, while earplugs and foam pads were used to reduce noise and head motion. During scanning, subjects were informed to keep their eyes closed but warned not to fall asleep.

2.4. Data Processing. As suggested by the forerunners [37], we used the voxel-based morphometry (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm8/) to process the structural MRI data, which were incorporated into the Statistical Parametric Mapping (SPM8) software. The VBM8 processing steps included bias correction, tissue segmentation, and spatial normalization (Montreal Neurological Institute space, resampled to $1.5\ mm^3$ isotropic voxels) by using Diffeomorphic

Table 1: Demographic and clinical characteristics.

Characteristic	Group; mean ± SD or no. (%) HC ($n = 56$)	SZ ($n = 46$)	BD ($n = 35$)	$F/\chi^2/t/H$	p value	Post hoc analysis
Age, year[a]	29.54 ± 9.41	29.70 ± 8.90	32.20 ± 10.50	0.966	0.383	—
Male sex[b]	21 (37.5%)	13 (28.3%)	10 (28.6%)	1.260	0.533	—
Education, year[a]	14.48 ± 3.30	12.96 ± 3.03	13.83 ± 3.37	2.821	0.063	—
Handedness, right[b]	56 (100%)	46 (100%)	35 (100%)	—	—	—
First episode, yes[b]	—	27 (58.7%)	10 (28.6%)	7.269	0.007∗	SZ>BD
Duration (month)[c]	—	42.15 ± 55.36 ($n = 40$)	56.81 ± 57.43 ($n = 32$)	1.071	0.304	—
Medication, yes[b]	—	42 (91.3%)	29 (82.9%)	1.311	0.252	—
Antipsychotic[b]	—	38 (86.4%)	17 (58.6%)	7.242	0.007∗	SZ>BD
Mood stabilizer[b]	—	7 (15.9%)	17 (58.6%)	14.450	<0.001∗	BD>SZ
Antidepressant[b]	—	11 (25.0%)	6 (20.7%)	0.182	0.670	—
HAMD-17, total score[d]	1.11 ± 1.53	3.27 ± 3.98	2.37 ± 2.29	13.537	0.001∗	SZ>HC ($p = 0.002$ ∗) BD>HC ($p = 0.024$ ∗) SZ vs. BD ($p = 1.000$)
YMRS, total score[d]	0.18 ± 0.61	0.67 ± 1.62	0.63 ± 1.57	3.274	0.195	—
BPRS, total score[d]	18.54 ± 1.04	21.93 ± 4.35	20.94 ± 5.22	24.500	<0.001∗	SZ>HC ($p < 0.001$ ∗) BD>HC ($p = 0.003$ ∗) SZ vs. BD ($p = 0.186$)

BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; F, one-way ANOVA; H, Kruskal-Wallis test; HAMD-17, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; HC, healthy control; SZ, schizophrenia; SD, standard deviation; t, independent-samples t-test; YMRS, Young Mania Rating Scale; χ^2, Chi-square test; [a]One-way ANOVA; [b]Chi-square test; [c]independent-samples t-test; [d]Kruskal-Wallis test. ∗Significant at $p < 0.05$; post hoc analysis is the Bonferroni correction.

