Antidepressant Effects of Electroconvulsive Therapy Unrelated to the Brain’s Functional Network Connectivity alterations at an Individual Level

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Abstract

Background: Electroconvulsive therapy (ECT) can alleviate the symptoms of treatment-resistant depression (TRD). Functional network connectivity (FNC) is a newly developed method to investigate the brain’s functional connectivity patterns. The first aim of this study was to investigate FNC alterations between TRD patients and healthy controls. The second aim was to explore the relationship between the ECT treatment response and pre-ECT treatment FNC alterations in individual TRD patients.

Methods: This study included 82 TRD patients and 41 controls. Patients were screened at baseline and after 2 weeks of treatment with a combination of ECT and antidepressants. Group information guided-independent component analysis (GIG-ICA) was used to compute subject-specific functional networks (FNs). Grassmann manifold and step-wise forward component selection using support vector machines were adopted to perform the FNC measure and extract the functional networks’ connectivity patterns (FCP). Pearson’s correlation analysis was used to calculate the correlations between the FCP and ECT response.

Results: A total of 82 TRD patients in the ECT group were successfully treated. On an average, 8.50 ± 2.00 ECT sessions were conducted. After ECT treatment, only 42 TRD patients had an improved response to ECT (the Hamilton scores reduction rate was more than 50%), response rate 51%. 8 FNs (anterior and posterior default mode network, bilateral frontoparietal network, audio network, visual network, dorsal attention network, and sensorimotor network) were obtained using GIG-ICA. We did not find that FCPs were significantly different between TRD patients and healthy controls. Moreover, the baseline FCP was unrelated to the ECT treatment response.

Conclusions: The FNC was not significantly different between the TRD patients and healthy controls, and the baseline FCP was unrelated to the ECT treatment response. These findings will necessitate that we modify the experimental scheme to explore the mechanisms underlying ECT’s effects on depression and explore the specific predictors of the effects of ECT based on the pre-ECT treatment magnetic resonance imaging.

Key words: Electroconvulsive Therapy; Functional Network Connectivity; Functional Network Connectivity Pattern; Multivariate Pattern Analysis; Treatment-resistant Depression

INTRODUCTION

Major depressive disorder is one of the most common mental disorders in patients. The one- to two-thirds of major depressive disorder (MDD) patients who do not respond to individual antidepressants and the 15–33% who do not improve with multiple antidepressants are defined as having treatment-resistant depression (TRD).1[1]
Electroconvulsive therapy (ECT) has been recommended as an effective therapy for TRD by many national treatment guidelines. Clinical data have also demonstrated that ECT may be used as an augmentation strategy for treatment-resistant schizophrenia.

Previous studies have shown that ECT can induce cerebral blood flow, neurotransmitter activity, neuronal metabolites, and brain functional connectivity alterations in TRD patients. In the last 5 years, high-level research has suggested that the anti-depression effects of ECT are related to the alterations of brain networks and functional connectivity subsequent to undergoing ECT. Many studies have determined that resting-state functional connectivity alterations could represent a biomarker for depression and are most likely correlated with treatment outcome. For example, the dorsomedial prefrontal cortex functional network (FN) (including the dorsolateral prefrontal cortex, orbitofrontal cortex, and posterior cingulate cortex) and the anterior cingulate cortex (ACC) FN (including the dorsolateral prefrontal cortex, sensorimotor cortex, parahippocampal gyrus, and midbrain) have been reported to be prognostic neuroimaging biomarkers that can predict the outcome of ECT in TRD patients and can also be used to guide personalized treatment decisions.

With the advance of the pattern recognition technique, this method is being increasingly used in depression-related neuroimaging studies to characterize specific brain FN alterations at an individual subject level. Successful applications of pattern recognition techniques in depression-related neuroimaging studies indicate that the neural mechanisms underlying the effects of ECT on depression using this technique from multiple perspectives should be explored.

