

Research report

Changes of functional connectivity of the subgenual anterior cingulate cortex and precuneus after cognitive behavioral therapy combined with fluoxetine in young depressed patients with suicide attempt

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ABSTRACT

This single-center, randomized, single-blind, parallel-controlled study aimed to analyze the changes in resting-state functional connectivity (RSFC) in young patients with a suicide attempt caused by depression before and after cognitive-behavioral therapy (CBT) combined with fluoxetine or fluoxetine alone by functional magnetic resonance imaging (fMRI). Before treatment, functional connectivity of the right subgenual anterior cingulate cortex (R-sgACC), left subgenual anterior cingulate cortex (L-sgACC) and right precuneus (R-PCu) was lower in depressed patients with a suicide attempt than that of healthy controls. After treatment, compared with the fluoxetine group, functional connectivity between the R-sgACC and left posterior cerebellar lobe in the CBT group was increased, while this group also showed increased RSFC between the L-sgACC and right anterior cingulate cortex/ medial prefrontal cortex. On the contrary, the functional connectivity between the R-PCu and right parietal lobe was reduced ($P < 0.001$). It was also found there were some changes in different brain regions in pre- and post-treatment within both the CBT and MG group. The functional connectivity of the R-sgACC and the left posterior cerebellum lobe was negatively correlated with the SSI score. The functional connectivity of the R-PCu and right middle frontal cortex was negatively correlated with the HAMD score before treatment. After treatment, functional connectivity between the R-PCu and right superior frontal gyrus was positively correlated with the SSI scores in the CBT group. After 8 weeks of combined CBT, the strength of the functional connectivity in the bilateral sgACC and bilateral PCu was significantly changed.

1. Introduction

Suicide is a threat to the public health worldwide. According to the report of the Centers for Disease Control and Prevention (CDC), the suicide rate increased by 33% from 1999 to 2017 in the United States [1]. Depression is a high-risk factor for suicide [2] and is characterized by persistent depression, lack of pleasure, retardation of thinking, and decreased behaviors [2,3]. Depression has a high recurrence rate, high suicide rate, and high disease burden [4]. In the United States, the prevalence of depression in the young people aged 18–25 years is 9.6% [4]. The lifetime prevalence of depression is 6.8% in China [5].

Cognitive-behavioral therapy (CBT) is a very effective psychotherapy for suicide attempts and achieves results over a short term [6]. CBT

can be used to improve cognitive distortion and negative beliefs by changing the thinking, beliefs, and behaviors, thus eliminating the negative emotions and behaviors of the patients [7–9]. CBT has the advantages of simple operation, quick effect, and significant reduction of recurrence rate. A meta-analysis showed that short-term CBT decreases suicidal ideations, decreases the suicide risk, and improves suicide-related depressive emotions [10]. Raj et al. [11] revealed that compared to routine medical treatment, CBT improves the symptoms of anxiety, depression, suicidal ideation, despair and dysfunctional attitudes in patients with self-injury. Hollon et al. [12,13] reported that 40%–60% of patients without taking medications for depression show significant improvements in their symptoms after CBT. Brown et al. [13] showed that 76% of patients had no suicidal behaviors after CBT, while

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this proportion was only 58% in the conventional treatment group. Mewton et al. [9] analyzed 15 studies on the efficacy of CBT in reducing suicide rates and concluded that CBT reduces suicidal ideations and behaviors. Most symptoms can be managed in the early phase of CBT, i. e., in the first 4 weeks of CBT treatment [14]. Currently, there are many hypotheses and theories for the mechanism of CBT in the treatment of depression [15,16], but the neurobiological mechanism of CBT remains unclear.

Functional magnetic resonance imaging (fMRI) offers the potential to explore the pathogenesis of depression and the biological basis of the mechanism of CBT [17,18]. Abnormalities in functional connectivity have been found between the left prefrontal cortex and amygdala in patients with major depressive disorder using grey matter volume or amplitude of low-frequency fluctuation [17,18]. Previous studies revealed abnormal functional changes of several brain regions, including the anterior cingulate cortex and precuneus, in young patients with major depressive disorders [18–23]. In addition, some studies showed that the functional connectivity between the anterior cingulate cortex and the frontal lobe is decreased in depressed patients with a suicide attempt, and simultaneously suggested that the functional change in the anterior cingulate cortex could be a neurobiological marker for the assessment of depressed patients with suicide attempts [19–23]. Zhang et al. [21] showed that the functional connectivity of the right precuneus is decreased in depressed young patients with a suicide attempt. Some studies showed that the functional connectivity of the bilateral anterior cingulate cortex is increased after CBT [24], while Yoshimura et al. [25] found that the functional connectivity between the anterior cingulate cortex and medial prefrontal cortex in the resting state is reduced after CBT. To date, there is no study which has used resting-state fMRI (rs-fMRI) to explore the clinical efficacy of CBT combined SSRIs in treating depressed young patients with suicide attempts, as well as the association with the mechanisms of potential neural effects. Therefore, in the present study, the bilateral subgenual anterior cingulate cortex (sgACC) and bilateral precuneus (PCu) were pre-defined as the seed points for a full-brain functional connectivity analysis to preliminarily investigate the changes in brain functions and the associated neural effects after CBT combined with drug therapy. The sgACC and precuneus are involved in emotion experience and processing; the former has the function of negative emotion creation and antidepressant treatment response; the latter could conduct spontaneous, insight thoughts and emotions [26,27]. Those four regions were selected according to a preliminary study and the literature [24,25,28,29].

2. Methods

2.1. Study design

This study was a single-center, randomized, single-blind, parallel-controlled study. The subjects were diagnosed by psychiatrists (attending physician or above) using the Patient version (SCID-I/P) of the Structured Clinical Interview for DSM-IV. Assessment and clinical scale scoring were completed by researchers who had received standard trainings, and the assessors were blind. In addition, all subjects were informed of the main contents of the study. They signed the informed consent forms voluntarily. The Medical Ethics Committee of the Second People's Hospital of Guizhou Province approved this study. The study was registered with Chinese Clinical Trial Registry (ChiCTR1900024989).

Based on the conventional treatment with an antidepressant drug (fluoxetine), the CBT group received a structural CBT intervention for eight sessions. The monotherapy (MG) group was treated with fluoxetine alone. The rs-fMRI data of the subjects were collected at baseline and after 8 weeks of treatment (the control group was scanned only once). Assessments with the HAMD24 and SSI scales were performed before and after 8 weeks of treatment.

2.2. Subjects

Young depressed patients with suicide attempts were recruited from the Second People's Hospital of Guizhou Province from March 2017 to June 2019. In addition, healthy volunteers were enrolled as healthy controls (HC), matched for age, sex, and education level with the patient group.