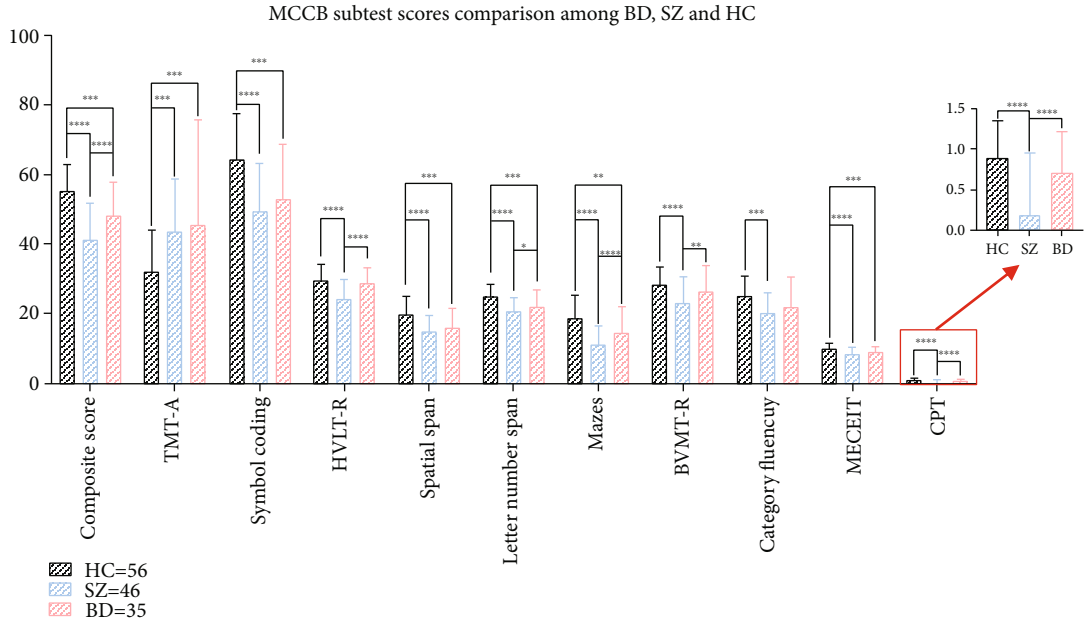

Figure 1: MCCB subtest scores comparison among BD, SZ and HC. TMT-A, Trail Making Test A; HVLT-R, Hopkins Verbal Learning Test-Revised; BVMT-R, Brief Visuospatial Memory Test-Revised; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; CPT-IP, Continuous Performance Test-Identical Pairs. Note: ∗$p < 0.05$, ∗∗$p < 0.01$, ∗∗∗ $p < 0.005$, ∗∗∗ ∗$p < 0.001$.

Anatomical Registration Through Exponentiated Lie algebra (DARTEL) [38], modulation process (nonlinear deformations), and smoothing (Gaussian kernel with 8 mm full width at half-maximum).

2.5. Statistical Analysis. Three groups' (SZ, BD, and HC) analyses of the demographic and clinical data were performed in the SPSS 20.0 software (SPSS Inc., Chicago, Illinois) using one-way analysis of variance (ANOVA),

Table 2: Clusters showing significant differences across BD, SZ, and HC groups with one-way ANCOVA.

Cluster	Brain regions	Voxels	Peak MNI coordinate			F	p	Post hoc analysis
			x	y	z			
A	R-dorsolateral superior frontal gyrus	1638	24	49.5	28.5	11.629	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD < HC (P = 0.022∗) SZ vs BD (p = 0.336)
B	L-orbital middle frontal gyrus L-middle frontal gyrus L-orbital superior frontal gyrus	1444	-28.5	60	-2.84	12.008	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.036$ ∗) SZ vs. BD ($p = 0.191$)
C	L-rectus R-rectus	1420	-7.5	36	-21	11.090	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.03$ ∗) SZ vs. BD ($p = 1.000$)
D	R-insula R-temporal pole-superior temporal gyrus R-amygdala	1319	34.5	7.5	-19.5	13.476	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.010$ ∗) SZ vs. BD ($p = 0.298$)
E	L-superior temporal gyrus	943	-61.5	-58.5	15	15.155	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD vs. HC ($p = 0.243$) SZ<BD ($p = 0.006$ ∗)
F	L-insula	906	-33	7.5	19.5	12.144	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.017$ ∗) SZ vs. BD ($p = 0.341$)
G	L-dorsolateral superior frontal gyrus L-middle frontal gyrus L-anterior cingulate and paracingulate gyri	856	-19.5	58.5	25.5	15.475	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.006$ ∗) SZ vs. BD ($p = 0.196$)
H	L-insula L-opercular inferior frontal gyrus L-temporal pole-superior temporal gyrus	811	-48	16.5	1.5	14.456	<0.001∗	SZ < HC (P < 0.001∗) BD < HC (P = 0.004∗) SZ vs BD (p = 0.421)
I	R-medial superior frontal gyrus	797	3	60	-1.5	10.622	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD<HC ($p = 0.007$ ∗) SZ vs. BD ($p = 1.000$)
J	R-supramarginal gyrus	565	64.5	-16.5	28.5	11.030	<0.001∗	SZ<HC ($p < 0.001$ ∗) BD vs. HC ($p = 1.000$) SZ<BD ($p = 0.004$ ∗)

