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Changes in functional connectivity and suicidality after electroconvulsive therapy in depressed patients

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Abstract

Objective Suicidality is a common and serious symptom of depression and patients with depression and suicidality often respond to electroconvulsive therapy (ECT), but the mechanism of its effect is poorly understood. We used resting-state functional magnetic resonance imaging (rs-fMRI) to explore changes in brain connectivity before and after ECT in depressed patients with suicidality.

Methods Twenty-three depressed patients with suicidality underwent rs-fMRI at baseline and after 8–12 ECT sessions. Thirty-two age-, sex-, and education-matched healthy controls (HCs) underwent rs-fMRI once. We used functional connectivity (FC) analysis to identify brain regions with altered connectivity in patients compared to HCs and assess changes in FC before and after ECT. We also assessed the clinical symptoms using the Hamilton Depression Scale, 17-item (HAMD-17), and Beck Scale for Suicide Ideation (BSSI).

Results Compared to HCs, at baseline, patients had reduced FC between the left orbitofrontal cortex (OFC_Ant_L) and left angular gyrus (Angular_L) ($t=3.849$, $P<0.05$) with OFC_Ant_L as ROI. With left superior frontal gyrus (Frontal_sup_L) as ROI, patients also had reduced FC between Frontal_sup_L and left superior medial frontal gyrus, medial orbital (Frontal_Med_Orb_L) and left precuneus (Precuneus_L) ($t=3.650$, $P<0.05$), and increased FC between Frontal_sup_L and right middle frontal gyrus (Frontal_Mid_R) ($t=-4.220$, $P<0.05$). After ECT, with Frontal_sup_L as ROI, patients showed increased FC between Frontal_sup_L and Angular_L after ECT ($t=-3.982$, $P<0.05$) and decreased FC between Frontal_sup_L and right superior and inferior parietal gyrus (Parietal_Sup&Inf_R). In ECT responders, the change in FC between Frontal_sup_L and Angular_L was negatively correlated with the change of the score of BSSI ($r=-0.645$, $P=0.042$), and the change in FC between Frontal_sup_L and Parietal_Sup&Inf_R was positively correlated with the change of the score of BSSI ($r=0.714$, $P=0.023$). There was no correlation between changes in FC with changes in HAMD-17 score (all $P>0.05$).

Conclusion Our findings suggest that FC between Frontal_sup_L and Angular_L, and FC between Frontal_sup_L and Parietal_Sup&Inf_R may be involved in the mechanisms by which ECT exerts its effects on suicidality in patients with depression. Our findings provide insights into the neural underpinnings of ECT and may inform the development of more targeted novel therapeutic strategies for suicidality.

Trial registration Chinese Clinical Trial Registry, ChiCTR2100048182, Registered 04 July 2021, www.chictr.org.cn

Keywords Functional connectivity, Electroconvulsive therapy, Suicidality, Depression, Functional MRI (fMRI)

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1 Introduction

Suicidality, the intention or act of ending one's own life, is a common and serious symptom of many severe mental illnesses, particularly major depressive disorder (MDD) and bipolar disorder. Despite progress in psychiatric treatment, suicidality remains a significant public concern, contributing to approximately 800,000 deaths annually worldwide (Parekh and Phillips, 2014). Previous studies suggested that suicide may be a unique phenomenon, different from other depressive symptoms and it may also have a different underlying mechanism (Dobbertin, et al., 2023). Electroconvulsive therapy (ECT) has emerged as a highly effective treatment for severe depression, including those with significant suicide risk. However, the mechanism by which ECT improves suicidality remains poorly understood.

Several previous studies have explored brain structures and function activity changes related to ECT in depressed patients with suicidality. For example, a previous study in adolescents with depression and suicidal ideations found that ECT was associated with an increase in gray matter volume (GMV) in the gyrus of the superior frontal and right superior temporal. The same study also observed alterations in the amplitude of low-frequency fluctuations (ALFF) in various brain regions after ECT treatment, including an increase in the right middle occipital gyrus, and a decrease in the right inferior frontal gyrus (especially the opercular part), right frontal middle gyrus, and left temporal pole (Li, et al., 2022). Another study showed a significant decrease in ALFF and the fractional amplitude of low-frequency fluctuations (fALFF) in the right precentral gyrus reduced significantly after ECT, with these changes inversely correlated with reductions in SI scores (Li, et al., 2021). Furthermore, the study found increased regional homogeneity (ReHo) in the left inferior temporal gyrus and right middle occipital gyrus (Li, et al., 2021). In young depressed patients with suicidality, a study suggested that the fALFF in the left superior frontal gyrus (SFG) and orbital frontal cortex (OFC) significantly increased and was inversely correlated with the reduction of suicidality severity (BSSI scores) whereas no correlation was found with changes in the severity of depressive symptoms (HAMD-17scores) (Wang, et al., 2023), suggesting the changes might be specific for suicidality.

