Journal of Affective Disorders 276 (2020) 822–828

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Fractional amplitude of low-frequency fluctuation (fALFF) alterations in young depressed patients with suicide attempts after cognitive behavioral therapy and antidepressant medication cotherapy: A resting-state fMRI study

Yanping Shu[a,b], Li Kuang[a,*], Qiankun Huang[c], Lihui He[c]

[a] *Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, No.1, Youyi Road, Yuzhong District, Chongqing 400016, China*
[b] *Department of Psychology, The Second People's Hospital of Guizhou Province, No. 318, The Southern Section of new Road, Yunyan district, Guiyang 550004, Guizhou, China*
[c] *Zunyi Medical University, no. 201, Dalian road, Inovance distric, Zunyi, China*

A R T I C L E I N F O

Keywords:
Suicide attempts
Depression
Cognitive behavioral therapy
Resting-state functional magnetic resonance imaging
Fractional amplitude of low-frequency fluctuations

A B S T R A C T

Background: Fractional amplitude of low-frequency fluctuation (fALFF) alterations in young depressed patients with suicide attempts after cognitive behavioral therapy (CBT) and antidepressant medication cotherapy were evaluated.
Methods: Seventy-eight subjects (age: 18–28) were recruited from April 2017 to March 2019. Forty young depressed patients who attempted suicide were divided into CBT (8 weeks of structured CBT sessions and antidepressant medication cotherapy) and monotherapy (MG: antidepressant therapy alone) groups, and 38 healthy volunteers constituted a healthy control (HC) group. Resting-state functional magnetic resonance imaging (rs-fMRI) was conducted before and after treatment.
Results: Before treatment, spontaneous brain activity in the left posterior cerebellar lobe (L-PCL), right anterior cingulate cortex, left caudate nucleus and left superior frontal cortex was higher in untreated patients than in HCs. After treatment, fALFF in the left middle occipital cortex and left precuneus was significantly increased in the CBT compared with the HC group. fALFF in the right middle frontal cortex, right inferior frontal cortex, L-PCL, and left anterior cerebellar lobe (L-ACL) were increased, while fALFF in the L-mPFC and L-SgACC were reduced, in the CBT compared with the MG group. Pearson correlation analyses provided information about clinical scale scores and mean fALFF relationships.
Limitations: There was insufficient evidence to confirm that these spontaneous brain activity alterations were the result of CBT or spontaneous recovery.
Conclusion: CBT and medication cotherapy can significantly change spontaneous activity in the left cerebellum and default-mode network, thereby regulating and reshaping emotional and cognitive processing.

1. Introduction

Depression is a serious mental illness characterized by an overwhelming feeling of sadness or a loss of interest and pleasure in most usual activities, and it is considered a high-risk factor that leads to suicide (Bostwick and Pankratz, 2000). One-quarter of all patients with depression have suicidal behaviors (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). According to 2019 statistics in China, the lifetime prevalence rate of depression is 6.8% (Huang et al., 2019).

At present, first-line treatment methods for depression mainly include medication and psychotherapy. Cognitive behavioral therapy (CBT) is an effective short-term psychotherapeutic treatment for depression (Jiang, 2009). In CBT, the treatment content can be structured and stereotyped, and the treatment course is relatively short, with obvious effects (Bryan, 2019; Mewton and Andrews, 2016). There are many cognitive behavioral theories and hypotheses regarding the psychological mechanisms of CBT for treating depression, but the neurobiological mechanisms of CBT remains unclear. It is of great significance to understand the neural mechanisms of CBT in depressed

* Corresponding author.
E-mail address: KuangLi0606@163.com (L. Kuang).

https://doi.org/10.1016/j.jad.2020.07.038
Received 30 October 2019; Received in revised form 13 April 2020; Accepted 2 July 2020
Available online 18 July 2020
0165-0327/

patients who are attempting suicide to select the treatment plan and predict the curative effect.

Functional magnetic resonance imaging (fMRI) is an important approach to explore brain function and neurobiological mechanisms in patients with depression. The structure and functional activities of the brain in patients with depression show significant abnormalities. However, to date, there has been no resting-state functional magnetic resonance imaging (rs-fMRI) study on the effects of CBT on depression in youth with suicide attempts, especially using fractional amplitude of low-frequency fluctuation (fALFF) analysis. The present study conducted an fALFF analysis to explore alterations in whole-brain spontaneous activity before and after cotherapy with CBT and antidepressant medication in depressed patients with suicide attempts.

2. Methods

2.1. Subjects

From March 2017 to May 2019, 40 Chinese patients with depression who attempted suicide were recruited from Guizhou 2nd Provincial People's Hospital. According to the Columbia classification algorithm (C-CASA) (Posner et al., 2007), a person with a suicide attempt is defined as “A person with suicidal intention and self-harm behavior, but without success, and there is clear evidence of suicide attempt from his/her behavior and environment.” Forty healthy volunteers matched for age, gender and education level were recruited as the healthy control (HC) group. All subjects knew the main content of this study and voluntarily signed the informed consent form. This study was approved by the ethics committee of Guizhou 2nd Provincial People's Hospital. The study was registered (China Clinical Trial Registration Center, #ChiCTR1900024989).

The inclusion criteria for the patients were as follows: 1) Han nationality, aged 18–28 years, and right-handed; 2) junior high school level of education or above; 3) criteria met for a "depressive episode" according to the American Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); 4) Hamilton depression scale (HAMD24) (Hamilton, 1960) score >35 points; 5) at least one suicide attempt; and 6) no antidepressant treatment, electroconvulsive therapy or transcranial magnetic stimulation within 1 month prior to enrollment in this study.