Although previous studies were successful, the FN connectivity (FNC)/functional networks connectivity pattern (FCP) alterations in TRD patients and the relationship between the FNC/FCP of pre-ECT treatment and ECT treatment response remain unclear. Based on the review and systematic analysis of previous studies involving multivariate pattern recognition methods, we conducted this study to explore the specific alterations of brain network connectivity of TRD patients and investigate the relationship between pre-ECT treatment FNC/FCP alterations and symptomatic improvement in TRD patients who received treatment with a combination of antidepressants and ECT. The first aim of this study was to investigate FNC alterations between TRD patients and healthy controls. The second aim was to explore the relationship between ECT treatment response and baseline FNC alterations in individual TRD patients.

**Methods**

**Participants and study design**

This study enrolled 82 TRD patients and 41 well-matched healthy controls. All the participants were assessed using the Structured Clinical Interview for DSM-IV to confirm the diagnosis of depression in patients and rule out psychiatric illness in healthy controls and their first-degree relatives. Inclusion criteria were as follows: patients with MDD who do not respond adequately to appropriate treatment courses of at least two antidepressants. The exclusion criteria were as follows: (a) bipolar disorder; (b) age <18 or >45 years; (c) left handedness; (d) history of brain trauma with loss of consciousness for more than 5 min, neurological disease, or serious physical diseases (respiratory disorders, cardiovascular disease, etc.); (e) history of substance abuse; and (f) contraindications for magnetic resonance imaging (MRI). The study was approved by the Ethics Committee of Jining Medical University. All the participants provided written informed consent. All the patients were hospitalized for a serious depressive episode. Therefore, they received a combination of fixed-dose antidepressants and ECT for 2 weeks. The Hamilton Depression Scale (HAMD) was used to evaluate depressive symptoms in the TRD patients before and after ECT treatment. The treatment response of each patient was measured by changes in its HAMD scores normalized by the baseline scores. Patients were considered remitters if they had a 50% reduction in pretreatment HAMD and a maximum posttreatment score of 10 following the ECT series. In 82 patients, seventy patients’ illness duration was more than 5 years, and for 12 patients, it was more than 7 years. All the patients had experienced episodes of major depressive symptom more than ten times. All the patients had been treated by more than two types of different antidepressants or combined with mood stabilizers, such as venlafaxine, fluoxetine, mirtazapine, citalopram, sertraline, valproate, risperidone, and lithium because the antidepressants used in the TRD patients were so complicated that we cannot identify specific subgroups with satisfactory sample size for comparison. Similarly, many of the TRD patients could not remember their exact illness durations, thus making the comparison of different illness durations unavailable. Therefore, we only briefly summarized the clinical information in this paper.

**Electroconvulsive therapy**

ECT was performed using an integrated instrument (MECTA spECTrum 5000Q, MECTA Corp, USA). Bilateral ECT was applied to patients from 8:30 a.m. to 9:30 a.m. The stimulus intensity was adjusted accordingly by an energy percentage based on the patients’ ages. Electrocardiograms, electroencephalograms, and electromyography were performed, and the patients’ oxyhemoglobin saturation and blood pressure were monitored. ECT was applied four
times during the 1st week and four times during the 2nd week. During ECT, patients received fixed-dose antidepressants.

Image acquisition
Structural and resting-state functional MRI (rsfMRI) scans were performed on all the patients, and the TRD patients were scanned within 24 h before ECT treatment. The MRI data were acquired using a 3-Tesla Siemens Trio scanner. Comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. During data acquisition, the participants were told to close their eyes, relax, and remain awake. All the participants were monitored to ensure they were not asleep. Sagittal three-dimensional T1-weighted structural images were acquired using a brain volume sequence (TR = 2.53 ms; TE = 7.22 ms; TI = 1.2 s; flip angle = 7°; field of view [FOV] = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, slice gap = 1.05 mm). T2-weighted functional images were acquired with a gradient-echo EPI sequence (TE = 9 ms; TR = 2 s; flip angle = 75°; slice thickness = 3.5 mm, slice gap = 1.05 mm; FOV = 240 mm, matrix size = 64 × 64, voxel size = 3.75 × 3.75 × 4.55 mm). Resting-state scans were acquired over a minimum of 300 s, 16 s in duration (158 volumes). All the participants were instructed to keep their eyes open during the scan and stare passively at a fixation cross.