For the patients, the inclusion criteria were: 1) 18–28 years old; 2) Han nationality; 3) right-handed; 4) years of education at least 9; 5) diagnosed with “depressive episode” according to the American Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); 6) Hamilton Depression Scale (HAMD₂₄) score [30] ≥ 35 points; 7) suicide attempt for at least one time; 8) did not receive antidepressant medication or psychotherapy within 1 month before enrollment; and 9) without the history of electroconvulsive therapy.

For the patients, the exclusion criteria were: 1) with other mental disorders: such as personality disorder, anxiety disorder, mental retardation, manic episode, schizophrenia, etc.; 2) Hamilton Anxiety Scale (HAMA) score ≥ 14 points; 3) symptoms of depression caused by organic diseases or drugs; 4) brain organic diseases; 5) a history of substance abuse or familial history of psychiatric illnesses; (6) severe physical diseases; or 7) pregnant, or MRI scanning contraindications.

For the HC group, the inclusion criteria were: 1) Han nationality; 2) 18–28 years old; 3) right-handed; 4) years of education at least 9; 5) HAMD₂₄ score < 8 points; and 6) not received psychotherapy before. The exclusion criteria were: 1) severe somatic diseases; 2) with a HAMA score < 7 points; 3) diagnosed with psychiatric disorders such as mental retardation, schizophrenia, depression, manic episode, or anxiety disorder; 4) a history of substance abuse or familial history of psychiatric illnesses; 5) pregnant; or 6) MRI scanning contraindications.

According to the Columbia Classification Algorithm for Suicide Assessment (C-CASA) [31], the suicide attempt in this study was defined as: “those with a willingness to end their lives, have taken self-harming behaviors but did not succeed, definite evidence of the suicide attempt or it can be inferred from their behaviors and situations.”

2.3. Grouping

In this study, 100 participants (30 in the CBT group, 30 in the MG group, and 40 in the HC group) were recruited at the beginning. Eleven participants dropped out before the treatment was completed, of whom five were in the CBT group (drop-out rate of 16.7%), and six were in the MG group (drop-out rate of 20.0%). In addition, five participants (three in the MG group and two in the HC group) were excluded due to head movement of $> 2^\circ$ during MRI scanning. Finally, 25, 21, and 38 participants were analyzed in the CBT, MG, and HC groups, respectively (Figs. 1 and 2). None of the participants in this study experienced a seizure due to drug overdose.

2.4. Interventions

The antidepressant that the patients took was fluoxetine dispersible tablets (Lilly Suzhou Pharmaceutical Co., Ltd.), with a dose of 20–50 mg/d. Benzodiazepines can be used in combination during the treatment. The participants in the CBT group received both CBT and fluoxetine. The therapist was the deputy chief physician of the psychiatry department, who had received the CBT special training of the Chinese Association for Mental Hygiene. CBT therapists were supervised by a superior chief physician at intervals of 2 weeks. The individual CBT was performed once a week for a total of eight times, for 35–50 min each time. The first session aimed to understand the concept and treatment methods of depression and the characteristics of CBT. The second session aimed to identify automatic thoughts and their effects on emotions, understand the depressive cognitive triad and implement of behavioral training strategies. The third session aimed to understand and confront distorted cognition, receive self-confidence trainings to establish the

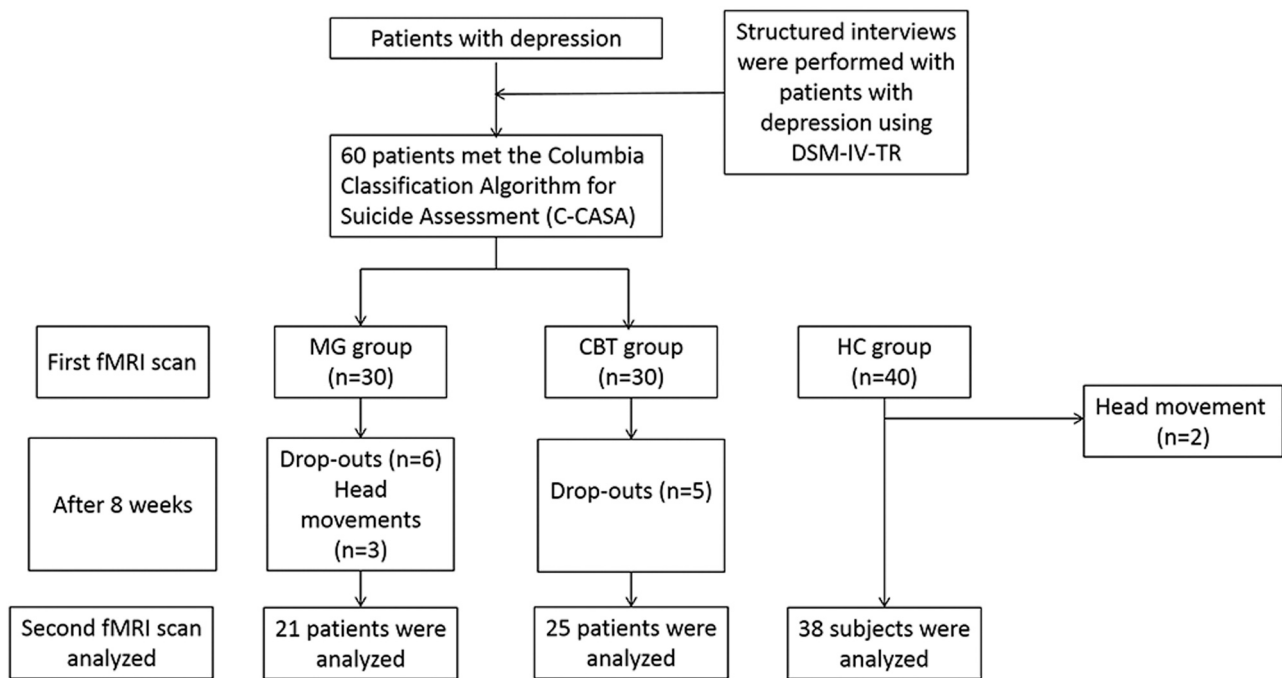


Fig. 1. Study flowchart.

alternative thinking, understand the meaning of behavioral functions, and reduce thinking rumination. The fourth to sixth sessions aimed to identify distortion cognition and to change attribution styles, learn to deal with self-blame and develop task levels, use task decomposition to complete work, build self-confidence, cope with setbacks, and accumulate positive thinking. The seventh session aimed to identify negative core beliefs and use positive thinking to overcome distortion cognition. The eighth session aimed to summarize and develop future plans to prevent a recurrence. At the end of each individual CBT session, the patients were required to complete some homework, including a list of expectations, records of thinking, the exercise of alternative thinking, and activity arrangements [32].