The exclusion criteria for the patients were as follows: 1) diagnosed with other mental disorders, such as bipolar disorder, schizophrenia, personality disorder, mental retardation, etc.; 2) score on the Hamilton anxiety scale (HAMA) >14; 3) brain organic diseases; 4) depressive symptoms caused by other organic diseases or medications; 5) history of substance addiction or family history of psychiatric disease; 6) MRI scanning contradictions, pregnant or breast-feeding women, or women planning to be pregnant; or 7) severe physical diseases.

The termination criteria were as follows: severe adverse reactions during treatment and the failure to complete expected treatment procedures, such as failure to complete homework or absence from CBT for more than 2 weeks.

The inclusion criteria for the participants in the HC group were as follows: 1) Chinese Han; 2) 18–28 years of age; 3) right-handed; 4) junior high school or higher educational level; and 5) HAMD24 score <8 points. The exclusion criteria for the participants in the HC group were as follows: 1) diagnosis of mental disorders such as depression, personality disorder, anxiety disorder, mental retardation, manic episode, or schizophrenia; 2) HAMA score <7 points; 3) severe physical diseases; 4) history of substance abuse or family history of psychiatric disorders; 5) MRI scanning contradictions; or 6) pregnant or breast-feeding women or women planning to be pregnant.

2.2. Grouping and interventions

The patients who signed the informed consent form were assigned to the combined CBT group and the monotherapy group (MG) group according to a random number table. The patients in the MG group were treated with fluoxetine dispersible tablets (Lilly Suzhou Pharmaceutical Co., Ltd.) at a dose of 20–50 mg/d. The patients in the CBT group were treated 8 times with structured individual CBT, in combination with fluoxetine. The manufacturers and doses of fluoxetine prescribed for patients in the CBT group were consistent with those in the MG group. The form of CBT intervention was one-on-one individual CBT sessions, 35–50 min each, which were performed once weekly for eight sessions in total. The psychotherapists had received CBT training and certificates from the Chinese mental health association. During the eight weeks of treatment, the therapist was supervised by a superior every two weeks. The contents of CBT mainly included psychological education, identification of automatic thinking, correction of core beliefs, detagging, implementation of behavioral strategies, presentation of problems, use of task decomposition methods, and construction of relapse prevention techniques (Jesse et al., 2010). At the end of each session, the corresponding homework was assigned to the patients, including records of thinking, a list of expectations, exercises for alternative thinking, and activity arrangements, all of which should be completed by the patients as required (Jesse et al., 2010).

2.3. Assessment indicators

The $HAMD_{24}$ was used to estimate depressive symptoms and severity. The $HAMD_{24}$ is a classic scale widely used in the clinical assessment of depression symptoms and has good reliability and validity. The Scale for Suicidal Ideation (SSI) (Beck et al., 1979) was used to assess suicidal ideation as well as the risk of suicide. All clinical scale evaluations were double-blinded.

In this study, the clinical efficacy criterion for treatment was the $HAMD_{24}$ score reduction rate (Dunlop et al., 2017). A reduction rate in the $HAMD_{24}$ score $\geq 50\%$ was considered significantly effective; $a \geq 30\%$ and $<50\%$ reduction rate in the $HAMD_{24}$ score was considered medium efficacy; and a reduction rate in the $HAMD_{24}$ score $<30\%$ was considered ineffective.

Resting-state fMRI was used to observe alterations in fALFF. We used fALFF as an indicator of brain activity. Compared with other analytical methods, fALFF analyses can reduce interference from the cerebrospinal fluid and veins, reduce physiological noise, and improve the signal detection rate of brain activity in relevant cortex, and it has good sensitivity and specificity regarding the spontaneous neuronal activity of the resting brain (Zou et al., 2008).

2.4. Image acquisition

Images were obtained on a 3T GE Signa HDxt MRI system (General Electric Medical Systems, Waukesha, WI, USA). The resting state refers to the supine position during the scan, in which the participants stay awake, remain quiet, close their eyes, breathe peacefully and evenly, and do not engage in active thinking. Compared with task-state fMRI, resting-state fMRI can exclude the influence of external stimuli, allows the subjects to easily pay attention, places the subjects in a relatively simple state of brain activity, and better reduces biases in the research results. Therefore, resting-state fMRI has the advantages of high consistency and repeatability, simple operation and no need to design a task, and therefore, it has been widely used in the field of brain function assessment. Blood oxygen level-dependent (BOLD) imaging was performed using gradient- echo-planar imaging (EPI), and the following parameters were applied for functional imaging: repetition/echo time (TR/TE) = 3000/40 ms, slice thickness = 4 mm, 34 slices, field of view (FOV) = 24 cm × 24 cm, matrix = 64 × 64, 90° flip angle, and 232 volumes. During scanning, the doctor examined the scanned images and removed or rescanned images with obvious artifacts and distortions.