Reports about the mechanism of ECT on suicidality are inconsistent and this may be due to several factors, including (1) small sample sizes, due to difficulty in recruiting severe cases with suicide risks (Loh, et al., 2013). (2) the variability of clinical samples in terms of gender, age, diagnosis, clinical presentations, and the different statistical methods used (Botvinik-Nezer, et al., 2020). Moreover, different brain regions

have been implicated in the mechanism of ECT on suicidality, suggesting that ECT may affect the brain connectivity of multiple brain areas rather than specific brain regions.

Based on the neuroimaging evidence reviewed above we propose that ECT improves symptoms by correcting or resetting this abnormality through the action on these dysfunctional circuits. Depression is associated with abnormal patterns of functional connectivity in various brain networks (Beall, et al., 2012; Wang, et al., 2012; Kaiser, et al., 2015), and ECT may alter connectivity in a way that contributes to patients' improved symptoms (Wang, et al., 2020). Previous research has shown that ECT may increase within-network connectivity of the Central Executive Network (CEN) and the between-network connectivity of the default mode network (DMN), CEN, and salience network, which are all involved in depression (Wang, et al., 2018, 2020). Given these findings, we hypothesize that ECT may exert its effects on suicidality in depressed patients by altering neural connectivity, a hypothesis not yet explored before in adult depressed patients with suicidality.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a widely used imaging technique for studying psychiatric disorders such as depression. It can reveal the brain's structure, activity, and blood flow perfusion. Resting-state functional connectivity (FC) refers to the temporal correlation between spatially remote neurophysiological events in a resting state, expressed as the deviation in statistical independence (temporal correlation) between these events in the distribution of neuronal groups and regions (Fingelkurts, et al., 2005). This method measures the spontaneous fluctuations of BOLD signals throughout the brain. The region of interest (ROI)-based FC analysis allows us to examine the connectivity patterns of specific regions that have been identified in previous studies.

The neurobiology of suicidality is attributed to circuit-level dysfunction, commonly referred to as the "suicide circuit". Previous studies of MDD patients who died by suicide found abnormal connections among specific brain regions, including the left anterior limb of the internal capsule, the left middle frontal cortex, the orbital prefrontal cortex, the left thalamus, and the parietal lobule, particularly in the angular gyrus (Yang, et al., 2015; Lee, et al., 2016; Zhang, et al., 2018). Based on the neuroimaging evidence, we hypothesize that ECT may improve symptoms by correcting or resetting dysfunction within these suicide circuits. A prior study from our research group identified abnormalities in suicide-associated brain regions, especially in the left superior frontal gyrus (SFG) and orbital frontal cortex (OFC) (Wang, et al., 2023). Therefore, we selected SFG and OFC as ROIs to explore

changes in connectivity within the broader context of global brain function.

The primary objective of our study was to investigate how ECT induces alteration in the functional brain network. We employed ROI-wise FC analysis to examine the mechanism through which ECT mitigates suicidality in adult patients with depression. We compared the brain connectivity before and after ECT in patients. We aimed to determine whether improvement in suicidality after ECT was associated with functional connectivity changes. We also explored the existence of a functional connectivity signature indicative of ECT-induced improvement in suicidality within our patient sample.

2 Materials and methods

2.1 Participants

Patients were recruited from Beijing Anding Hospital, Capital Medical University, Beijing, China. The inclusion criteria were as follows: aged 18–45 years, right-handed; diagnosed with depressive episodes (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, DSM-5) (American Psychiatric Association, 2013). Additionally, patients needed to score 17 or higher on the Hamilton Rating Scale for Depression, 17-item (HAMD-17) (Melzer, et al., 2012), and had suicidal symptoms within the past two weeks, including suicidal ideation or suicidal attempt (SA). ECT was recommended by their treating psychiatrists. Patients with BD were also on mood stabilizers combined with antidepressants. The medications remained low dosage during the ECT sessions to minimize the effects on seizures.

The exclusion criteria are: Patients who had a history of other severe mental disorders such as schizophrenia or intellectual disability, neurodegenerative or neurological disorders (including Alzheimer's disease, epilepsy, severe brain injury), current drug or alcohol disorder, MRI contraindications, allergy to muscle relaxants or anesthetics, pregnancy, previous ECT or other neuromodulation therapy such as transcranial electrical stimulation within the past 90 days.

Healthy controls (HC) were matched in terms of sex, age, and educational level with patients and recruited from the community. The exclusion criteria mirrored those for depressed patients, with additional considerations for a history of psychiatric disorder or family history of psychiatric disorder or suicidality.

The study protocol was reviewed and approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University (registration (2021) Scientific No.56). All participants or their family members provided written informed consent before participating in the study.

2.2 Clinical symptom and cognitive function evaluation

The HAMD-17 and BSSI (Beck, et al., 1979) were used to assess depressive symptoms and suicidality respectively. BSSI is a self-rating scale aimed at assessing recent suicidal thoughts, plans, and behaviors. BSSI has 19 items and the total score range from 0 to 100. Higher scores indicated higher suicide risk. The HAMD-17 is a widely used clinical tool for assessing the severity of depression in patients. It has 17 items and the item scores range from 0 to 4 or 0 to 2 depending on the item. The total score can range from 0 to 52, with higher scores indicating more severe depression.