The therapy discontinued when serious adverse reactions happened during the intervention.

2.5. Selection of the coordinates

According to the preliminary results of the present study, the function of brain regions such as the anterior cingulate cortex and the anterior cuneiform lobe was abnormally altered in depressed youth with attempted suicide [24]. Previous studies reported a decreased functional connectivity activity in the anterior cingulate cortex and frontal lobe in patients with attempted suicide or depression [19–23]. Zhang et al. [21] found a weakened functional connection of the right anterior cuneiform lobe in young depressed patients with attempted suicide. Yoshimura et al. [24,25] found that the functional connection between the anterior cingulate cortex and the medial prefrontal lobe in the resting state showed a significant decrease after CBT. Finally, by combining previous studies and the related literature, the bilateral sgACC (MNI coordinates: $x = \pm 12$, $y = 36$, $z = 6$) and bilateral PCu (MNI coordinates: $x = \pm 5$, $y = -78$, $z = 30$) were selected as the regions of interest (ROIs), and with this as the center, ROI of $r = 6$ mm was used as the seed point, and the voxel-wise functional connectivity was calculated.

2.6. Assessment indicators

The changes in functional connectivity in subjects before and after treatment were investigated using the rs-fMRI. In addition, in the

analysis of functional connectivity, the selected seed points were the R-sgACC, L-sgACC, R-PCu and L-PCu.

This study used HAMD₂₄ to assess depressive symptoms and their severity [30]. The Scale for Suicide Ideation (SSI) [33] was used to assess the suicidal ideation of the subjects. The HAMD₂₄ reduction rate after treatment was used as the clinical efficacy standard [29]: significantly effective, HAMD₂₄ reduction rate $\geq 50\%$; moderately effective, $30\% \leq \text{HAMD}_{24}$ reduction rate $< 50\%$; and ineffective, HAMD₂₄ reduction rate $< 30\%$.

2.7. fMRI

Data were collected using a 3-T GE Signa HDxt MRI system (General Electric Medical Systems, Waukesha, WI, USA). During the scan, the subjects were in the horizontal position, keeping awake but quiet, eyes closed, with calm and even breathing, and did not take active thinking activities. The specific scanning process, sequence, and parameters were: 1) 3D-T1 structure imaging, the 3D magnetization inversion recovery-prepared fast spoiled gradient-echo (3D FSPGR-IR) was used, and the parameters were: TR/TE (ms) = 12.5/5.4, slice thickness = 1.2 mm, scanning 232 layers, 20° flip angle, FOV = 240 mm \times 240 mm, matrix = 256 \times 256, total scan time: 4 min 43 s; 2) T2 weighted FLAIR imaging, fluid attenuation inversion recovery (FLAIR) sequence, and the scanning parameters were: TR = 8400 ms, TE = 150 ms, slice thickness = 6.0 mm, slice spacing = 2.0 mm, field of view (FOV) = 240 mm \times 240 mm, matrix = 256 \times 192; acquisition was performed for 1 time, and there were a total of 16 layers for the axial surface from the skull base to the parietal lobe, and scanning time was 2 min 49 s; and 3) BOLD imaging, gradient echo-echo planar imaging (Gradient Echo EPI) was used, and the scanning parameters were: TR/TE = 3000/40 ms, slice thickness/spacing = 4.0/0 mm, FOV = 240 mm \times 240 mm, matrix = 64 \times 64, 4352 layers in total with flip angle of 90° , and a total of 128 time points were collected, and the scanning time was 6 min 24 s.