2.5. Data preprocessing

The rs-fMRI data were preprocessed using Data Processing and Analysis for Brain Imaging (DPABI) software (Yan et al., 2016) (http://rfmri.org/dpabi) running in MATLAB (Mathworks, Natick, MA, USA). The preprocessing of fMRI data included 8 steps: 1) data format conversion (DICOM to NIFTI): DICOM format data were converted into the 3D format of NIFTI (Neuroimaging Informatics Technology Initiative; nii format); 2) removal of first time point: the first 10 images were removed because of the inaccuracy in the data caused by the subject and instrument maladjustments at the beginning of the scan, thereby reducing deviation in the results; 3) slice timing: since the data in each layer obtained by MRI was collected by the machine at different time points, the data in all collected layers need to be calibrated to a time point by means of time correction; 4) realignment: functional time series was realigned to correct for head motion across the time series; 5) normalize: brain images for each subject were transferred to a standard space to reduce differences between individuals for the next step of the intergroup analysis; 6) smoothing: the influence of spatial noise and the differences in brain structure between subjects was reduced using a smoothing kernel that was 4 mm × 4 mm × 4 mm; 7) detrend; and 8) filter: since time courses of low-frequency (0.01–0.10 Hz) fluctuations in the resting brain were observed to have a high degree of temporal correlation within these regions (Biswal et al., 1995; Huotari et al., 2019), this low-frequency band wave was used to remove the influence of high frequency signals from respiratory heartbeats and high frequency noise. In addition, two subjects from the HC group were excluded for having more than 2° angular displacement.

2.6. fALFF analysis

fALFF analysis was conducted in MATLAB using the statistical parametric mapping software package (SPM12-Statistical Parametric Mapping; https://www.fil.ion.ucl.ac.uk/spm/software/spm12). The fast Fourier transform was used to transform the time series of each voxel to the frequency domain to obtain the power spectrum. The square root was calculated at each frequency of the power spectrum, and the mean square root was obtained across 0.01–0.10 Hz band for each voxel. Finally, fALFF in each voxel was divided by mean fALFF of the global brain within a brain mask to standardize for voxels in the entire brain.

2.7. Statistical analysis

SPSS 23.0 software was used to analyze the general demographic and clinical variables, and the Kolmogorov-Smirnov (K-S) test was performed to evaluate the normality of the distribution of scale scores. Before treatment, age and education level of the HC, CBT and MG groups were analyzed by one-way analysis of variance (ANOVA), and the variables with statistically significant differences in ANOVA were compared by the least significant difference test (Waller and Duncan, 1974). A chi-square test was conducted to compare gender ratios. The reduction rates for the $HAMD_{24}$ and SSI scores in the CBT and MG groups were analyzed by the chi-square test. Before and after treatment, the independent sample t-test was used to compare whether there were significant differences between the CBT group and the MG group. The significance level was set to be equal to 0.05.

RESTplus V1.21 software (http://www.restfmri.net/forum/REST) was used for the statistical analyses of the fALFF data. At baseline, independent sample t tests were applied to detect fALFF differences between the CBT and HC groups. After treatment, independent sample t tests were conducted to analyze alterations in whole-brain spontaneous activity between the CBT and MG groups. The fALFF analyses were performed with a significance threshold of $p < 0.01$ for AlphaSim multiple comparison correction. The AlphaSim correction parameters were as follows: edge connected, connection criteria (rmm) = 5, $P < 0.01$, and minimum cluster size of 18. Pearson correlation analyses were performed between the mean fALFF values across all voxels in the brain regions with abnormal fALFF in the CBT group and clinical scale scores.

3. Results

3.1. Demographic and clinical variables

A total of 107 subjects were initially included in the study. Among them, 15 subjects in the MG group and 12 subjects in the CBT group were excluded because they did not complete the study. Two subjects in the HC group were excluded due to motion problems during scanning. Finally, 78 patients finished the study, including 38 subjects in the HC group, 21 in the CBT group and 19 in the MG group. Demographic information for the subjects is presented in Table 1. The inclusion process of the subjects is shown in Fig. 1. The main reasons for drop-out were as follows: 1) unwillingness of the patient to receive a second MRI scan; 2) the patient failed to return for follow-up consultation and for a second MRI scan; and 3) the patient changed treatment plans, such as switching to nonconvulsive electroconvulsive therapy.

Statistical analysis showed that at baseline, there were no significant differences in age, gender, or educational level between the HC, CBT, and MG groups. After 8 weeks of treatment, the clinical effects in the CBT group showed significant efficacy in 61.90%, moderate efficacy in 33.33% and a lack of efficacy in 4.76%. The clinical effects in the MG group showed significant efficacy in 52.63%, moderate efficacy in 31.58%, and a lack of efficacy in 15.79%.

After treatment, there were significant differences in HAMD24 and SSI scores between the CBT and MG groups, indicating that the improvement in depressive symptoms and suicidal ideation was greater in the CBT group than in the MG group (Table 1).

3.2. zfALFF analysis

Before the treatment, the areas with increased zfALFF values in the CBT group compared with the HC group were as follows: the left posterior cerebellar lobe (L-PCL), right anterior cingulate cortex (R-ACC), left caudate nucleus and left superior frontal cortex (L-SF) (Table 2). After treatment, the zfALFF values in the left middle occipital cortex and left precuneus (L-PCu) in the CBT group was significantly higher than those in the HC group (Figs. 2 and 3). There were no significant differences in zfALFF values between the CBT and MG groups at baseline. The difference in zfALFF values between the MG and HC groups

Table 1.
Comparison of psychological assessment scales among HC, CBT and MG groups ($\bar{R}$).