GRF, Gaussian random field corrections; MNI, Montreal Neurological Institute; L, left; R, right; x, y, z, coordinates of peak voxel. ∗Significant at $p < 0.05$. Post hoc analysis is the Bonferroni correction.

independent-samples t-test, or the Kruskal-Wallis test for continuous variables, and the Chi-square test for categorical variables. The MCCB scores among three groups were also compared in SPSS, using a one-way analysis of covariance (ANCOVA) with diagnosis as an independent factor, and gender and age as covariates. The GMVs were analyzed in SPM8 and Data Processing Assistant for Resting-State fMRI (DPABI, 2.3, Advanced edition), and ANCOVA was also used with diagnosis as an independent factor, and gender and age as covariates. To determine the significant brain regions statistically, which were identified by the Anatomical Automatic Labeling (AAL) template, we set $p < 0.001$ for each voxel and $p < 0.05$ for multiple comparisons (Gaussian random field (GRF) correction). GMVs were extracted from these significantly different regions and compared between each pair ($p < 0.05$, Bonferroni correction). Then, the partial correlation analysis was employed to analyze the relationship between abnormal MCCB scores and extracted significantly GMV values with gender and age as controlled factors, and the significance level at $p < 0.05$ (false discovery rate (FDR) correction).

3. Results

3.1. Demographic and Clinical Analyses. Among the SZ, BD, and HC groups, the differences in age, gender, and education were not significant, and all participants were right-handed. For scale scores, significant group effects were found in HAMD-17 ($p = 0.001$) and BPRS ($p < 0.001$), but not YMRS among the three groups. The duration of the illness and the proportion of the medication use were not significantly different between the SZ and BD groups, but the type of drug was different. The SZ group used more antipsychotic drugs ($p = 0.007$), while the BD group utilized more mood stabilizers ($p < 0.001$). The first-episode status was different between the two patient groups ($p = 0.007$). More analyses about the first-episode status and medication are listed in the supplemental file (Tables S1–S6). Details about demographic and clinical data are presented in Table 1.

3.2. Cognitive Assessment Results. ANCOVA showed significant differences in cognitive function among the three groups. First, the composite score of the patients with SZ

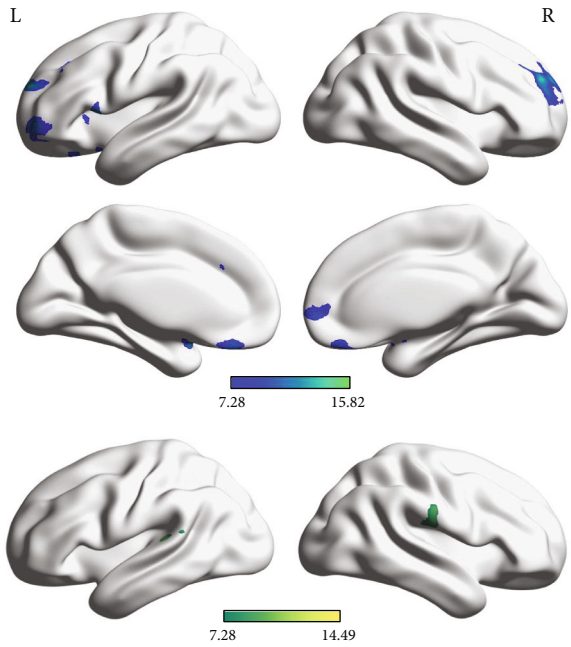

Figure 2: GMV alteration among BD, SZ, and HC. Significant at $p < 0.05$ with voxel $p < 0.001$ (GRF correction). Blue colour indicates relatively lower GMVs values in both BD and SZ. Green colour indicates relatively lower GMVs values in SZ.

and BD was lower than that of the HC subjects, but SZ manifested worse than BD. For MCCB subtests, post hoc analyses revealed that compared with HC, the SZ group showed impairments in all 10 cognitive tasks, while the deficits of the BD group were detected in 6 tasks, including Trail Making Test A (TMT-A), Symbol Coding, Spatial Span, Letter Number Span, Mazes, and Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT). Finally, the distinction between patients with SZ and BD in the Hopkins Verbal Learning Test (HVLT-R), Letter Number Span, Mazes, Brief Visuospatial Memory Test-Revised (BVMT-R), and Continuous Performance Test-Identical Pairs (CPT-IP) was significant ($p < 0.05$, Bonferroni correction; Figure 1).