2.8. Quality control

In order to ensure that the fMRI images met the standards, the

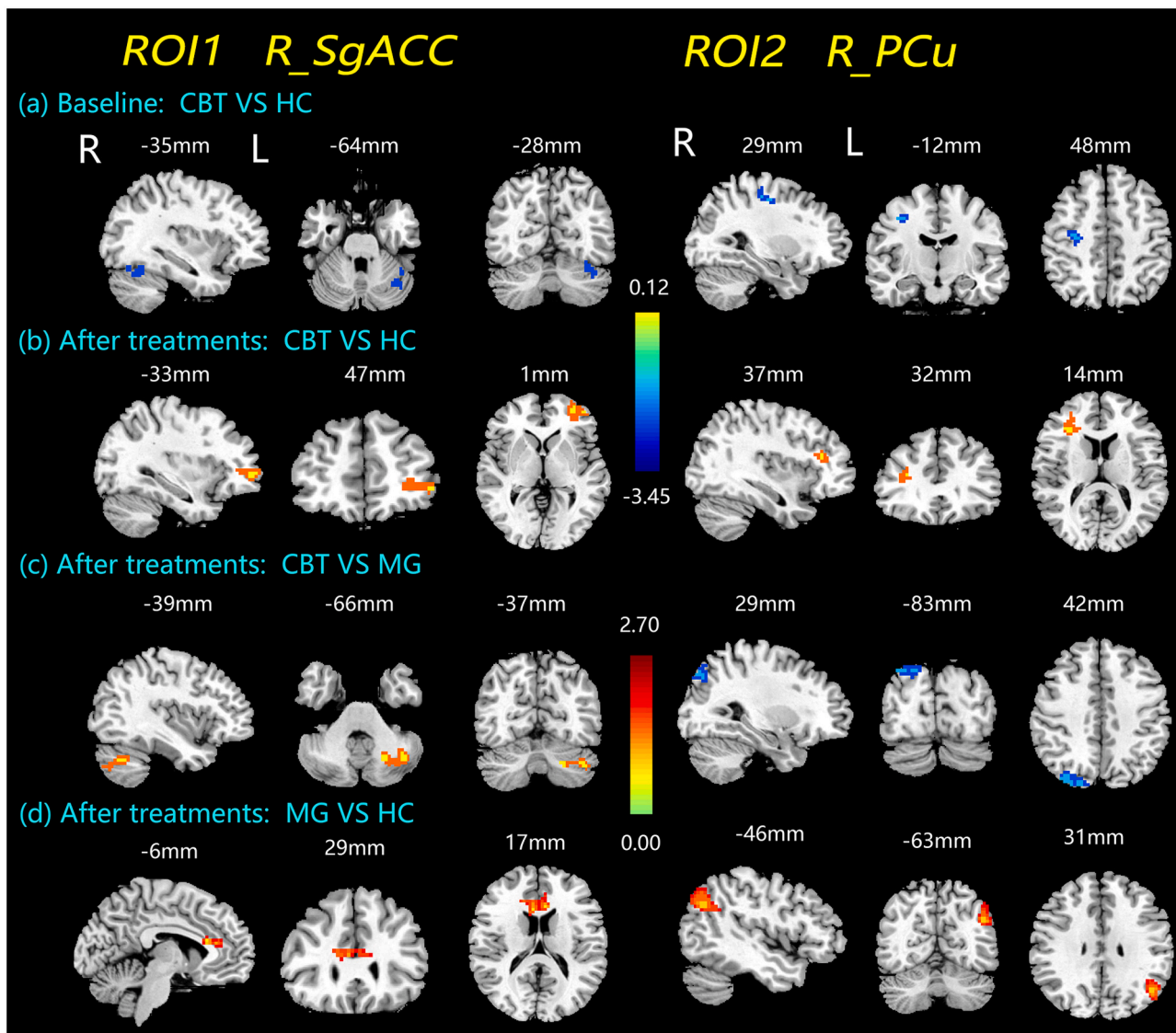


Fig. 2. Brain regions with significant differences in functional connectivity (FC) before and after treatment. (a) Before treatment, brain regions with significant differences in FC value between the CBT group and HC groups. (b) After 8 weeks of intervention, brain regions with significant differences in FC value between the CBT and HC groups. (c) After 8 weeks, brain regions with significant differences in FC value between the CBT and MG groups. (d) After 8 weeks, brain regions with significant differences in FC value between the MG and HC groups. (e) After 8 weeks, using R-SgACC as seed point, brain regions with significant differences in FC value between the CBT and MG groups. (f) After 8 weeks, using R-PCu as seed point, brain regions with significant differences in FC value between the CBT and MG groups.

doctors gave uniform instructions before the scan, including to stay as calm as possible and not to move during the scanning process. When it is scanning, the doctors observed the original image, and eliminated or rescanned the images with obvious artifacts or distortion.

2.9. Image processing

fMRI data processing mainly included two steps, the raw data preprocessing and the statistical analysis of image data. Data preprocessing was performed by using the DPABI_V4.0_190305 software (DPABI: a toolbox for Data Processing & Analysis for Brain Imaging The R-fMRI Network <http://rfmri.org/dpabi>) that run under the Matlab_2013b (Mathworks, Inc) environment [34]. The preprocessing included eight steps: 1) data format conversion; 2) deletion of the first ten time points; 3) slice timing; 4) the subjects' range of head movement were translational movement ≤ 2 mm, and rotation $\leq 2^\circ$; if exceeding these ranges, the data were eliminated; 5) space normalization; 6) spatial smoothing; the full width at half maximum (FWHM) used in this study

was $4 \times 4 \times 4$ mm; 7) detrending; and 8) low-pass filtering (0.01–0.10 Hz).

2.10. Demographic data and clinical scale assessment

Age, sex, education level, past history, and other related data were collected. The clinical psychological scale assessment of the severity of depressive symptoms and the degree of suicidal ideation was performed by consistently trained assessors. The assessment was conducted in a combination of conversation and observation, which was performed within 24 h after enrollment and 8 weeks after treatment.

2.11. Mean functional connectivity values (zFC) correlation analysis

The RESTplus V1.21 software (<http://www.restfmri.net/forum/REST>) was used to extract the zFC of the brain regions with significant statistical differences before and after treatment. The zROI values were obtained by using the fast Fourier transform (FFT). For the

pre-treatment RSFC analysis, the RESTplus V1.21 software was used for the one-sample *t*-test analysis of the baseline HC, CBT, and zROI values in the groups to obtain the brain images of the bilateral sgACC, bilateral PCu, and voxel of the whole brain. The brain regions were corrected by multiple comparison correction with AlphaSim. $P < 0.001$, $rmm = 5$. After the one-sample *t*-test was conducted, the fusion set of the brain images of the two groups was obtained and used as the mask template for the subsequent statistical analyses. Finally, the independent-sample *t*-test was conducted to investigate the functional connectivity strength between the HC and depressed young patients with a suicide attempt. The statistical results of the brain images were displayed as images by the REST slice view software. Linear regression was used to remove the covariates (such as head movement parameters, cerebral white matter and cerebrospinal fluid) and to eliminate possible differences in single-individual time.

For the post-treatment analysis, the paired *t*-test was used to compare the zROI values in the CBT with MG groups before and after treatment, and to explore the changes of the functional connectivity of the brain before and after treatment. The post-treatment data in the CBT and MG groups were analyzed by an independent-sample *t*-test to investigate the differences of combined CBT treatment and single-drug therapy in brain functional activity changes. Finally, after 8 weeks of treatment, the independent sample *t*-test was conducted for the comparisons between the HC and CBT groups, as well as between the MG and CBT groups. Xjview and BrainNet were used for the calculation and analysis of the positions, coordinates, volumes, and activation intensities of the brain regions. Multiple comparison correction with AlphaSim was conducted, $P < 0.001$.

The Pearson correlation analysis was performed with the clinical psychological scales HAMD₂₄ and SSI scores to explore the clinical depressive symptoms of patients, the correlation between suicidal ideation, and the presence of abnormally active brain regions.

2.12. Statistical analysis

The participants that met the following criteria were not included in the analysis: 1) the patient not underwent the second MRI scanning; 2) the treatment strategies of the patients changed during the treatment; for instance, some patients received modified electroconvulsive therapy; and 3) head movement $> 2^\circ$ during MRI scanning.

Analyses of general demographic data and clinical scales were performed using SPSS 23.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the continuous variables followed the normal distribution. One-way analysis of variance (ANOVA) was performed regarding age, education levels, and scale scores in the CBT, MG, and HC groups. The chi-square test was performed for sex. The LSD *t*-test was used for pair-wise comparison of the variables with statistically significant differences in the ANOVA analysis results. A paired-sample *t*-test was performed on the clinical scale score. The McNemar test was performed on the HAMD₂₄ reduction rate of the two groups. The zROI values were subjected to a one-sample *t*-test within the group, an independent-sample *t*-test between groups, and a paired-sample *t*-test before and after treatment. Brain regions corrected by multiple comparison correction AlphaSim, $P < 0.001$, $rmm = 5$. Multiple correlations were adjusted using the Bonferroni method.

3. Results

3.1. Baseline demographic data and clinical psychological scales

Among the 84 patients included in this study, there were 17 males and 21 females in the HC group; the mean age was 23.0 ± 2.2 years. There were 10 males and 15 females in the CBT group; the mean age was 22.1 ± 2.8 years. There were nine males and 12 females in the MG group; the mean age was 23.4 ± 3.6 years (Table 1; the pair-wise comparisons are presented in Supplementary Table S1).