Variables	HC (*N* = 38) Mean ± SD	MG (*N* = 19) Mean ± SD	CBT (*N* = 21)	*P value*
Age (years)	23.00 ± 2.22	23.63 ± 3.64	22.24 ± 2.95	0.297 [a]
Gender (male/female)	17/21	9/10	8/13	0.824 [b]
Years of education	14.63 ± 2.27	13.37 ± 3.30	13.10 ± 3.55	0.107 [a]
At baseline				
SSI	3.18 ± 2.23	42.11 ± 7.17	43.48 ± 10.66	0.640 [c]
$HAMD_{24}$	3.63 ± 2.27	53.37 ± 8.69	51.67 ± 8.33	0.531 [c]
After 8 weeks of treatment				
SSI		13.53 ± 10.32	5.95 ± 5.25	0.005 [c]
$HAMD_{24}$		28.89 ± 13.45	18.29 ± 8.37	0.004 [c]
Markedly		10 (52.63%)	13 (61.90%)	0.504 [b]
Moderately		6 (31.58%)	7 (33.33%)	
Ineffective		3 (15.79%)	1 (4.76%)	

SD = Standard deviation

[a] using ANOVA; $HAMD_{24}$ = Hamilton Rating Scale for Depression; SSI = Scale for Suicidal Ideation

[b] represent using chi-square test; [c] represent using independent sample t-test to analyze the CBT and MG groups; Markedly effective, $HAMD_{24}$ reduction rate ≥50%; Moderately effective, 30% <$HAMD_{24}$ reduction rate ≤50%; Invalid, $HAMD_{24}$ reduction rate ≤30%.

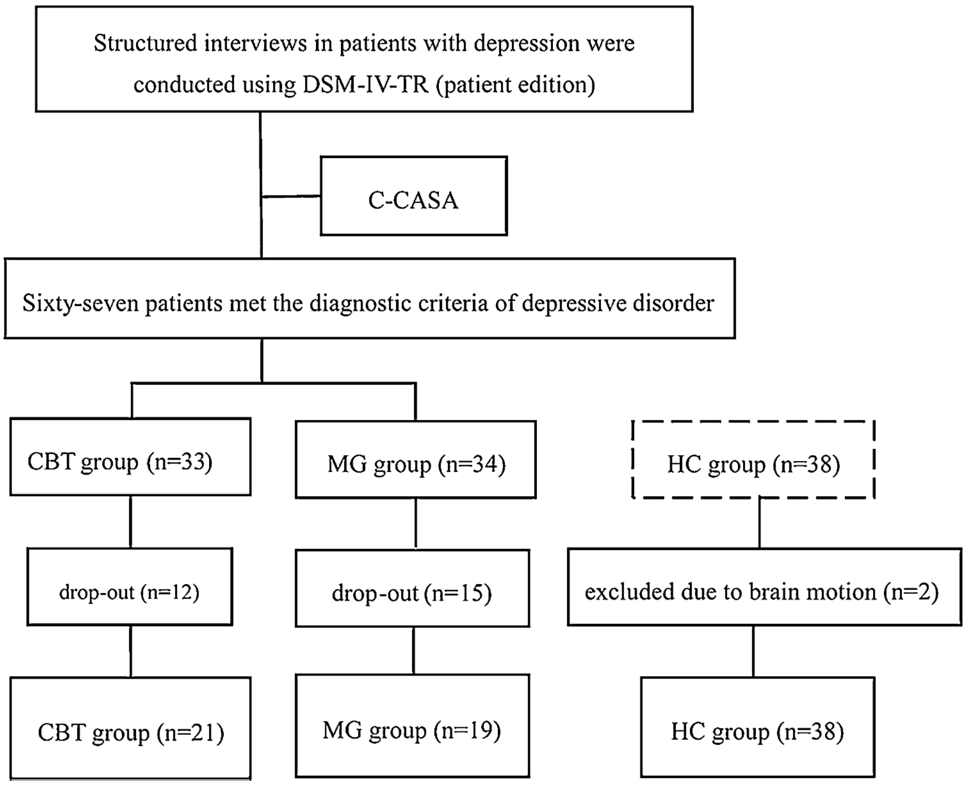

Fig. 1. Flowchart of the selection process for subjects.

was the same as that between the CBT group and HC group.

After 8 weeks of cotherapy with CBT and antidepressant medication, the results revealed that zfALFF values in the CBT group were higher than those in the MG group in the following brain regions: right middle frontal cortex, right inferior frontal cortex, L-PCL, and left anterior cerebellar lobe (L-ACL). In the CBT group, zfALFF values were lower than those in the MG group in the following brain regions: left medial prefrontal cortex (L-mPFC) and left subgenual anterior cingulate cortex (L-sgACC) ($P < 0.01$, AlphaSim correction) (Table 2 and Fig. 3).

3.3. Correlation analysis of clinical scale scores and fALFF value

To assess whether the depressive symptoms and suicidal ideation were related to fALFF values, RESTplus V1.21 software (http://www.restfmri.net/forum/REST) was used to extract and relate the mean fALFF values in brain regions with significant differences in the above analyses to the clinical scale scores. Pearson correlation analyses showed that before treatment, mean fALFF values in the L-SF in the CBT group was positively correlated with SSI scores ($r = 0.386$, $P = 0.014$), and mean fALFF values in the R-ACC in the CBT group were positively

Table 2
Regions that changed before and after treatment in CBT, MG and HC groups.