3.3. Differences in GMV Groups. Significant group effects were detected in 10 clusters across 17 brain regions. Compared with HC, SZ and BD groups had decreased GMVs in the bilateral insula, bilateral temporal pole-superior temporal gyrus (TPOsup), limbic system (right amygdala and left anterior cingulate and paracingulate gyri (ACG)), as well as several regions of the frontal cortices (bilateral dorsolateral superior frontal gyrus (SFGdor), right medial superior frontal gyrus (SFGmed), left middle frontal gyrus (MFG), left opercular inferior frontal gyrus (IFGoperc), left orbital middle frontal gyrus (ORBmid), left orbital superior frontal gyrus (ORBsup), and bilateral rectus (REC)). Besides, there were 2 regions (i.e., left superior temporal gyrus and right supramarginal gyrus) reduced only in the SZ group ($p < 0.05$, Bonferroni correction; Table 2 and Figure 2).

3.4. Correlation between GMVs and MCCB. No correlation was observed between MCCB scores and GMVs in subjects with SZ anywhere across 17 altered brain regions. Nevertheless, a series of links were detected in the BD group, concentrating on the cognitive subtest across Spatial Span and Letter Number Span, which comprised working memory. Specifically, the scores of Spatial Span were relevant to the right SFGdor, and the scores of Letter Number Span were affected by the right insula, amygdala, TPOsup, and SFGmed. ($q < 0.05$, FDR correction; Figure 3).

4. Discussions

This study focused on probands with remitted SZ and BD, from cognitive impairments, GMV alterations, and the correlation between them, in which substantial similarities and differences were observed.

Considering the composite cognition, all patients with SZ and BD had deficits, and the performance of SZ was poor, which was consistent with the findings of prior studies on cognitive deficits [4, 39], wherein SZ has a worse composite score than BD. In terms of every cognitive subtest of MCCB, the SZ group showed impairments in overall 7 cognitive domains, whereas the BD group presented cognitive impairments only in 4 domains, that is, processing speed, working memory, problem solving, and social cognition, just like the findings of several cross-sectional studies [6, 40, 41]. However, some studies have found other impaired cognitive domains in patients with BD, such as deficits in visual and verbal learning found by Van Rheenen and Rossell [34]. Another study that selected BD patients during the onset found no problem solving or social cognitive abnormalities [35]. These conflicting results may be due to the emotional states of patients which were different from our study. Additionally, the BD group performed better than the SZ group in verbal learning, working memory, problem solving, visual learning, and attention, which was similar to the result of another study that concentrated on the verbal episodic memory of SZ and BD [42]. According to the findings above, the cognitive impairments of patients with SZ were more severe than those of patients with BD, broad consent with previous studies [36, 43].

Regardless of probands with SZ or BD, the alterations of GMVs in every brain region which was discovered differences from HC were reduced. This result was supported by other authors. For example, several authors documented the entire cortex volume reductions in patients with SZ who had cognitive impairments [44], and others reported that cognitively impaired patients with SZ and BD exhibited small total brain volumes [45]. Relative to HC, the common brain structural changes in both patient groups were mainly concentrated on 4 areas, including insular, temporal cortex (bilateral TPOsup), limbic system (right amygdala and left ACG), and frontal cortices (bilateral SFGdor, right SFGmed, left MFG, left IFGoperc, left ORBmid, left ORBsup, and bilateral REC), which was consistent with the results of a review that summarized the findings of GMV comparisons between SZ and BD and pointed overlapping reductions in the insula and ACG [46], and following the results of a matched control study that indicated small GMVs within frontal and temporal regions in both SZ and BD [47]. This result also agreed with