Table 1

Comparison of the demographic data and psychological assessment scales among the HC, CBT, and MG groups.

Variable	HC (n = 38) Mean \pm SD	CBT (n = 25) Mean \pm SD	MG (n = 21) Mean \pm SD	P
Treatment baseline				
Age (years)	23.0 \pm 2.2	22.1 \pm 2.8	23.4 \pm 3.6	0.277 ^a
Sex (M/F)	17/21	10/15	9/12	0.933 ^b
Education (years)	14.6 \pm 2.3	13.0 \pm 3.3	13.4 \pm 3.2	0.069 ^a
HAMD ₂₄	3.6 \pm 2.3	52.6 \pm 8.2	54.1 \pm 8.8	0.552 ^c
SSI	3.2 \pm 2.2	43.2 \pm 9.8	42.5 \pm 7.2	0.792 ^c
Treatment				
Combined with Benzodiazepine, n (%)		19 (76.0)	17 (81.0)	0.530 ^b
Fluoxetine dose, n (%)				
20 mg		1	1	0.626 ^b
30 mg		5	6	
40 mg		10	7	
50 mg		5	4	
60 mg		0	1	
Average dose (mg)		39.1 \pm 8.3	39.0 \pm 9.9	
8 weeks after treatment				
SSI		8.5 \pm 8.6	16.6 \pm 13.8	0.023 ^c
HAMD ₂₄		21.6 \pm 11.1	30.0 \pm 13.2	0.020 ^c
Significantly effective		14 (56.0%)	10 (47.6%)	0.852 ^b
Moderately effective		7 (28.0%)	7 (33.3%)	
Ineffective		4 (16.0%)	4 (19.1%)	

SD, standard deviation; HAMD₂₄, Hamilton Depression Scale; SSI, Scale for Suicide Ideation.

Criteria of clinical efficacy assessment: significantly effective, HAMD reduction rate $\geq 50\%$; moderately effective, $30\% \leq$ HAMD reduction rate $< 50\%$; and ineffective, HAMD reduction rate $< 30\%$.

^a Analyzed with analysis of variances;

^b Analyzed with chi-square test;

^c Independent *t*-test for the comparisons between MG and CBT groups.

There were no significant differences in sex, age, and educational level among the CBT, MG, and HC groups (all $p > 0.05$). For the clinical scale scores, there was a significant difference between the HC group vs. the CBT and MG groups ($P < 0.001$). There was no significant difference between the CBT and MG groups ($p > 0.05$). The clinical scale scores of the CBT and MG groups were significantly higher than those of the HC group (Table 1; the pair-wise comparisons are presented in Supplementary Table S1).

3.2. Clinical efficacy after 8 weeks of intervention

There were no significant differences between CBT group and MG group in the dose of fluoxetine and benzodiazepines ($p > 0.05$). The SSI and HAMD₂₄ scores at baseline were not significantly different between MG and CBT groups. After 8 weeks of intervention, the SSI and HAMD₂₄ scores were significantly different between the MG and CBT groups (Table 1).

3.3. Resting-state functional connectivity analysis

The functional connectivity of pre- and post-treatment had significant differences in different brain regions. In the CBT group, after treatment, the functional connectivity between the R-sgACC and left posterior cerebellar lobe (L-IPL), and the R-Pcu and right Parietal lobe were higher, while the functional connectivity between the R-sgACC and occipital lobe, the L-sgACC and left anterior cingulate cortex, and the L-Pcu and left medial prefrontal cortex were lower than that of pre-treatment.

In the MG group, after the treatment, the functional connectivity between the R-sgACC and left anterior cingulate cortex, R-Pcu and right superior frontal gyrus/posterior central gyrus, and L-sgACC and left superior parietal lobule were higher, while it between the L-Pcu and

bilateral medial prefrontal cortex were lower than that of pre-treatment.

Before treatment, the analysis results of functional connectivity based on the R-sgACC as the seed point showed that compared with the HC group, the functional connectivity strength between the R-sgACC and left posterior cerebellar lobe (L-PCL) in young depressed patients with suicide attempt was lower in the CBT group. Compared with the HC group, the functional connectivity based on the L-sgACC as the seed point showed the functional connectivity between the L-sgACC and bilateral occipital lobe was also lower in CBT group. Results based on the R-PCu as the seed point showed that the functional connectivity strength between the R-PCu and right middle frontal cortex (R-MF) and right precentral gyrus for patients in the CBT group was also significantly lower than that in the HC group. ($P < 0.001$, AlphaSim multiple comparison corrections).

After 8 weeks, the brain functional connectivity for patients in the CBT group was significantly changed. The functional connectivity strength between the R-sgACC and left middle frontal cortex was higher than that in the HC group. Similarly, the functional connectivity between the L-sgACC and bilateral anterior cingulate cortex was higher than that in the HC group. Besides, the functional connectivity strength between the R-PCu and right superior frontal cortex (R-SF) was higher than that in the HC group ($P < 0.001$).

After treatment, when comparing the MG group with the HC group, the results of R-sgACC as seed point indicated that the functional connectivity of the bilateral anterior cingulate cortex were significantly enhanced. The connectivity between the L-sgACC and the left anterior cingulate cortex was higher than that in the HC group. The result of R-PCu as the seed point showed that the functional connectivity of R-PCu to right the parietal lobe and right angular gyrus was significantly increased. Analyses based on the R-sgACC as the ROI showed that the functional connectivity value of the left posterior cerebellar lobe (L-PCL) in the CBT group was higher than that in the MG group. Analysis based on the L-sgACC as the ROI showed that the functional connectivity of the right anterior cingulate cortex/ medial prefrontal cortex in the CBT group was higher than that in the MG group. Analysis based on the R-PCu as the seed point showed that the functional connectivity value of the right parietal lobe in the CBT group was decreased compared with the MG group ($P < 0.001$). Likewise, the functional connectivity between L-PCu and left Medial prefrontal cortex was lower in the CBT group than that in the MG group (Table 2).

3.4. Correlation analysis of the clinical scale scores and functional connectivity values

To evaluate whether the suicidal ideation and depressive symptoms were associated with the FC value, the RESTplus V1.21 software was used to extract the average FC values of the ROIs with significant differences before and after treatment in the HC and CBT groups. The values were subjected to the Pearson correlation analysis with clinical scale scores. The findings showed that the average FC value at baseline was significantly lower in the CBT group than in the HC group. The average FC values between R-sgACC and L-PCL were negatively associated with the SSI score in the CBT group, and the average FC values of the R-PCu and R-MF were also negatively associated with the HAMD₂₄ score in the CBT group. After the patients were treated for 8 weeks, compared with HC group, the average FC values between R-PCu and R-SF were significantly higher in the CBT group. In addition, the average FC values between R-PCu and R-SF were positively associated with the SSI score (changes in SSI scores before and after treatment) (Fig. 3).

