Potential Mechanism for the Elimination of Suicide Attempts by Modified Electroconvulsive Therapy in Drug-naive Patients with Suicidal Depressive Episode: A Pilot Study Report

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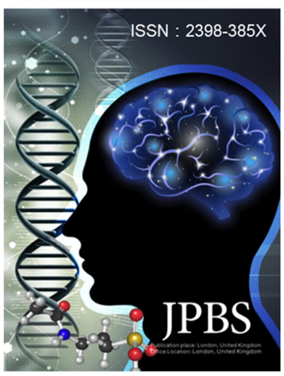

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ABSTRACT

Background: Modified electroconvulsive therapy (MECT) can rapidly eliminate suicide attempts in patients with suicidal depression. However, no study has investigated the neural mechanisms by which MECT eliminates suicide attempts. Currently, we conducted a study to explore the potential mechanisms by which MECT eliminates suicide attempts in patients with suicidal depressive episodes.

Methods: Four drug-naive patients with suicidal depressive episode underwent structural and resting-state functional magnetic resonance imaging scanning before and after MECT treatment. The voxel-based morphometry (VBM) and functional connectivity density mapping(FCDM) methods were used to analyze the imaging data. The gray matter volume (GMV) and resting-state global functional connectivity density (rs-gFCD) were used to evaluate the structural and functional alterations, respectively, that occurred subsequent to MECT.

Results: The VBM analysis revealed that MECT induced a GMV increase that was primarily localized to the left dorsolateral prefrontal cortex and bilateral thalamus. The FCDM analysis revealed that MECT induced an rs-gFCD decrease that was mainly localized in the left medial superior frontal gyrus and bilateral orbitofrontal cortex. No overlap existed between brain regions that exhibited structural and functional alterations.

Conclusion: The structural and functional alterations subsequent to MECT were mainly located in the brain regions that are related to the suicide attempts in suicidal depressive patients. The brain regions that exhibited structural alterations did not overlap with those that exhibited functional alterations, which suggests that the structural and functional alterations contributed independently to the efficacy of MECT in the elimination of suicide attempts in patients with suicidal depression.

Key Words: Suicide attempt; depression; modified electroconvulsive therapy; gray matter volume; functional connectivity density

INTRODUCTION

Many depressive patients attempt suicide, and 2-12% of depression patients die by suicide;(1,2) hence, suicide attempts during the major depressive episode should be given urgent status to ensure that adequate and effective treatment is administered as soon as possible.(3,4) Modified electroconvulsive therapy(MECT) had been confirmed as a rapidly effective treatment for patients with suicidal depressive episodes,(5,6) and many national treatment guidelines recommend MECT as the preferred method to rapidly alleviate suicide attempts in patients suffering a major depressive episode.

Although MECT exhibits superior efficacy in the elimination of suicide attempts, the specific neural mechanisms responsible for this efficacy remain unclear. In recent decades, many studies have utilized multiple neuroimaging techniques to investigate the anti-depressive mechanisms of MECT. (7-10) Some previous studies reported that major depressive disorder patients with a history of suicide attempts had decreased fractional anisotropy(FA) in the left anterior limb of the internal capsule(11) and that MECT induced functional alterations in left dorsolateral prefrontal cortical, dorsal anterior cingulate (ACC), mediodorsal thalamus (mdTh), hippocampus, right anterior temporal, medial parietal, and posterior cingulate cortex in the depressed patients (10, 12). These findings suggested that depressive suicide attempts may be associated with some brain structural alterations and MECT may alleviate the depressive symptoms by inducing functional or structural alterations in some brain regions.

However, to the best of our knowledge, no studies have been reported regarding the specific mechanisms by which MECT rapidly eliminates suicide attempts in suicidal depressive patients. Exploration of the specific mechanisms by which MECT eliminates suicide attempts would provide valid information that would aid clinicians in selecting tailored treatment strategies to prevent suicide attempts as rapidly as possible. To achieve this goal, a longitudinal study enrolling a large sample of drug-naive patients with first suicidal depressive episodes must be conducted to compare the structural and functional alterations that occur in the brain subsequent to MECT to explore the specific mechanisms by which MECT rapidly eliminates suicide attempts. Furthermore, this longitudinal study will enable us to attempt to establish an efficient neuroimaging data-based predictor of the sensitivities of individual patients to this treatment to maximize the prevention of suicide attempts.