2.3 ECT procedure

ECT was administered using the Thymatron equipment (Somatics Thymatron®, Venice, FL, USA) in Beijing Anding Hospital, China. The bifrontal electrode placement was set for stimulus sites and the half-age method was used to determine the stimulus dosage (Petrides and Fink, 1996). Prior to anesthesia induction, all patients received intravenous atropine (0.5 mg). Anesthesia was induced with propofol (1.5 mg/kg) intravenously. Succinylcholine intravenously (0.4 mg/kg for females, 0.5 mg/kg for males) was used to achieve muscle relaxation.

A total of 8–12 ECT sessions were performed based on the individual treatment responses of patients. The treatment sessions were scheduled on days 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16, 18, 20 with additional sessions if deemed necessary.

2.4 MRI image acquisition

This study utilized a Siemens 3.0 T MRI scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) for the scans by professional radiology technicians in the Radiology Department in Beijing Anding Hospital, Beijing, China. A standard 64-channel head-neck coil was used. Participants were instructed to close their eyes but not fall asleep. Structural MRI scan parameters were as follows: 3D-T1 weighted structural image with a magnetization-prepared rapid gradient-echo (MPRAGE) sequence. The pulse repetition time (TR) was 2530 ms, the echo time (TE) was 1.85 ms, the field of view (FOV) was 256×256 mm², the flip angle (FA) was 90 degrees, voxel size was $1.0 \times 1.0 \times 1.0$ mm³, slice thickness was 1.0 mm, and the matrix size was 256×256 . The rs-f MRI scan parameters: An EPI sequence was employed with a TE of 30 ms, TR of 3000 ms, FOV of 216×216 mm², FA of 90 degrees, 47 slices, matrix size of 64×64 , slice thickness of 3.0 mm, voxel size of $3.0 \times 3.0 \times 3.0$ mm³, and an acquisition time of 6 min and 8 s.

2.5 MRI data preprocessing and resting-state Functional Connectivity (FC) analysis

Using the DPABI V7.0 toolbox (Yan, et al., 2016) in MATLAB 2020a, the following preprocessing steps were applied to the RS-fMRI image data based on Statistical Parametric Mapping (SPM) (<http://www.fil.ion.ucl.ac.uk/spm>): (1) Conversion from DICOM format to NIFTI format for the raw images. (2) Removal of the first 10 time points from the raw images to ensure signal stability. (3) Slice timing correction to account for differences in the acquisition time of slices within each volume. (4) Re-alignment of images to correct for head motion, and exclusion of participants with excessive motion (Mean FD_Jenkinson>0.2 mm) using the Friston-24 model at the individual level (Yan, et al., 2013). (5) Spatial normalization to the Montreal Neurological Institute (MNI) standard space using the DARTEL method and resampling to a 3 mm×3 mm×3 mm voxel size. (6) Segmentation of structural images into gray matter, white matter, and cerebrospinal fluid for voxel-based morphometry (VBM) analysis. (7) Spatial smoothing of all images using a 4 mm×4 mm×4 mm full-width at half-maximum Gaussian kernel to improve signal-to-noise ratio. (8) Linear detrending to reduce the influence of MRI machine noise. (9) Band-pass filtering in the 0.01–0.1 Hz frequency range to reduce the impact of physiological noise. (10) Regression of cerebrospinal fluid and white matter signals as covariates to remove confounding effects from these sources.

Voxel-wise FC analysis was conducted. Previously identified brain regions (left OFC and SFGs) that exhibited statistical differences in our previous research (Wang, et al., 2023) were selected as ROIs. The time series data from these ROIs were extracted, and Pearson's correlation coefficients were computed between the mean time series of each ROIs and the time series of each voxel within the brain, resulting in functional connectivity maps between the ROIs and the whole brain. Subsequently, Z-standardization was applied to make the data more comparable and improve the normality. The values of FC were computed both before and after ECT in patients and HCs. A t-test was conducted to examine the changes in FC between groups (patients *vs.* HCs) and times (pre-ECT *vs.* post-ECT). Using Gaussian Random Field (GRF) for multiple comparison correction, set the threshold levels at voxel *P*=0.005 and cluster *P*=0.05.

2.6 Statistical analysis

We used SPSS statistical software (version 26.0; IBM Corp., USA) to analyze the data. At baseline, chi-square tests for categorical variables including gender, and t-tests for continuous variables including age were used to test differences between the patient group and HCs. We performed the paired sample t-test to test the

difference in the HAMD-17 and BSSI scores before and after ECT in the patient group.