4. Discussion

The present study showed that before treatment, the functional connectivity of the bilateral sgACC and R-PCu was lower in depressed patients with a suicide attempt than that of (in) HC.

After treatment, compared with the MG group, functional

Table 2

Brain regions with significant differences in FC between CBT and HC group before and after treatment.

Brain regions	Slide	BA	Peak MNI coordinate			Mass size (voxel)	Peak intensity
			x	y	z		
Seed 1: R-sgACC (Peak MNI: 12, 36, 6)							
Baseline CBT<HC							
Posterior cerebellar lobe	L	–	-45	-51	-18	97	-3.451
After 8 weeks of treatment							
CBT>HC							
Middle frontal cortex	L	10	-45	51	-3	64	2.696
MG > HC							
Anterior cingulate cortex	R/ L	24/32	-6	24	18	61	5.287
CBT>MG							
Posterior cerebellar lobe	L	–	-42	-63	-36	92	2.728
CBT post-treatment > pre-treatment							
Occipital lobe	R	–	27	-66	6	63	2.979
CBT post-treatment < pre-treatment							
Anterior cingulate cortex	L	–	18	15	30	86	-5.255
MG post-treatment > pre-treatment							
Medial prefrontal cortex	R/ L	–	6	18	21	99	5.211
Seed 2: R-Pcu (Peak MNI: -5, -78, 30)							
Baseline CBT<HC							
Middle frontal cortex/ Precentral gyrus	R	6/3	36	-12	45	74/35	-4.710
After 8 weeks of treatment							
CBT>HC							
Superior frontal cortex	R	10	30	30	15	47	2.735
MG > HC							
Parietal Lobe/ Angular Gyrus	R	39/40	-48	-66	30	76/52	4.825
CBT < MG							
Parietal lobe	R	19	33	-81	42	50	-3.092
CBT post-treatment > pre-treatment							
Superior frontal gyrus/ posterior central gyrus	R	6	12	6	72	79	3.430
MG post-treatment > pre-treatment							

(continued on next page)

Table 2 (continued)

Brain regions	Slide	BA	Peak MNI coordinate			Mass size (voxel)	Peak intensity
			x	y	z		
Medial prefrontal cortex	L	9	-21	12	45	77	4.164
Posterior cingulate cortex/precuneus	L	23	-6	-54	12	101	4.095
Seed 3: L-sgACC (Peak MNI: -12, 36, 6)							
Baseline CBT < HC							
Occipital lobe	R/L	17/18	21	-75	12	104	-3.856
After 8 weeks of treatment							
CBT > HC							
Anterior cingulate cortex	R/L	32/10	-12	36	6	99	31.054
CBT > MG							
Anterior cingulate cortex /Medial prefrontal cortex	R	32/10	-3	51	9	101	4.217
MG > HC							
Anterior cingulate cortex	L	10	-12	36	6	147	31.785
CBT post-treatment < pre-treatment							
Superior Parietal Lobule	L	7	-30	-69	48	71	-3.014
MG post-treatment > pre-treatment							
Inferior Frontal Gyrus	L	-	-21	30	3	72	4.112
Seed 4: L-Pcu (Peak MNI: 5, -78, 30)							
After 8 weeks of treatment							
CBT < MG							
Medial prefrontal cortex	L	10	-12	60	18	68	-3.678
CBT post-treatment < pre-treatment							
Medial prefrontal cortex	L/R	10	-3	63	21	82	-3.012
MG post-treatment < pre-treatment							
Superior Frontal Gyrus	L/R	6	-12	-6	72	86	3.544

p < 0.001, AlphaSim correction.

MNI: Montreal Neurological Institute; BA: Brodmann brain area; -: not in the BA

area. The peak point was the one with the most significant difference in brain regions.

connectivity between the R-sgACC and left posterior cerebellar lobe as well as between the L-sgACC and right anterior cingulate cortex /medial prefrontal cortex in the CBT group were increased, while the functional connectivity between the R-PCu and right parietal lobe as well as between the L-PCu and medial prefrontal cortex was reduced ($P < 0.001$). The functional connectivity between the R-sgACC and the left posterior cerebellum lobe was negatively correlated with the SSI score, while the functional connectivity between the R-PCu and right middle frontal cortex was negatively correlated with the HAMD₂₄ score before treatment. After treatment, functional connectivity between the R-PCu and right superior frontal gyrus was positively correlated with the SSI scores in the CBT group.

In the CBT group, after treatment, the functional connectivity between the R-sgACC and left posterior cerebellar lobe (L-IPL) were higher, while the functional connectivity between the R-sgACC and occipital lobe were lower than that of pre-treatment. Comparing with the functional connectivity of pre-treatment, the functional connectivity between the R-Pcu and right Parietal lobe were higher, while it between the L-sgACC and left anterior cingulate cortex, L-Pcu and left medial prefrontal cortex were lower after treatment.

In the MG group, after the treatment, the functional connectivity between the R-sgACC and left anterior cingulate cortex, R-Pcu and right superior frontal gyrus/posterior central gyrus, and L-sgACC and left superior parietal lobule were higher, while it between the L-Pcu and bilateral medial prefrontal cortex was lower than that of pre-treatment.

However, there is no sufficient evidence currently available to confirm the specificity of the functional activities of such brain regions with the changes, we could not accurately explain whether such changes in brain functional activities were caused by CBT combined with drug therapy or spontaneous recovery. Current data and results are still insufficient to explain how does CBT exerts its effects, and thus a conclusion cannot be reached.

The previous studies were mostly comparative studies before/after the treatment of depression and did not address depression with attempted suicide [21,24,25,28,35]. The innovation between this study and the previous ones is that the subjects had attempted suicide, and precisely because they were major depressive patients with attempted suicide, the use of purely psychological interventions (CBT interventions) was not feasible (unethical), so the grouping approach was a combination of therapy and medication [20–24].