Resting-state functional magnetic resonance imaging data preprocessing
Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), Analysis of Functional Neuromage software (http://afni.nimh.nih.gov/afni), and the FMRIB Software Library (http://fsl.fmrib.ox.ac.uk/fsl/) were used for the image preprocessing procedure. The first six volumes of the functional images were discarded to allow for magnetization equilibrium. The preprocessing procedure initially comprised slice-timing correction and head motion correction. Each fMRI scan was intensity scaled to yield a whole-brain mean value of 10,000. Temporal band-pass filtering (0.01 Hz < f < 0.08 Hz) was adopted, and the time series in the white matter and cerebrospinal fluid and six affine motion parameters were also regressed out of the data. Linear and quadratic trends were also removed. The fMRI scans were nonlinearly normalized to the Montreal Neurological Institute space, with the deformation field obtained with their co-registered T1 scans using DARTEL within SPM8 and resampled to 3 × 3 × 3 mm³. Finally, the data were smoothed using a Gaussian kernel of 6 × 6 × 6 mm full-width at half maximum.

Functional connectivity networks calculation
Functional connectivity networks (FNs) were computed for each rsfMRI scan using independent component analysis (ICA). GIFT software (http://mialab.mrn.org/software/gift/) was used to perform group independent components (ICs). Based on the acquired group ICs, we adopted a new method, group-information guided (GIG)-ICA, which can simultaneously optimize the spatial correspondence and independence of subject-specific ICs using a multi-objective optimization strategy to compute subject-specific ICs.[13]

Functional networks connectivity analysis
In this study, the number of components based on GIG-ICA was empirically determined to be 20. We selected 82 TRD patients and 41 healthy controls for the data set to complete the multivariate data analysis on the Grassmann manifold and step-wise forward component selection using the support vector machines to obtain the FNs. Using the aforementioned combination methods, we performed the FNC measure and subsequently extracted the functional connectivity patterns (FCPs) from among the FNs.

In our methods, the time courses of the intrinsic FNs were used in the FNC analysis. The FNs comprised the optimal FCP for each participant and were taken two at a time to yield several pairwise combinations. The correlation coefficient (r value) between the time courses of each pair of combinations was calculated and transformed into Fisher’s Z-values. The differences in the FNCs among the healthy control and two patient groups were evaluated using ANOVA analysis followed by post-hoc t-tests. The statistical significance level was set at P < 0.05 and corrected for multiple comparisons using the Bonferroni or false discovery rate correction.

Correlation analysis between aberrant functional networks connectivity patterns and the Hamilton Depression Scale scores
We used Spearman’s rank correlation coefficient (i.e., a nonparametric measure of statistical dependence between two variables) in the correlation analysis to explore the relationship between clinical symptom alleviation and alterations in the strength of the FCPs after ECT.

Results
Demographics
The general sociodemographic data are summarized in Table 1. Chi-square test was performed to evaluate the differences in gender, one-way ANOVA was used to test the difference in age and education across the three groups, and two-sample t-test was conducted to estimate the differences in HAMD between NRD and RD groups before and after ECT treatment. No significant differences in age or gender were found between the two groups of patients with TRD or the healthy controls. There were no significant differences in the HAMD scores between the two TRD groups (P < 0.05). Similarly, there were no significant differences in the average age of two TRD patients and the severity of illness.

Clinical efficacy results
Eighty-two TRD patients in the ECT group were successfully treated without developing adverse effects. On an average, 8.50 ± 2.00 ECT sessions were conducted. HAMD scores
after treatment were lower in the two groups than before treatment. The response of 42 TRD patients to ECT treatment was improved (the Hamilton scores reduction rate was more than 50%), response rate 51%.. All the aforementioned data are presented in Table 1.