Here, we have conducted a pilot study to investigate the structural and functional alterations that occur subsequent to MECT at a time point at which suicide attempts are completely eliminated to explore the potential mechanisms by which ECT rapidly eliminates suicide attempts to provide basic information for a large-sample longitudinal study. Considering pivotal findings of previous studies, we hypothesized that the potential mechanisms by which MECT eliminates suicide attempts in patients with suicidal depressive episodes may be related to the structural and functional alterations in some key brain regions associated with the depressive symptoms, such as dorsolateral prefrontal cortex, thalamus, and other brain regions.

Gray matter volume (GMV) is a typical index for representing structural alterations of the brain in depression. GMV is routinely used as a structural biomarker in clinical applications in neuropsychiatric disorders.(13,14) Resting-state global functional connectivity density (rs-gFCD) is an index that reflects the connectivity of single voxels with other voxels in the whole brain and can be used to investigate functional alterations in the brain and as a biomarker for clinical applications in neuropsychiatric disorders.(15-18) Therefore, in this pilot study, armed with voxel-based morphometry (VBM) and functional connectivity density mapping (FCDM) methods, we investigated the GMV and rs-gFCD alterations that occurred subsequent to MECT treatment at the time point at which suicide attempts were completely eliminated. By this pilot study, we expected to find the specific structural and functional mechanisms of the effect of MECT on suicide attempts in the patients with suicidal depressive episodes.

METHODS

Participants

All participants were enrolled from the second affiliated hospital of Tianjin Medical University between

July 2014 and February 2015. Before the study began, ethical approval was obtained from the Institutional Review Board of Tianjin Medical University. After receiving full information about the study, the guardians of the patients provided written informed consent. All patients were diagnosed by 2 senior professional psychiatrists based on the DSM-IV diagnostic criteria for a major depressive episode. (19) The inclusion criteria were the following: 1) age ≥ 18 years old, 2) persistent suicide attempts exist at least 1 week, and 3) no history of the use of antidepressants, mood stabilizers and other neuroleptic drugs in the previous 4 weeks. The exclusion criteria were as follows: 1) neurological or neurodegenerative disorder, such as epilepsy, diagnosed by neurologist; 2) other mental disorders, such as current psychoactive substance abuse or dependence, schizophrenia, borderline personality disorder, etc.; 3) contraindications for MRI, including metal implants, claustrophobia, etc.; and 4) pregnant or breast-feeding female patients.

Clinical Assessments

Demographical information, including age, sex, education and illness duration, were derived from the guardians' and patients' reports. The Scale for Suicidal Ideation (SSI) (20) was used to evaluate the severity of the suicide attempts, and the Montgomery-Asberg Depression Rating Scale(MADRS) (21) was used to evaluate the severity of the depressive episodes. These two clinical assessments were completed by an independent professional psychiatrist who was blinded to the diagnostic and treatment statuses of all participants. The first assessment occurred within two days prior to the first MECT treatment, and during the course of the MECT treatment, the MADRS and SSI assessments were conducted once weekly.

Modified Electroconvulsive Therapy Procedures

MECT was administered thrice weekly using a brief-pulse, constant-current apparatus (0.9A) and brief-pulse (0.5 ms, bilateral, BLMECT) device. Etomidate (0.3 mg/kg body mass) was intravenously used to induce anesthesia, intravenous succinylcholine (0.5-1 mg/kg body mass) was used to induce muscle paralysis, and appropriate oxygenation (100% oxygen, positive pressure) was used to ensure oxygen adequacy until the resumption of spontaneous respiration. At the initiation of treatment, individual seizure thresholds were detected via standard stimulus dosing methods, and subsequent treatments involved the delivery of stimuli at 2-fold the threshold stimulus to ensure the induction of seizures. The MECT treatment was ceased if the patient exhibited an adequate clinical response or failed to exhibit ideal improvement after the last two ECT sessions based on the clinical decisions of the psychiatrist. (5,6)