The FC values after ECT differing significantly from baseline were extracted and correlation analysis was used to explore the association of FC change with the score of BSSI and HAMD-17. The efficacy was expressed by a reduction rate of HAMD score after ECT compared with baseline (≥ 65% defined as responders and < 65% defined as non-responders). The associations between the change of FC value (post-ECT minus pre-ECT) and the change of score of clinical symptoms (HAMD and BSSI scores, pre-ECT minus post-ECT) were examined by an analysis of correlation analysis. The threshold of statistical significance was set at *P*<0.05.

3 Results

3.1 Clinical characteristic information and outcome

Twenty-three depressed patients (MDD=16, BD=7) and 32 HCs completed the entire study protocol. At baseline, there were no significant differences between the patient group and HCs regarding age, sex, marital status, and education level were not found differences between the patient group and HCs (all *P*>0.05). All depressed patients reported either recent SA (*N*=7) or SI (*N*=16). See Table 1.

Table 1 Comparison of demographic information between 36 healthy controls (HCs) and 23 Depressed patients with suicidality

Characteristic	HCs (n = 32)	Patients (n = 23)	t/χ ²	P
Age(years)	29.63 ± 7.53	28.87 ± 7.29	0.372	0.712
Gender (n, %)			2.458	0.117
Male	10(31.30)	3(13.00)		
Female	22(68.80)	20(87.00)		
Marriage (n, %)				0.661 ^a
Unmarried	17(53.10)	12(52.20)		
Married	15(46.90)	10(43.50)		
Divorced	0(0.00)	1(4.30)		
Education (n, %)				0.178 ^a
Secondary school	4(12.50)	6(26.10)		
University	22(68.80)	16(69.60)		
Master degree or above	6(18.80)	1(4.30)		
Suicidal symptoms (n, %)				
SI		16(69.60)		
SA		7(30.40)		
Diagnosis (n, %)				
MDD		16(69.60)		
BD		7(30.40)		

* *P* < 0.05
^a Fisher exact probability

After completing 8–12 sessions of ECT treatment, all 23 patients achieved remission of suicidal risk, with a score of 0 on the BSSI. Eight patients (8/23, 34.8%) demonstrated a 75% or higher reduction in the HAMD score, classifying them as responders. Overall, the HAMD-17 scores after ECT decreased significantly from baseline ($P<0.001$). See Table 2.

All 23 patients had blood oxygen saturation between 96–99% during ECT. The mean of seizure in 8 responders was (31.93 ± 7.09) s, and the other non-responders was (31.41 ± 10.35) s. There were no significant differences between responders and non-responders regarding antidepressants, antipsychotics, and mood stabilizers. See supplement 1.

3.2 Comparisons of FC in HCs and depressed patients with suicidality at baseline

This study used the Mean FD_Jenkinson as a covariate to analyze the global brain functional connectivity between the HCs and depressed patients with suicidality. In the patient group, with the left anterior orbitofrontal cortex (OFC_Ant_L) as ROI, the FC between OFC-Ant-L and left angular gyrus (Angular_L) reduced significantly compared to HCs ($t=3.849$, $P<0.05$). Using the left superior frontal gyrus (Frontal_sup_L) as ROI, the FC between

Frontal_sup_L and left superior medial frontal gyrus, medial orbital (Frontal_Med_Orb_L) and left precuneus (Precuneus_L) significantly decreased compared to the HCs ($t=3.650$, $P<0.05$). In contrast, the FC between Frontal_sup_L and right middle frontal gyrus (Frontal_Mid_R) significantly increased in the patient group compared to the HCs ($t=-4.220$, $P<0.05$). See Table 3 and Fig. 1 for more details.

3.3 Changes in FC in depressed patients with suicidality before and after ECT

In our study, we used the Mean FD_Jenkinson as a covariate to analyze the global brain functional connectivity before and after ECT treatment in patients. The results showed that, with Frontal_sup_L as ROI, the FC between Frontal_sup_L and Angular_L significantly increased after ECT compared to baseline ($t=-3.982$, $P<0.05$). Conversely, the FC between Frontal_sup_L and right superior and inferior parietal gyrus (Parietal_Sup&Inf_R) decreased significantly after ECT compared to baseline ($t=4.627$, $P<0.05$). See Table 4 and Fig. 2 for details.

3.4 Correlation analysis

In the patient groups as a whole, there was no significant correlation between the changes of FC between Frontal_sup_L and Angular_L after ECT, the change of FC between Frontal_sup_L and Parietal_Sup&Inf_R after ECT, and the change of HAMD-17 and BSSI total scores after ECT (all $P>0.05$). In responders, a significant inverse correlation was found between the change of FC value between Frontal_sup_L and Angular_L with the change of the score of BSSI ($r=-0.645$, $P=0.042$) while no correlation with the score changes of HAMD-17 scores ($P>0.05$). Additionally, there were significant positive correlations between the change of FC between Frontal_sup_L and Parietal_Sup&Inf_R after ECT with the change in the BSSI scores after ECT ($r=0.714$, $P=0.023$) while no significant correlation was found with the change of HAMD-17 scores ($P>0.05$). In non-responders, no significant correlations were found