**Functional networks status in treatment-resistant depression patients and the relationship with electroconvulsive therapy treatment effect**

The following FNs, anterior default mode network (DMN), posterior DMN, left frontoparietal network, right frontoparietal network, audio network (AN), visual network (VN), dorsal attention network (DAN), and sensorimotor network (SMN) [Figure 1], were selected in the forward components selection process. Compared with healthy controls, TRD patients showed no significant differences in these 8 FNs distributions or the functional connectivity strength among them. After ECT treatment, 42 TRD patients had an improved response to ECT, whereas 40 TRD patients responded more poorly. Surprisingly, comparisons among these two subgroups of patients and 41 healthy controls did not demonstrate any difference in FNs spatial distribution, FNC, or FCP. These astonishing findings indicate that effective ECT treatments were not related to the FNs spatial distribution, FNC, or FCP.

**DISCUSSION**

The present study explores the effects of ECT on FNs in patients with TRD by combining functional MRI data and machine-learning techniques. Although we did not find significant differences in resting-state brain FNC between two TRD patients with different ECT treatment response and the healthy controls, our results most likely provide some useful information for studying the neural mechanisms and predictors for the treatment outcome of TRD from different perspectives.

The brain networks extracted using the GIG-ICA and FNC from all the participants included the anterior and posterior DMN, bilateral frontoparietal network (FP), AN, VN, DAN, and the SMN. As discussed earlier, previous evidence from functional connectivity and multimodal studies based on inter-group fMRI data information reported that the widespread alterations involved in some brain regions and circuits are related to the symptoms of depression disorders. For example, most of the previous studies reported that cortical-limbic connectivity alteration was positively correlated with improvement of depressive symptomatology, whereas the changes in DMN do not significantly correlate with clinical improvement. Information based on the intergroup fMRI data was less accurate in guiding disease treatment or diagnosis compared with the information based on the fMRI data at an individual level. Although these eight FNs were primarily located in the aforementioned neural circuits, we did not find in the present study that there were significant differences in the eight FNs between TRD patients and healthy controls.

With the advance of fMRI data postprocessing techniques, many methods have been established to explore the FNC/FCP at an individual level, yielding some pivotal findings. For example, Rashid B et al. found that FNC features can accurately differentiate individual participants...
into appropriate diagnostic groups.[22] He et al.[23] reported that FNC alterations can be used as a biomarker to discriminate bipolar disorder and unipolar disorder. The FN level differences in prefrontal networks located in the dorsolateral/ventrolateral prefrontal cortex and ACC made the largest contribution to the classification of bipolar disorder versus unipolar depression disorder. More interestingly, Abbott et al. reported an increased FNC between the posterior default mode and left dorsal lateral prefrontal cortex following ECT to be specific to those who responded to the treatment.[28] Unfortunately, our study did not find the FNC/FCP alterations before or after ECT treatment. The reason for these negative results may be due to multiple factors, but it is difficult to analyze with a single study which is the primary reason. The inconsistencies between the study of Abbott et al. and this study may be due to the unknown misusage of the FNC algorithm based on GIG-ICA or differences in the fMRI parameters. These questions compel us in the future studies to modify our experimental schemes to explore the mechanisms of antidepressants and ECT and the specific predictors of the effects of ECT on treating depression.

The present study has some limitations. First, after ECT treatment was performed, we did not acquire the fMRI data. Without these data, we could not compare the FNC/FCP alterations before and after ECT treatment. Therefore, we did not explore the mechanisms underlying the effects of ECT on depression. However, many earlier studies have confirmed that ECT can normalize the aberrant FNC, thereby alleviating depressive symptoms. In the future, we plan to conduct a follow-up study to explore the mechanisms underlying ECT’s effects on depression and establish predictors that can help clinical psychiatrists make optimal treatment plans. Second, all the patients had already received many different types of antidepressants before the study. Antidepressants can influence functional activity; therefore, there is no straightforward way to explore brain functional alterations that are specific to depression. This also merits further investigation.

In conclusion, although the present study did not find FNC alterations between TRD patients and the baseline, a relationship between baseline FNC and ECT treatment outcomes was discovered. We believe that our findings can most likely provide some useful information for future investigation of neural mechanisms and predictors for treatment outcome of TRD from other perspectives.

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Conflicts of interest

There are no conflicts of interest.

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