Brain regions	Left/Right	BA	MNI coordinate			Clusters(voxel)	Peak intensity
			x	y	z		
At baseline							
CBT>HC							
Posterior cerebellar lobe	L	N/A	0	54	−39	74	4.312
Anterior cingulate cortex	R	4	21	21	39	69	4.079
Caudate nucleus	L	N/A	−9	12	6	52	4.109
Superior frontal cortex	L	6	−24	15	45	35	5.191
After 8 weeks of treatment							
CBT > HC							
Middle occipital cortex	L	18	−27	−84	15	83	6.876
Precuneus	L	7	−27	−84	15	18	6.876
CBT>MG							
Middle frontal cortex	R	47	42	30	−15	32	3.456
Inferior frontal cortex	R	47	42	30	−15	82	3.456
Posterior cerebellar lobe	L	N/A	−45	−51	−42	224	5.120
Anterior cerebellar lobe	L	N/A	−45	−51	−42	137	5.120
CBT<MG							
Medial prefrontal cortex	L	10	−18	51	9	210	−4.045
Subgenual anterior cingulated cortex	L	32	−18	51	9	74	−4.045

MNI = Montreal neurological institute; BA = Bruderman area. $HAMD_{24}$ = Hamilton Rating Scale for Depression; SSI = Scale for Suicidal Ideation.

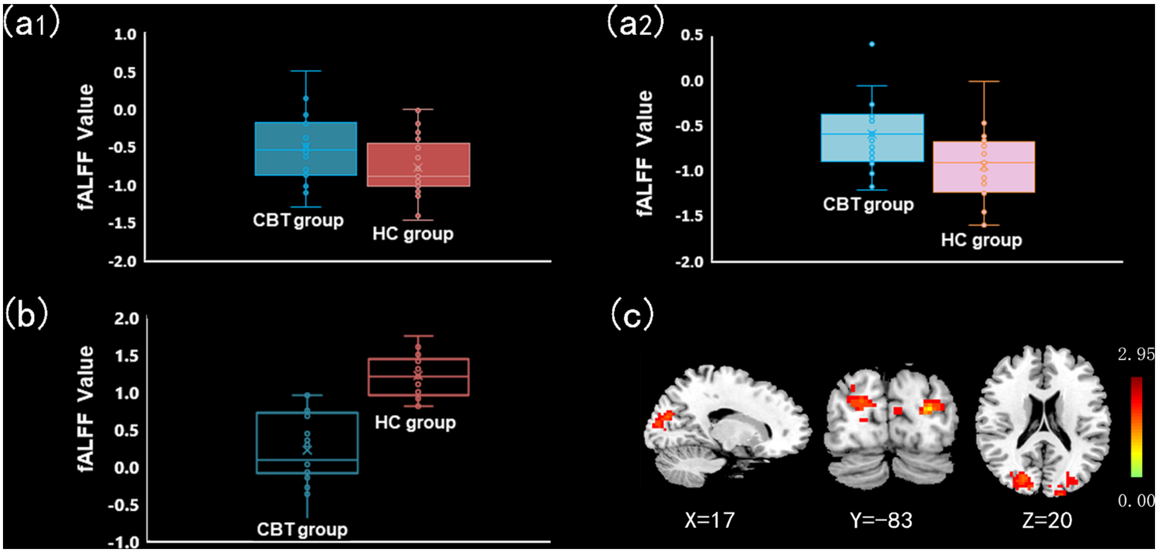

Fig. 2. Mean fALFF values and brain regions in the CBT group that were significantly different from those in HC group. (a1) Before treatment, the average fALFF value in the R-ACC in the CBT group was higher than that in the HC group. (a2) Before treatment, the average fALFF value in the L-SF in the CBT group was higher than that in the HC group. (b) After treatment, the mean fALFF value in the left middle occipital cortex and L-PCu in the CBT group was higher than that in the HC group. (c) After treatment, there were significant differences in brain areas between the CBT group and the HC group.

correlated with SSI scores (r = 0.460, P = 0.003). After 8 weeks of treatment, mean fALFF values in the R-sgACC in the CBT group were positively correlated with $\triangle HAMD_{24}$ scores (the score after treatment minus the score before treatment) (r = 0.483, P = 0.027), and mean fALFF values in the mPFC were positively correlated with $\triangle$SSI points (r = 0.564, P = 0.008). The results of the correlation analysis in the MG group at baseline were the same as those in the CBT group, and no significant correlation was found between mean fALFF values and clinical scale scores in the MG group after treatment.

4. Discussion

In the present study, young depressed patients with suicide attempts were randomly assigned to treatment with CBT combined with antidepressant medication or antidepressant monotherapy for 8 weeks. A resting-state fALFF analysis was performed to investigate the features of spontaneous brain activity in the patients before and after treatment. Spontaneous brain activity in the L-PCL, R-ACC, left caudate nucleus and L-SF in untreated patients at baseline was higher than that in healthy subjects. After 8 weeks of treatment, the spontaneous brain