Previous studies revealed abnormalities of functional connectivity in the neural circuit of the left prefrontal cortex to the amygdala in patients with MDD [17,18]. In addition, the functional connectivity of the default mode network is also changed in the resting state. Some authors reported that the functional connectivity between the left hippocampus and the straight right gyrus is increased substantially in depressed patients with suicide attempts [17,18]. Cao et al. [36] found that compared with healthy individuals, the functional connectivity in various brain regions (including the cerebral cortex and limbic system) is changed in adolescents with a suicide attempt, and suggested that the adolescent suicidal behaviors are potentially related to the frontal lobe-limbic system circuit, frontal lobe-parietal lobe-cerebellar circuit, frontal-parietal network, and brain default network [37]. The abnormalities in the activation modes of the anterior cingulate cortex and frontal cortex in depressed patients with a suicide attempt were demonstrated by several authors, who used functional connectivity analysis to reveal that the activities of the anterior cingulate cortex and insula were decreased, while the functional connectivity of the striatum and motor sense network was increased [19,20,38], suggesting that the risk of suicide in depressed patients is closely associated with the structural and functional changes of the prefrontal cortex. In addition, the suicide risk in such patients is also associated with abnormalities in the neural circuit. These findings indicated that the frontal lobe-striatum

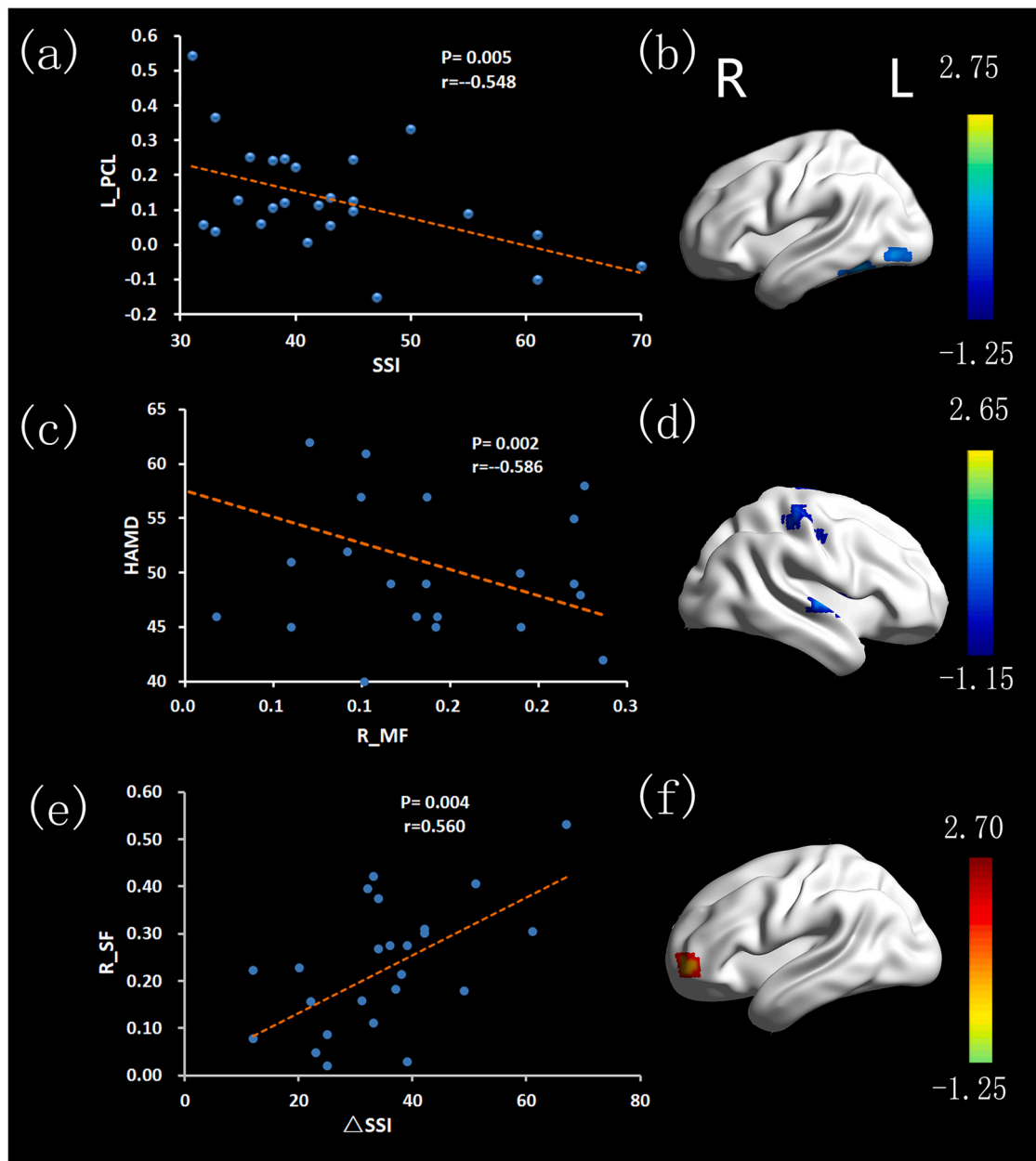


Fig. 3. Correlation analysis of the average functional connectivity (FC) value and clinical psychological scale before and after treatment. (a) Before intervention, the average functional connectivity (FC) values of R-sgACC and L-PCL in the CBT group were negatively correlated with the SSI score. (b) Before intervention, brain regions with a significant decrease in the FC value of R-sgACC and L-PCL in the CBT group. (c) Before intervention, the average FC values of R-PCu and R-MF in the CBT group were negatively correlated with the HAMD₂₄ score. (d) Before intervention, brain regions with a significant decrease in the FC value of R-PCu and R-MF in the CBT group. (e) After 8 weeks of intervention, the average FC values of R-PCu and R-SF in the CBT group were positively correlated with the different values of the SSI score. (f) After 8 weeks of treatment, brain regions with a significant increase in the average FC value of R-PCu and R-SF in the CBT group.

circuit abnormality might be an important potential mechanism of suicide in depressed patients [21,22]. Zhang et al. [23] also suggested that the changes of brain function in the anterior cingulate cortex, striatum, and orbital frontal lobe could be the neurobiological markers for the assessment of depressed patients with a suicide attempt. The seed point-related functional connectivity analysis was adopted by Zhang et al. [23] and the results of the present study showed that the connectivity of the right precuneus is decreased in young depressed patients with a suicide attempt, which indicates that the abnormal functional connectivity in the precuneus and left cerebellum can be used as a neurological marker to predict suicidal behavior in young depressed patients. Therefore, the brain regions of the limbic system are associated with emotion regulation, social cognition, executive function, and

attention control, and the anterior cingulate cortex could be an important brain region with functional changes after treatment of severely depressed patients [37,38].