MRI Data Acquisition Procedure

The MRI data were acquired using a 3.0-Tesla MR system (Siemens Magnetom Trio Tim, Germany). All subjects were instructed to keep their eyes closed, relax, move as little as possible, think of nothing in particular, and not fall asleep during the MRI scans. Sagittal 3D T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time (TR) = 1900ms; echo time (TE) = 2.34 ms; inversion time (TI) = 900 ms; flip angle (FA) = 9°; field of view (FOV)=250 mm×250 mm; matrix=250 ×250; slice thickness = 1 mm, no gap; and 176 sagittal slices. Resting-state fMRI data were acquired using a gradient-echo single-short echo planar imaging sequence with the following parameters: TR/TE = 2500/30 ms; FOV = 220 mm×220 mm; matrix = 64×64; FA = 90°; slice thickness = 4 mm; gap = 0.5mm; 31 interleaved transverse slices; and 180 volumes. In the present study, we conducted second MRI scans after the suicide attempts were completely eliminated according to the assessments of the professional psychiatrists using based on the SSI scale and the reports provided by the patients.

MRI Data Preprocessing

The resting-state fMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes for each subject were discarded to allow the signal to reach equilibrium and for the participants to adapt to the scanning noise. The remaining volumes were corrected for the acquisition time delay between slices. Then, realignment was performed to correct the motion between time points. All subjects' fMRI data were within the defined motion thresholds (i.e., translational and rotational motion parameters below 2 mm or 2°). We also calculated the frame-wise displacement (FD), which indexes the volume-to-volume changes in head position. Several nuisance covariates (six motion parameters, their first time derivations, and the average BOLD signals of the ventricular and white matter) were removed using multiple linear regression analysis. Recent studies have reported that the signal spike caused by head motion significantly contaminates the final resting-state fMRI results even after regressing out the linear motion parameters. Therefore, we further regressed out the spike volumes when the FD of the specific volume exceeded 0.5. The datasets were then band-pass filtered in a frequency range of 0.01 to 0.08 Hz. In the normalization step, the individual structural images were linearly co-registered with the mean functional image. The structural images were then nonlinearly co-registered to MNI space. Finally, each filtered functional volume was spatially normalized to MNI space using the co-registration parameters and resampled into 3mm cubic voxels.

Gray Matter Volume Calculation

The GMVs of each voxel were calculated using VBMas implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). The structural MR images weresegmented into gray matter (GM), white matter and cerebrospinal fluid using the standard segmentation model. After an initial affine registration of theGM concentration map into the Montreal Neurological Institute (MNI) space, the GM concentration images were nonlinearly warpedusing diffeomorphic anatomical registration through the exponentiated Lie algebra (DARTEL) technique, and the results were resampled to a voxel size of 1.5 mm ×1.5 mm ×1.5 mm. The relative GMV of each voxel was obtained by multiplying the GM concentration map by the non-linear determinants that were derived from the spatial normalization step. Finally, the GMV images were smoothed using a Gaussian kernel of 6 mm×6 mm× 6 mm full-width at half-maximum (FWHM). After spatial preprocessing, the smoothed GMV maps were used for statistical analyses.

rs-gFCD Calculations

The rs-gFCDvalue for each voxel was calculated using an in-house script that was written on the Linux platform according to the method described by Tomasi and Volkow(15-17). Pearson's linear correlations were used to evaluate the strengths of the functional connectivities between voxels. Two voxels with a correlation coefficient of R > 0.6 were considered significantly connected. This threshold has been proposed to be the optimal threshold for calculating rs-gFCD in a previous study.(15-17) The rs-gFCD calculations were restricted toa cerebral gray matter mask. The rs-gFCD at a given voxel x0 was computed as the total number of significantly functional connectionsk (x0) between x0 and all other voxels. This calculation was repeated for all x0 voxels in the brain. The grand mean scaling of the rs-gFCD was obtained by divided by the mean value of allbrain voxels to increase the normality of the distribution. Finally, the rs-gFCD maps were spatially smoothed using a 6 mm × 6 mm × 6 mm FWHM Gaussian kernel.