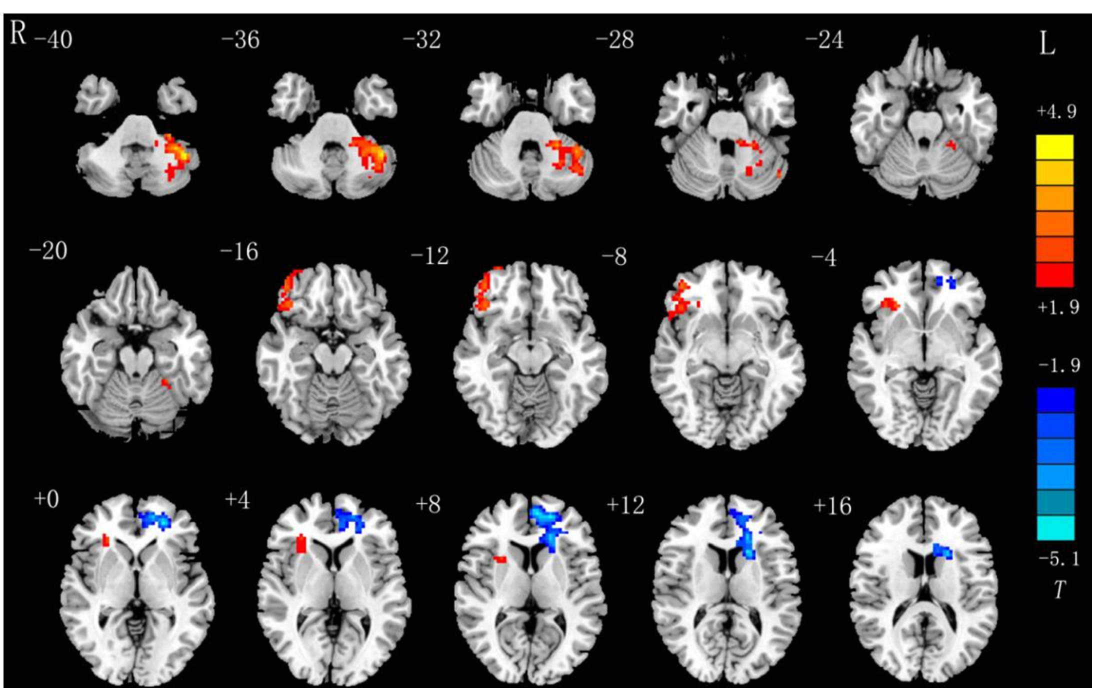

Fig. 3. Regions that changed after treatment between the CBT and MG groups.

activity in the left middle occipital cortex and L-PCu in the CBT group was significantly increased compared with that in the group of healthy subjects. fALFF values in the right middle frontal cortex, right inferior frontal cortex, L-PCL, and L-ACL in the CBT group were increased, while fALFF values in the L-mPFC and L-SgACC in the CBT group were reduced, compared with the MG group, as shown in Table 2. In addition, the results showed that the improvement in depressive symptoms and suicidal ideation in the patients treated with the combination therapy was significantly higher than that in the patients treated with the monotherapy.

4.1. Higher fALFF values in untreated patients at baseline

The most common symptoms of depression are cognitive dysfunction and rumination. Patients tend to process information in a negative cognitive bias mode and tend to ignore positive information, thereby making errors during information processing. This constantly leads to further expansion of negative information. Under the influence of these negative cognitions, patients are more prone to despair and suicidal tendencies, eventually leading to suicidal behavior. Our current study confirmed that spontaneous brain activity in the L-PCL, R-ACC, left caudate nucleus and L-SF in untreated young depressed patients with suicide attempts was significantly increased. Previous researchers have also found significant brain abnormalities in these areas in patients with depression and suicide attempts. The results of Zhang et al. (2016) suggested that abnormal connectivity in the left cerebellum may be a predictor of suicidal behavior in depressed adolescents. Another functional study of the suicidal brain in major depressive disorder (MDD) found that suicide attempters showed significantly increased resting-state functional connectivity of the left amygdala with the left superior orbitofrontal area (Kang et al., 2017). The findings of Wang et al. (2020) provided evidence that the amygdala and prefrontal cortex may be closely related to the pathogenesis of suicidal behavior in MDD and further implicated these regions as potential targets for suicide intervention. Several researchers have identified that the frontal gyrus, ACC and caudate nucleus were implicated in the depressed suicidal brain (Peng et al., 2014). In addition, another important finding in the current study was that the Pearson correlation analysis showed that the mean fALFF values of the L-SF and R-ACC in young depressed patients with suicide attempts were positively correlated with SSI scores, suggesting that the degree of spontaneous brain activities in the L-SF and R-ACC were positively correlated with suicidal ideation. These findings add to the literature suggesting abnormalities in spontaneous brain activity in young depressed patients with suicide attempts and may be helpful for understanding the pathophysiology and underlying neural mechanisms of depression with suicide attempts.

4.2. fALFF alterations in patients after cotherapy with CBT and antidepressant medication

Previous studies have shown that CBT could significantly alter brain function in depressed patients. However, there has been no unified conclusion on the underlying neural mechanisms of CBT in severe depression patients with suicide attempts. Yoshimura et al. (2014 Yoshimura et al., 2017) tried to explain the neurobiological mechanisms after CBT by fMRI, and the results revealed that the activities of the mPFC and ventral anterior cingulate cortex (vACC) in patients with depression following exposure to positive stimuli demonstrated higher activity after 12 weeks of CBT. Following exposure to negative incentives, there was a negative correlation between vACC activity and the intervention effects of CBT. A subsequent whole-brain functional connectivity analysis was performed using the mPFC as a seed region and found that mPFC-vACC functional connectivity was reduced in patients with depression after CBT. Goldapple et al. (2004) found that after 15–20 weeks of CBT treatment, the activity of the PCu, mPFC, SF and inferior parietal lobe was decreased, while dACC and hippocampal activity were increased. Dunlop et al. (2017) treated 122 patients, which included 85 patients treated with medications and 37 patients treated with CBT intervention for 12 weeks. The results revealed that the resting-state functional connectivity between the bilateral subcallosal cingulate cortex (SCC) and three regions, the left frontal operculum, left ventromedial prefrontal cortex and dorsal midbrain, was changed.