Table 2 Comparison of HAMD-17 and BSSI scores between post-ECT and baseline in depressed patients with suicidality

Characteristic	Baseline	Post-ECT	t	P
HAMD-17	28.91 ± 5.95	11.43 ± 3.12	12.894	< 0.001*
Anxiety somatization factor	7.26 ± 2.22	4.30 ± 1.02	5.998	< 0.001*
Weight factor	1.17 ± 0.65	0.13 ± 0.34	7.091	< 0.001*
Cognitive impairment factor	6.74 ± 2.16	2.57 ± 1.27	8.194	< 0.001*
Retardation factor	8.83 ± 1.53	3.26 ± 1.25	13.371	< 0.001*
Sleep disorder factor	3.96 ± 1.40	0.65 ± 0.57	10.223	< 0.001*
BSSI	43.74 ± 20.83	0.00	10.070	< 0.001*

* $P<0.05$

Table 3 Significant differences in FC between HCs and depressed patients with suicidality

ROI	Area	Hemisphere	BA	Cluster size	Peak MNI coordinates			Peak t values
					X	Y	Z	
OFC_ant_L	Angular	Left	40	15	-51	-45	36	3.849
Frontal_sup_L	Frontal_Med_Orb	Left	11	19	-3	45	-12	4.372
	Precuneus	Left	30	10	0	-60	18	3.650
	Frontal_Mid	Right	10	15	33	39	24	-4.220

GRF (voxel $P=0.005$, cluster $P=0.05$)

Covariate: Mean FD_Jenkinson

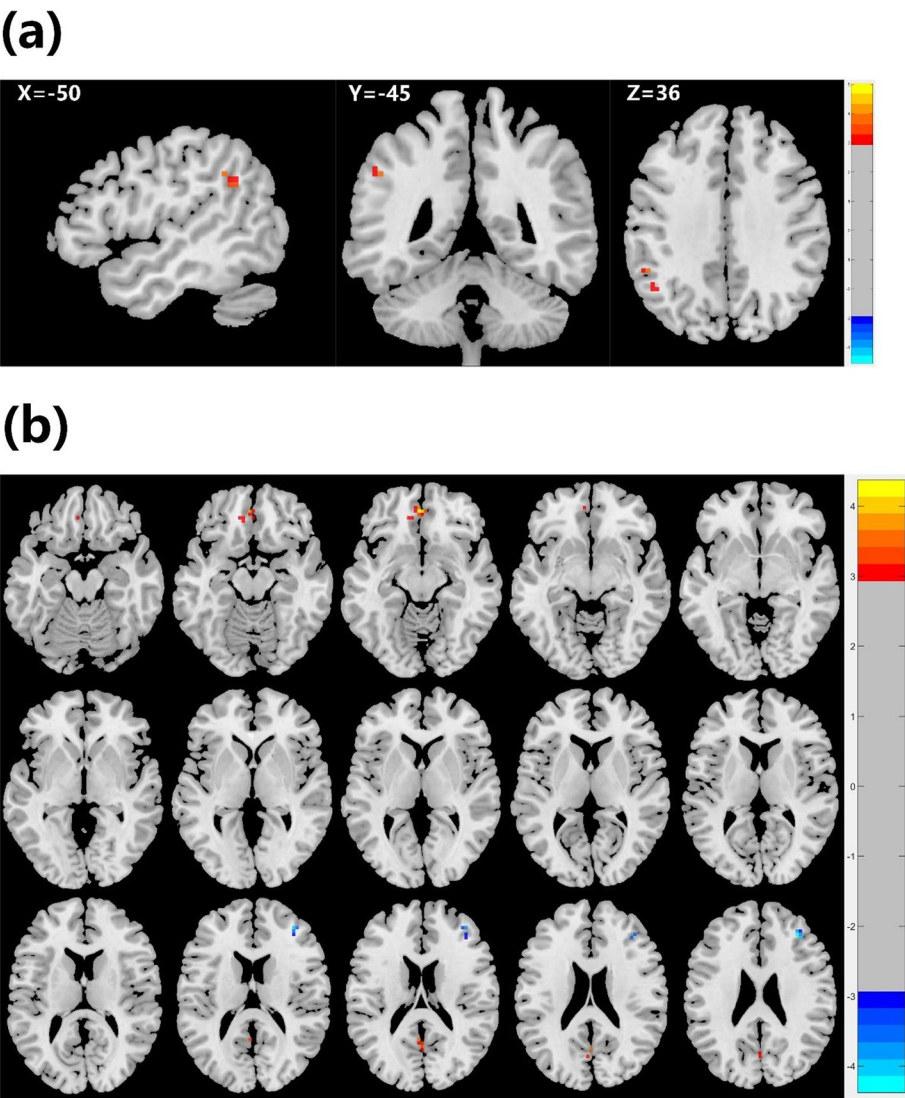


Fig. 1

Table 4 Significant differences in FC between post-ECT and baseline in depressed patients with suicidality