Statistical Analysis

Paired two-sample t-tests were performed to test the differences in the GMVs and rs-gFCDs of the depressed patients before and after electroconvulsive therapy. Corrections for multiple comparisons were performed using Monte Carlo simulations, which resulted in a corrected threshold of P<0.05 and cluster sizes of at least 340 voxels for the GMV and 43 voxels for the rs-gFCD (AlphaSim program in REST software. Parameters: for GMV, voxelwise P = 0.01, FWHM = 9.2 mm × 9.0 mm × 9.0 mm, cluster connection radius r = 2.5 mm, with a GM mask and a resolution of 1.5 × 1.5 × 1.5 mm^3; for rs-gFCD, voxelwise P = 0.01, FWHM = 7.4 mm × 8.3 mm × 7.4 mm, cluster connection radius r = 5 mm, with a GM mask and a resolution of 3 × 3 × 3 mm^3).

RESULTS

Participants' Demographic and Clinical Assessments

In the current pilot study, we recruited only 4 subjects for the collection of clinical MECT and MRI data (1 male, 3 female), 2 subjects were the first major depressive episode patients, and 2 subjects were the repetitive major depressive patients. All the 4 subjects had none history of the use of antidepressants, mood stabilizers and other neuroleptic drugs in the last 4 weeks. The average age of these patients was 35.0 ± 4.8 years. The average MADRS was 38.0 ± 1.4, the average SSI severity score was 56.9 ± 9.0, and the average duration of existing persistent suicide attempts was 22.0 ± 27.5 days. In this pilot study, when the suicide attempts were completely eliminated, all of the patients had received 8.5 ± 2.0 treatments (6-11 treatments). The post-MECT MADRS was 17.5 ± 9.4, and this result also confirmed the anti-depressive effect of MECT.

Structural and Functional Alterations Subsequent to MECT

As shown in Fig.1, increased GMV was observed in the left dorsolateral prefrontal cortex and bilateral thalamus in the suicidal depression patients following MECT treatment compared with these patients prior to MECT treatment (P<0.05, AlphaSim corrected). As shown in Fig.2, the rs-gFCD was significantly decreased in the left medial superior frontal gyrus and bilateral orbitofrontal cortex in the suicidal depression patients following MECT treatment compared to these patients prior to ECT treatment (P<0.05, AlphaSim corrected). None decreased GMV and increased rs-gFCD was observed in any brain regions in the suicidal depression patients following MECT treatment compared to these patients prior to MECT treatment.

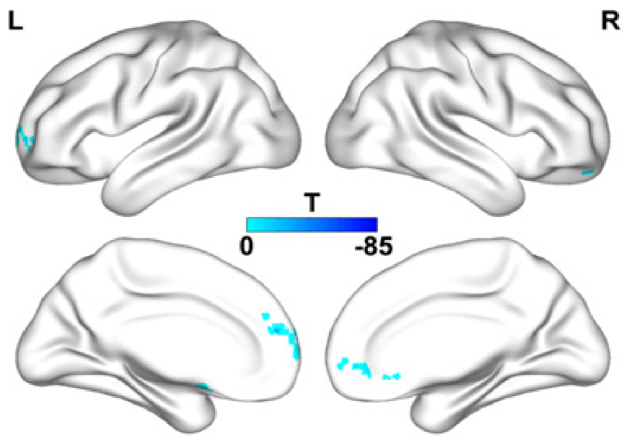

Fig.1 Regions Exhibiting Significant Changes in GMV in the Patients Subsequent to MECT

Table 1. Regions Exhibiting Significant Changes in GMV in the Suicidal Patients Subsequent to MECT

Brain Regions	Brodmann areas	Cluster size (Voxels)	Peak t values	Coordinates in MNI (x, y, z)
After >Before				
Bilateral thalamus		698	55.5	3, -13.5, 4.5
Left dorsolateral prefrontal cortex	10	392	27.4	-4.5, 57, 16.5

Abbreviations: GMV, gray matter volume; MNI, Montreal Neurological Institute.