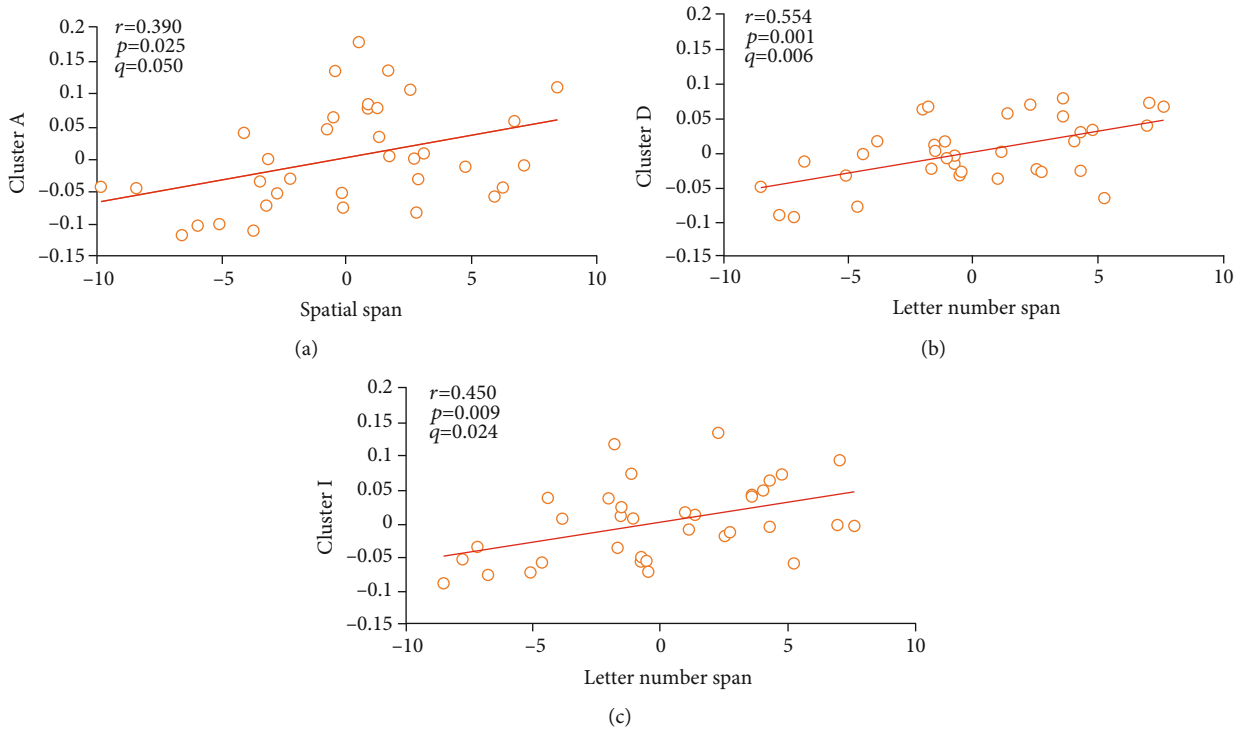

Figure 3: Correlations between MCCB scores and GMVs in BD. Significant at $q < 0.05$, FDR correction.

the findings of other studies [21, 25, 29]. Besides, as early studies detected, our study also reported that GMV damages in patients with SZ covered more areas than those with BD, that is, primarily left STG and right SMG [46, 48].

The results of the correlation analysis showed that only the BD group had associations between cognitive impairments and GMV alterations. The decreased working memory of BD was related to reduced GMVs of the right hemisphere, containing the right insula, amygdala, TPOsup, SFGmed, and SFGdor. However, the study on the association between cognitive deficits and GMV damages in patients with BD was limited. There was a study on the gray matter density of pediatric patients with BD, in which the reductions of the left orbitofrontal cortex are associated with working memory [49]. The differences from us may be due to the age range of the participants, because the gray matter of the child is still in the developmental stage. As for other cognitive impaired domains of BD, they were independent of GMV alterations, including processing speed and social cognition, against previous surveys.