Our current results showed that CBT combined with antidepressant therapy altered spontaneous brain activity in the left cerebellar lobe in a resting state. The cerebellum is not only related to balance and motor coordination but also plays a key role in cognitive and emotional processes, as well as the occurrence and development of depression (Phillips et al., 2015). Therefore, it could be speculated that the alterations in spontaneous brain activity in the left cerebellar lobe may be a biomarker to identify the effects of combined therapy on patients.

Our study also confirmed that CBT combined with antidepressant therapy altered spontaneous brain activity in the ACC, prefrontal cortex, and L-PCu in the resting state in young depressed patients with suicide attempts. The ACC is mainly involved in emotional processing, especially its self-referential aspects, of individuals. In addition, the ACC is also responsible for monitoring reaction conflicts and errors and for evaluating the occurrence of false information, motivation and emotions. Therefore, the ACC plays an important role in decision making and control of volitional action. Abnormal anterior cingulate activity might lead to depression and suicidal behavior in patients with suicidal tendencies. The frontal cortex is closely linked to the individual's higher cognitive activities, such as emotion regulation, thinking processes, attention function, problem solving, motivation and behavior planning. The PCu is involved in many high-level cognitive functions, such as episodic memory, self-attention and information processing. Brain regions such as the ACC, mPFC, caudate nucleus and PCu are important nodes of the default mode network (DMN). The DMN refers to network in which there is a spontaneous increase in brain network activity in the resting state, which is even more active than that during task states and in a "dissociation mode" during functional activities (Sheline et al., 2009; Alexopoulos et al., 2012). The functions of these brain regions in the DMN showed close associations with cognition, memory, self-attention and emotional processing. The spontaneous brain activity changes in these areas reflect abnormal emotional control, thought processes and negative behavior in patients with depression who attempted suicide. Gotzsche et al. found that after undergoing CBT, the negative self-attention of patients with depression can be reduced, thereby re-establishing the ability to adjust emotions and significantly improving and reducing the patients' sense of hopelessness and self-harming behaviors (Raj et al., 2001, Gotzsche and Gotzsche, 2017). Our present results were consistent with these findings, suggesting that CBT combined with antidepressant therapy may enhance the emotional regulation function of the DMN by acting on spontaneous brain activity in the ACC, mPFC, caudate nucleus and PCu regions, which regulates the experience and cognitions related to negative emotional stimuli, improves depressive symptoms and reduces suicidal ideation.

However, the present study has limitations. There was insufficient evidence to confirm the specificity of spontaneous activity in these altered brain regions. The sample size was small and limited to Chinese individuals, limiting the generalizability of the results to patients of other ethnicities or languages. Biochemical assessments of the brain by MRI were not assessed, which could have provided further insights into the mechanisms of depression with suicide ideation and those of CBT.

In conclusion, the results of this study suggest that CBT activates cognitive processing systems in the brain by helping patients reconstruct the emotional processing process and helping patients adjust and manage the impact of negative stimuli, which results in improved depressive symptoms. The resting-state fALFF analysis confirmed the key role of neurobiological factors in the occurrence and recovery of young depression patients with suicide attempts, suggesting that CBT combined with antidepressant treatment significantly altered brain activity in the left cerebellum and DMN.

Declaration of Competing Interest

All authors declare no conflicts of interest.

Funding

This work was supported by the National Natural Science Foundation of China (#81671360), the Science and Technology Plan of Guizhou Science and Technology Department (#[2018]1090), the Guiyang Science and Technology Bureau Science and Technology Plan (#[2018]1-63, #[2019]9-3-1), and the Guizhou Provincial Health Planning Commission Science and Technology Fund (#gzwjkj2016-1-027). The funding bodies had no role in the design of the study, in the collection, analysis, and interpretation of data or in the writing of the manuscript.

Acknowledgment

None.

References

Alexopoulos, G.S., Hoptman, M.J., Kanellopoulos, D., Murphy, C.F., Lim, K.O., Gunning, F.M., 2012. Functional connectivity in the cognitive control network and the default mode network in late-life depression. J. Affect. Disord. 139, 56–65. https://doi.org/10.1016/j.jad.2011.12.002.

Beck, A.T., Kovacs, M., Weissman, A., 1979. Assessment of suicidal intention: the scale for suicide ideation. J. Consult. Clin. Psychol. 47, 343–352. https://doi.org/10.1037//0022-006x.47.2.343.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34 (4), 537–541. https://doi.org/10.1002/mrm.1910340409.

Bostwick, J.M., Pankratz, V.S., 2000. Affective disorders and suicide risk: a reexamination. Am. J. Psychiatry 157, 1925–1932. https://doi.org/10.1176/appi.ajp.157.12.1925.

Bryan, C.J., 2019. Cognitive behavioral therapy for suicide prevention (CBT-SP): implications for meeting standard of care expectations with suicidal patients. Behav. Sci. Law 37, 247–258. https://doi.org/10.1002/bsl.2411.

Dunlop, B.W., Rajendra, J.K., Craighead, W.E., Kelley, M.E., McGrath, C.L., Choi, K.S., Kinkead, B., Nemeroff, C.B., Mayberg, H.S., 2017. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am. J. Psychiatry 174, 533–545. https://doi.org/10.1176/appi.ajp.2016.16050518.

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1545–1602. https://doi.org/10.1016/s0140-6736(16)31678-6.

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., Mayberg, H., 2004. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch. Gen. Psychiatry 61, 34–41. https://doi.org/10.1001/archpsyc.61.1.34.