ROI	Area	Hemisphere	BA	Cluster size	Peak MNI coordinates			Peak t values
					X	Y	Z	
Frontal_sup_L	Angular	Left	39	8	-48	-63	33	-3.982
	Parietal_Sup&Inf	Right	7/40	8	36	-48	54	4.627

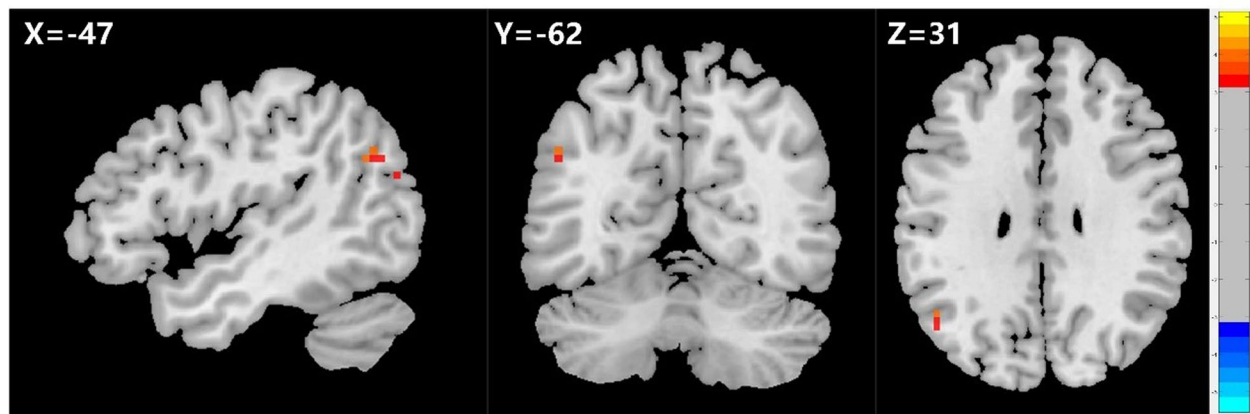
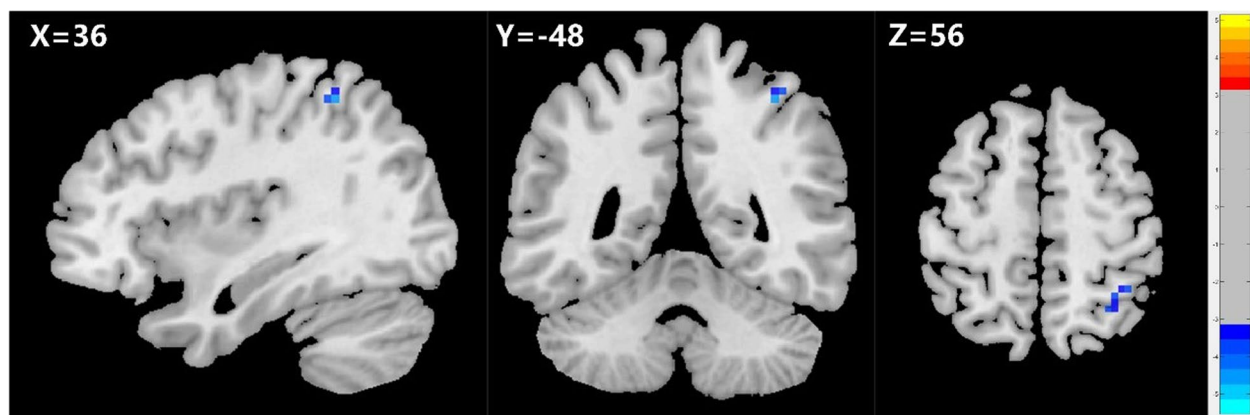
GRF (voxel $P=0.005$, cluster $P=0.05$)

Covariate: Mean FD_Jenkinson

between the changes in FC value between Frontal_sup_L and Angular_L after ECT, and the changes of FC between Frontal_sup_L and Parietal_Sup&Inf_R after ECT, and the changes in either HAMD-17 or BSSI total scores after ECT (all $P>0.05$).

4 Discussion

We used resting-state fMRI to investigate brain connectivity changes induced by ECT in depressed patients with suicidality. The aim was to evaluate therapeutic response in clinical practice and guide future ECT

(a)**(b)****Fig. 2**

treatment optimization. Our findings confirmed previous findings on the remarkable efficacy of in treating depressive symptoms and suicidality (Dobbertin, et al., 2023) sing ROI-wise FC analysis, we found a significant reduction in FC between the OFC_Ant_L and Angular_L, the Frontal_sup_L, Frontal_Med_Orb_L, and Precuneus_L. Conversely, FC between the Frontal_sup_L and Frontal_Mid_R increased significantly in the patient group compared to HCs. ECT enhanced FC between the Frontal_sup_L and the Angular_L while decreasing FC between the Frontal_sup_L and the Parietal_Sup&Inf_R. The altered FC between the Frontal_sup_L and Angular_L negatively correlated with the reduced BSSI scores after ECT, while in responders, the changed FC between the Frontal_sup_L and the Parietal_Sup&Inf_R positively correlated with the reduced BSSI scores after ECT. These results highlight the importance of functional connectivity between the frontal and parietal lobe in the

effect of ECT on suicidality, offering insights for future clinical practice and treatment optimization.