However, the probands with remitted SZ, who had more cognitive impairments and GMV alterations, were undetected any association between MCCB subtest scores and extracted values from changed brain regions. This result was different from those of prior studies. For example, one study in a Chinese Han population with SZ reported impaired working memory was correlated with GMV reductions and fractional anisotropy decrease in prefrontal and superior temporal area [50], but they applied a different method—multimodal fusion, to measure brain abnormity. Another study informed the link between hippocampal subregion volumes and cognitive performance in visual, verbal, and working memory [51], whereas we found no alterations around hippocampal. Because we aimed to identify neuroimaging substrates of cognitive impairments in psychiatric disorders, other nonaltered regions were not performed a correlation analysis, which may also be associated with cognition but not related to the diseases. Meanwhile, the findings of a Japanese research suggested that the anterior cingulate and medial frontal cortices volumes affect working memory in SZ [52]. Divergence may be considered since the patients included in the study were disease-onset, whereas the mood state and/or psychotic symptoms have an effect on GMVs [29]. Another important reason for the differences from others was that we used partial correlation analysis with gender and age as controlled factors, so that the results were net and little.

Whether the neurobiological mechanism behind SZ and BD cognitive impairment is consistent has been controversial. In recent years, some researchers propose a continuum between SZ and BD [53], so that the mechanism of the two diseases should be the same. However, our results supported the traditional view that the two diseases are independent of each other. Some studies have explored the mechanism by functional magnetic resonance imaging or white matter integrity [52, 54], and the results are also divergent. There cannot be a conclusion on this matter whether cognitive impairment is caused by a single lesion or multiple lesions, yet in terms of our results, the patterns of SZ and BD were different.

Overall, this is the first study that focused on probands with remitted SZ and BD from the neurobiological mechanism behind cognitive impairment, using MCCB to assess cognitive function and GMVs to measure brain structural

alterations. We eliminated the effects of the mood state and/or psychotic symptoms by strictly limiting the state of the disease. Our results added meaningful evidence for the study of cognitive impairment mechanisms in psychiatric illnesses.

5. Limitations

The major limitations of the study were the effects of the first-episode status and medication on cognition and GMV alterations. After analyzing these factors in the two patient groups, we made some findings. The first-episode status and the use of antipsychotic affected the working memory of both patient groups. The effect of mood stabilizer was only on the GMV alterations in the SZ group. Details were listed in the supplemental file (Tables S1–S6). Hence, additional large-scale surveys with strict limitations are needed.

6. Conclusions

SZ and BD groups had shared cognitive impairments and GMV alterations, but the SZ group was more severe than the BD group in both fields. The association between the two fields was mainly limited to the BD group. Consequently, the underlying pathophysiology of cognitive deficits, at least brain structure, may be diverse between two disorders.

Data Availability

The data that support the findings of this study are available upon reasonable request by contact with the corresponding author, Yanqing Tang.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (grant nos. 2018YFC1311604 and 2016YFC1306900 to Yanqing Tang), National Science Fund for Distinguished Young Scholars (grant no. 81725005 to Fei Wang), Liaoning Education Foundation (Pandeng Scholar to Fei Wang), Innovation Team Support Plan of Higher Education of Liaoning Province (grant no. LT2017007 to Fei Wang), Major Special Construction Plan of China Medical University (grant nos. 3110117059 and 3110118055 to Fei Wang), Joint Fund of National Natural Science Foundation of China (grant no. U1808204 to Feng Wu), and Natural Science Foundation of Liaoning Province (grant no. 2019-MS-05 to Feng Wu). The authors thank all participants in the study and investigators involved in conducting the study.

Supplementary Materials

Table S1: comparison of MCCB scores and cluster values between SZ patients in the first episode and SZ patients not in the first episode. Table S2: comparison of MCCB scores and cluster values between SZ patients with antipsychotic and SZ patients without antipsychotic. Table S3: comparison of MCCB scores and cluster values between SZ patients with mood stabilizer and SZ patients without mood stabilizer. Table S4: comparison of MCCB scores and cluster values between BD patients in the first episode and BD patients not in the first episode. Table S5: comparison of MCCB scores and cluster values between BD patients with antipsychotic and BD patients without antipsychotic. Table S6: comparison of MCCB scores and cluster values between BD patients with mood stabilizer and BD patients without mood stabilizer. *(Supplementary Materials)*

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