The sgACC is an important site of the ventral anterior cingulate cortex, which is mainly responsible for the negative emotional state and the functions of processing and remembering negative information [39]. In the present study, the findings showed that the functional connectivity strength between the R-sgACC and the left posterior cerebellar lobe as well as between the L-sgACC and bilateral occipital lobe in young depressed patients with a suicide attempt before treatment were lower than that in healthy controls. The average baseline FC values of the R-sgACC and L-PCL were negatively associated with suicide ideation in young depressed patients with a suicide attempt. These findings further

suggest that the functional activity change in the R-sgACC and L-PCL plays an important role in the pathogenesis of young depressed patients with a suicide attempt. After being treated for 8 weeks, the functional connectivity strength of the R-sgACC and left middle frontal cortex/L-sgACC and bilateral anterior cingulate cortex were significantly higher than that in the HC group. The functional connectivity of the R-sgACC and L-PCL/L-sgACC and right anterior cingulate cortex /medial prefrontal cortex was significantly higher in the CBT group than in the MG group after treatment. The Pearson correlation analysis showed that after 8 weeks of combined therapy, the functional connectivity between the R-PCu and R-SF was positively associated with the amplitude of changes in suicide ideation in the CBT group. The findings of this study further suggest that the functional connectivity activities of bilateral sgACC in young depressed patients with suicide attempts changed significantly after CBT combined with drug therapy, indicating that the bilateral sgACC were relatively sensitive to treatment, which is supported by Yoshimura et al. [24,25]. For instance, Yoshimura et al. [24,25] reported that after 12 weeks of CBT treatment, the activities of the medial prefrontal cortex (mPFC) and ventral anterior cingulate cortex (vACC) of depressed patients were increased by active stimuli, while the vACC activity was negatively associated with the treatment efficacy of CBT under negative stimuli. Yoshimura et al. [24,25] used the mPFC as the seed point to conduct the full-brain functional connectivity analysis, which showed that the functional connectivity of the vACC-mPFC is decreased significantly after CBT.

The precuneus is a critical component of the DMN, which plays an important role in the connection processes of episodic memory, spatial imaging, and self-processing of information. The findings of the present study showed that before treatment, the functional connectivity of the R-PCu with the right middle frontal cortex and right precentral gyrus were significantly lower in the young depressed patients with a suicide attempt than in the HC group, which could be associated with the fact that the precuneus can enhance the memory of a negative emotional experience, and is associated with increased self-regarding and maladjustment [40]. The findings are in agreement with the results reported by Yao et al. [41], suggesting that the functional connectivity in the frontal-parietal network is decreased, while such changes could induce disorders of cognitive processing, emotion processing, and attention control [42]. Yan et al. [43] also found that the functional connectivity strength in the default network of patients with recurrent depression is decreased. Willeumier et al. [44] used SPECT and observed hyper-perfusion of blood flow of the right precuneus in depressed patients with suicidal tendencies. The study conducted by Marchand et al. [45] showed that the functional connectivity between the right precuneus and putamen is substantially changed in patients with self-mutilation behaviors. Bluhm et al. [46] found that the functional connectivity between the Pc/PCC and the bilateral caudate nucleus is reduced, and suggested that such changes could be associated with the symptoms in depressed patients, including adynamia and interest drops. Dunlop et al. [29] conducted a 12-week CBT intervention in 37 depressed patients and found that the functional connectivity among three regions, including the left ventrolateral prefrontal cortex, insular lobe, dorsal midbrain, and left mPFC, and bilateral splenium corporis callosi (SCC) at the resting state is changed. Goldapple et al. [47] used PET and found that after being treated with CBT for 15–20 weeks, the activities in the PCu, mPFC, superior frontal gyrus, and inferior parietal lobe of the patients are decreased, while the activities in the dACC and hippocampus are increased. The findings of this study showed that after being treated for 8 weeks, the functional activity strength between the R-PCu and right superior frontal cortex increased in the CBT group, compared with the HC group. These findings suggest that the functional connectivity of R-PCu in young depressed patients with suicide attempts could change after CBT combined with drug therapy. In addition, at baseline, the average FC values between the R-PCu and R-MF in the CBT group were negatively associated with the HAMD score. Nevertheless, after 8 weeks of intervention, the average FC values between the R-PCu

and R-MF of the CBT group were positively associated with the amplitude of suicidal ideation. The prefrontal lobe plays an important role in attention, memory, and executive functions [48,49]. The functional connectivity of the prefrontal lobe in depressed patients changes after treatment, and therefore the depressive symptoms and suicidal behaviors could also change correspondingly.

In summary, this study investigated the importance of the effects of bilateral sgACC and bilateral PCu on the changes in brain functional activities in young depressed patients with suicide attempts after CBT combined with drug therapy. The findings suggest that the functional connectivity changes mediated by the bilateral sgACC and bilateral PCu could be the potential brain functional basis of the effects of CBT combined with drug therapy in young depressed patients with a suicide attempt. We speculated that the central nervous system circuits could be activated by the combined CBT treatment, which in turn downregulate the cognition and emotion levels of the patients, then increase the tendency of the patients to convert excessive self-regarding to the external environment, and therefore help the patients substantially improve their non-adaptive rumination and depressive state. The findings of this study strongly suggest that the downward regulation mode of the brain could be an important mechanism involved in the treatment effects of CBT combined with drug therapy. This study provides evidence for exploring the potential neuroimaging mechanisms of CBT intervention and drug therapy for depressed patients with a suicide attempt.

5. Limitations

Depression and anxiety are often comorbid [50], but the CBT approach for depression alone is different from the approach for depression combined with anxiety. Therefore, patients with HAMA score > 14 points were excluded, which could limit the generalizability of the conclusions. The brain regions with abnormal spontaneous activities and the brain regions with changed functional connectivity were not completely consistent with previous studies [19–23]. In addition, the depression severity, methods of suicidal behaviors, times of suicide attempts, and previous treatments were not included and analyzed in this study. In addition, subgroup analysis was also not conducted for primary and recurrent depressed patients, for the manner of suicide, or for the time of suicide. More clinical studies with larger sample sizes, especially longitudinal studies with longer follow up time, are still needed for further investigation. The calibration method we used in this study is Alphasim ($P < 0.001$) which is now less used and a new calibration method, such as the 3dclustsim with the ACF flag, will be needed in our further studied.

6. Conclusion

The present study suggests that altered functional connectivity mediated by the bilateral anterior cingulate cortex and the bilateral wedge anterior lobe is the basis for brain function in CBT combination therapy in young depressed patients with suicide attempts. This study provides a basis for exploring the underlying neuroimaging mechanisms of CBT intervention and pharmacotherapy in patients with depression and attempted suicide.

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Author Statement

All authors have approved the final article should be true and included in the disclosure. Each author has made an important scientific contribution to the study and is thoroughly familiar with the primary data. We declare that submitted manuscript does not contain previously published material and are not under consideration for publication elsewhere.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Acknowledgments

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.bbr.2021.113612](https://doi.org/10.1016/j.bbr.2021.113612).

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