This study represents the first investigation into the impact of ECT on brain functional connectivity related to suicidality in adult depressed patients. Previous studies have linked changes in FC after ECT and changes in clinical measures, primarily focused on the antidepressant effects of ECT that are related with brain FC. Previous studies have explored various aspects of ECT's effects on brain connectivity and depressive symptoms. For example, Vander Waarde et al. (2015) reported that networks centered in the dorsomedial prefrontal cortex (dmPFC) and anterior cingulate cortex (ACC) could predict ECT's treatment response to depressive symptoms (van Waarde, et al., 2015). According to Pang et al. (2022), baseline FC within the default mode network (DMN) and between the DMN and frontoparietal network (FPN) could predict the treatment response in

MDD patients. Furthermore, the FC changes between the medial prefrontal cortex (mPFC) and vLPFC were negatively correlated with symptom improvement (Pang, et al., 2022). Very similarly, Zhang et al. (2021) reported that the changed FC between dmPFC and dlPFC after ECT was associated with improvement in anhedonia, a core symptom of depression (Zhang, et al., 2021). Wang et al. (2017) reported increased FC between the left amygdala and left fusiform face area (FFA), and increased effective connectivity (EC) from FFA to the amygdala after ECT, the FC in patients became closer to levels in HCs (Wang, et al., 2017). Wei et al. (2018) and Mo et al. (2020) also reported that the FC strength of the left angular gyrus increased after ECT (Wei, et al., 2018; Mo, et al., 2020). However, Chen et al. (2017) suggested that the connectivity of the eight baseline functional networks, namely the anterior and posterior default mode network, bilateral frontoparietal network, audio network, visual network, dorsal attention network, and sensorimotor network, was unrelated to the antidepressant treatment response of ECT in MDD patients (Chen, et al., 2017). Of note, they did not acquire the fMRI data after ECT treatment and could not explore the mechanisms underlying the effects of ECT on depression. Our study built on the foundation by investigating pre- and post-ECT fMRI data, revealing enhanced FC between Frontal_sup_L and Angular_L and FC between Frontal_sup_L and Parietal_Sup&Inf_R. We also found the changed FC was correlated with the reduced BSSI scores after ECT but not with HAMD-17. Notably, angular gyrus is involved in cognitive functions, including memory, semantics, and social cognition (Lijie, et al., 2020; Seghier and M., 2013), which is an important component of the default pattern network, and it is closely related to rumination behavior in patients with depression (Baladi, et al., 2013; Hamilton, et al., 2015). Using rs-fMRI, Wagner et al. (2021) compared the brain activity of four groups: MDD patients who attempted suicide, MDD patients with SI, MDD patients without suicidal behavior, and healthy individuals. They found that the hippocampus, dorsolateral prefrontal cortex, and angular gyrus showed differences in ALFF and degree centrality between those who had SI and those who had attempted suicide (Wagner, et al., 2021). We found that the angular gyrus is involved in how suicidality works in the brain, along with the frontal lobe and parietal lobes. Our findings are consistent with other studies and also showed that suicidality was linked to how well the frontal and parietal cortex communicated with each other, and ECT improved this communication in patients who responded to ECT, consistent with previous findings. This study furthers our understanding of

the pathophysiological mechanism of suicidality and depressive symptoms.

Recent neuroimaging studies have increasingly demonstrated the neural effects of ECT, implicating various brain regions (Leaver, et al., 2022). However, debates persist regarding ECT-specific brain changes due to limited replication and a comprehensive mechanism of ECT remains elusive (Leaver, et al., 2022). A crucial challenge in ECT research is parsing the nonspecific effects from those specific effects related to different symptoms such as depressive symptom and suicidality in response to ECT. Some suggested that previously reported ECT-related changes may not underlie clinical outcome but instead reflect nonspecific physiological effects of ECT (Leaver, et al., 2019). Inconsistent results of different studies may be due to the different specific symptoms of the patients, emphasizing the need to recruit similar specific symptom-specific groups. Our study included a clinical sample of individuals with depression and suicidality, making it more homogenous in terms of symptoms. Of note, the inconsistency in FC abnormalities related to suicidality symptoms, particularly in the left precuneus, suggests variability in specific brain regions. Similar to the antidepressant effects of ECT, our findings indicate that ECT induces changes in the brain independent of antidepressant response (Leaver, et al., 2022). We propose that studies examining ECT effects a priori, while testing antidepressant response effects post hoc, are more likely to find the nonspecific effects of ECT rather than effects specifically related to the antidepressant effects (Ousdal, et al., 2020). The inconsistent FC changes at baseline and after ECT in our study may also due to the nonspecific effect of ECT on brain. ECT not only induces an exogenous electrical stimulus on brain, but also activates an endogenous stimulus leading to a generalized tonic-clonic (convulsive) seizure. The seizure has profound effects on activity of various brain regions, which may play a role in neuroplasticity. This is related to the outcomes of ECT, such as symptom improvement or cognitive impairment, as well as other effects that may not be related to the symptom improvement.