Gotzsche, P.C., Gotzsche, P.K., 2017. Cognitive behavioural therapy halves the risk of repeated suicide attempts: systematic review. J. R. Soc. Med. 110, 404–410. https://doi.org/10.1177/0141076817731904.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Huang, Y., Wang, Y., Wang, H., Liu, Z., Yu, X., Yan, J., Yu, Y., Kou, C., Xu, X., Lu, J., Wang, Z., He, S., Xu, Y., He, Y., Li, T., Guo, W., Tian, H., Xu, G., Xu, X., Ma, Y., Wang, L., Wang, L., Yan, Y., Wang, B., Xiao, S., Zhou, L., Li, L., Tan, L., Zhang, T., Ma, C., Li, Q., Ding, H., Geng, H., Jia, F., Shi, J., Wang, S., Zhang, N., Du, X., Du, X., Wu, Y., 2019. Prevalence of mental disorders in China: a cross-sectional epidemiological study. Lancet Psychiatry 6, 211–224. https://doi.org/10.1016/s2215-0366(18)30511-x.

Huotari, N., Raitamaa, L., Helakari, H., Kananen, J., Raatikainen, V., Rasila, A., ... Korhonen, V.O., 2019. Sampling rate effects on resting state fMRI metrics. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.00279.

Jesse, H., Wrigh, tmD, Donna, M., Sudak, 2010. High-yield Cognitive-Behavior Therapy for Brief Sessions an Illustrated Guide. American Psychiatric Association Publishing.

Jiang, K.D., 2009. Psychiatry (Advanced Course). Military Science Publishing House, Beijing.

Kang, S.G., Na, K.S., Choi, J.W., Kim, J.H., Son, Y.D., Lee, Y.J., 2017. Resting-state functional connectivity of the amygdala in suicide attempters with major depressive disorder. Prog. Neuro Psychopharmacol. Biol. Psychiatry 77, 222–227. https://doi.org/10.1016/j.pnpbp.2017.04.029.

Mewton, L., Andrews, G., 2016. Cognitive behavioral therapy for suicidal behaviors: improving patient outcomes. Psychol. Res. Behav. Manag. 9, 21–29. https://doi.org/10.2147/prbm.s84589.

Peng, H.J., Wu, K., Li, J., Qi, H.C., Guo, S.W., Chi, M.Y., Wu, X.M., Guo, Y.B., Yang, Y.L., Ning, Y.P., 2014. Increased suicide attempts in young depressed patients with abnormal temporal-parietal-limbic gray matter volume. Journal of Affective Disorders 165, 69–73. https://doi.org/10.1016/j.jad.2014.04.046.

Phillips, J.R., Hewedi, D.H., Eissa, A.M., Moustafa, A.A., 2015. The cerebellum and psychiatric disorders. Front. Public Health 3 (66). https://doi.org/10.3389/fpubh.2015.00066.

Posner, K., Oquendo, M.A., Gould, M., Stanley, B., Davies, M., 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am. J. Psychiatry 164, 1035–1043. https://doi.org/10.1176/ajp.2007.164.7.1035.

Raj, M.A., Kumaraiah, V., Bhide, A.V., 2001. Cognitive-behavioural intervention in deliberate self-harm. Acta Psychiatr. Scand. 104, 340–345. https://doi.org/10.1034/j.1600-0447.2001.00075.x.

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., et al., 2009. The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. USA 106 (6), 1942–1947. https://doi.org/10.1073/pnas.0812686106.

Waller, R.A., Duncan, D.B., 1974. A bayes rule for the symmetric multiple comparison problem. Ann. Inst. Stat. Math. 26 (1), 247–264.

Wang, L., Zhao, Y., Edmiston, E.K., Womer, F.Y., Zhang, R., Zhao, P., Jiang, X., Wu, F., Kong, L., Zhou, Y., Tang, Y., Wei, S., 2020. Structural and functional abnormities of amygdala and prefrontal cortex in major depressive disorder with suicide attempts. Front. Psychiatry 10, 923. https://doi.org/10.3389/fpsyt.2019.00923.

Yan, C.G., Wang, X.D., Zuo, X.N., Zang, Y.F., 2016. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics 14, 339–351. https://doi.org/10.1007/s12021-016-9299-4.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S., Yamawaki, S., 2014. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing,. Soc. Cogn. Affect. Neurosci. 9, 487–493. https://doi.org/10.1093/scan/nst009.

Yoshimura, S., Okamoto, Y., Matsunaga, M., Onoda, K., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S.I., Yamawaki, S., 2017. Cognitive behavioral therapy changes functional connectivity between medial prefrontal and anterior cingulate cortices. J. Affect. Disord. 208, 610–614. https://doi.org/10.1016/j.jad.2016.10.017.

Zhang, S., Chen, J.M., Kuang, L., Cao, J., Zhang, H., Ai, M., Wang, W., Zhang, S.D., Wang, S.Y., Liu, S.J., Fang, W.D., 2016. Association between abnormal default mode network activity and suicidality in depressed adolescents. BMC Psychiatry 16 (1), 337. https://doi.org/10.1186/s12888-016-1047-7.

Zou, Q.H., Zhu, C.Z., Yang, Y., Zuo, X.N., Long, X.Y., Cao, Q.J., Wang, Y.F., Zang, Y.F., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J. Neurosci. Methods 172, 137–141. https://doi.org/10.1016/j.jneumeth.2008.04.01.