Our findings, particularly the change in FC between the left superior frontal gyrus and left angular, FC change between the left superior frontal gyrus and right superior and inferior parietal gyrus, were correlated with the change of BSSI scores after ECT but not with the change HAMD-17 scores are interesting. This suggests that changes in FC are associated with remission of suicidality, not necessarily the improvement of depressive symptoms (as measured by HAMD-17). However, it is important to note that this relationship between change of FC with remission of suicidality was observed in ECT

responders, indicating the complexity and potentially unique neurophysiological mechanism underlying suicidality and depressive symptoms.

Moreover, recent studies suggest that depression is a highly heterogeneous syndrome with different clinical features that do not neatly align with a singular brain circuit (Siddiqi, et al., 2020). Functional connectivity patterns vary substantially across different subtypes of depression (Drysdale, et al., 2017), indicating that there might not be a single imaging marker for the mechanisms driving ECT-induced improvement, due to the complex antidepressant effects. Previous research has demonstrated that ECT can lead to anatomical and functional changes in several brain regions, and these changes may be linked to the antidepressant effects. For example, increased volume of the amygdala, hippocampus, and nucleus accumbens in response to ECT was found to be related to symptom improvement (Joshi, et al., 2016; Belge, et al., 2020). Graph theory analysis has revealed that an decrease in functional connectivity within a hippocampus thalamus-striatum network in ECT responders (Leaver, et al., 2021). Furthermore, increased cerebral blood flow in regions such as the dorsomedial thalamus and motor cortex near the ECT electrode, along with decreased cerebral blood flow in lateral frontoparietal regions have also been observed in ECT responders (Leaver, et al., 2019). Consequently, it is speculated that there may not be a single connectivity marker for global depressive symptomatology; instead, each symptom dimension may have its unique biological substrate. This notion is supported by a recent transcranial magnetic stimulation (TMS) study identifying two clusters of depressive symptoms responding to two distinct neuroanatomical treatment targets, with optimal TMS treatment targets situated in two competing functional networks (Siddiqi, et al., 2020). Future imaging studies may seek to identify the functional connectivity underpinnings of each symptom domain.

Several limitations in our study need to be considered. The sample size was quite small and a greater number of subjects would enhance the robustness of the findings. Second, we did not have a group of depressed patients without suicidality, therefore were unable to compare the differences between depressed patients with and without suicidality. Third, we included patients diagnosed with both MDD and bipolar disorder, and the brain mechanism may be inherently different. Fourth, all patients received medication throughout the study, so the effects of medications cannot be ruled out. Going forward, studies need to focus on a more homogeneous group of patients, ideally with ECT treatment alone. Finally, future studies should also consider using ECT as a treatment for suicidality as a trans-diagnostic symptom and examine the effects in different diagnostic groups.

5 Conclusion

In conclusion, we used the measure of functional connectivity as a metric to assess abnormalities in depressed patients with suicidality, and we examined the changes between pre-ECT and post-ECT. Compared with healthy controls, patients at baseline showed a significant decrease in FC between OFC_Ant_L and Angular_L, coupled with an increase in FC between Frontal_sup_L and Frontal_Med_Orb_L and Precuneus_L. Moreover, after ECT treatment, the FC between Frontal_sup_L and Angular_L increased, while the FC between Frontal_sup_L and Parietal_Sup&Inf_R decreased significantly compared to baseline, and these changes were correlated with changes in BSSI scores. These findings offer insights into potential mechanisms by which ECT affects suicidality and may provide guidance for optimizing ECT treatment. Additionally, exploring the mechanism of ECT on suicidality in other psychiatric disorders, such as schizophrenia, borderline personality disorder, is an important avenue for future research.

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Authors' contributions

Han Wu completed the analyses and wrote the first draft of the manuscript. Xue Wang administered neuropsychological and clinical measures, and assisted in writing and editing of the manuscript. Dan Wang, Wei Wang, Wen Wang and Wen-qing Jin recruited participants, administered neuropsychological and clinical measures. Wei Jiang treated patients by ECT. Yi-lang Tang assisted in writing and editing of the manuscript. Yan-ping Ren and designed the study, and assisted in writing and editing of the manuscript. Chun-lin Yang administered neuropsychological and undertook the MRI data processing.

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Availability of data and materials

All the data and materials are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University (registration (2021) Scientific No.56). All participants or their family members provided written informed consent before participating in the study.

Consent for publication

We, the undersigned, give our consent for the publication.

Competing interests

Neither of the authors declares that they have a conflict of interest.

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