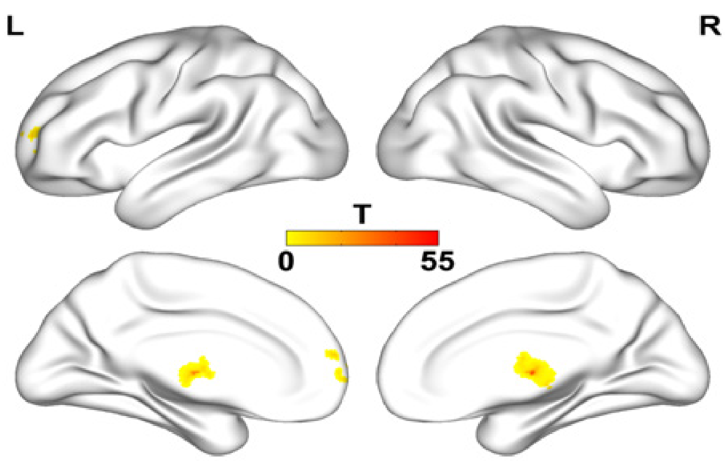

Fig.2 Regions Exhibiting Significant Changes in rs-gFCD in the Patients Subsequent to MECT

Table 2. Regions Exhibiting Significant Changes in rs-gFCD in Patients Subsequent to MECT

Brain Regions	Brodmann areas	Cluster size (Voxels)	Peak t values	Coordinates in MNI (x, y, z)
After <Before				
Left orbitofrontal cortex	25	39	-20.8	-12, 91, -21

Right orbitofrontal cortex	11	61	-22.5	12, 48, -3
Left medial superior frontal gyrus	9	72	-84.0	-21, 66, 6

Abbreviations: rs-gFCD, resting-state global functional connectivity density; MNI, Montreal Neurological Institute.

DISCUSSION

In the current pilot study, we first explored the structural and functional alterations that occurred in the brains of drug-naive suicidal depressive patients after the complete elimination of suicide attempts following MECT treatment. The participants in our study were drug-naive patients to avoid the influence of antidepressants and objectively reflect the effect of MECT. We found that accompanied with the elimination of suicide attempts, the GMVs of the left dorsolateral prefrontal cortex and bilateral thalamus increased. However, accompanied with the elimination of suicide attempts, the rs-gFCDof the left medial superior frontal gyrus and bilateral orbitofrontal cortex decreased. Our findings suggest that the structural and functional alterations that occurred subsequent to MECT both probably contributed to the elimination of suicide attempts, although these two categories of alterations exhibited independent disassociation patterns.

Some previous structural neuroimaging studies have reported that suicide attempts are associated with decreased gray matter volumes in some brain regions that are located in the frontal and temporal cortical lobes and other sub-cortical regions.(22-25) Disruptions of the structural connectivity of the fronto-thalamic circuit have also been reported to be associated with the suicidal histories of patients with depression[26]. For example, Benedetti et al. found that decreased GMVs in the dorsolateral prefrontal cortex, orbitofrontal cortex and other brain regions are associated with suicide attempts.(23) Giakoumatos et al. found reduced GMVs in some brain regions, such as the superior frontal and superior parietal cortices and the thalamus, in psychotic patients with suicidal behavior.(24) Jia et al. found that reduced fiber projections from the anterior limb of the internal capsule to the left medial frontal cortex, orbitofrontal cortex and thalamus are associated with suicide attempts.(26) Simultaneously, functional neuroimaging studies have reported that suicide attempts are associated with hyperactivity of the orbito-frontal and other cortical regions.(27-31) According to previous studies, the aforementioned brain regions are the important components of the cognitive processing and emotion regulation circuits(26,32-34). Structural integrity deficits and functional disturbances in these brain regions disrupt normal cognitive processing and emotional regulation, which subsequently influences the decision-making network and influences the vulnerability to suicidal behavior.(25-35) In the current pilot study, we found that increases in the GMVs of the frontal cortex and thalamus and decreases of the functional connectivity from the frontal cortex to the whole brain were associated with the elimination of suicide attempts. Our findings suggest that structural and functional normalizations in these suicide-attempt related brain regions can reduce suicide attempts.

Notably, our findings demonstrated that the brain regions that exhibited structural alterations subsequent to MECT did not overlap with the brain regions that exhibited functional alterations. This finding suggests that the structural and functional alterations that occur subsequent to MECT independently contribute to the efficacy of MECT in the elimination of suicide attempts. Disassociations of structural and functional alterations in depressed patients have been reported in previous studies.(36) For example, Guo et al. reported that functional and anatomical brain deficits are disassociated in major depression disorder and that both deficits independently contribute to the neurobiology of MDD.(36) Furthermore, van Heeringen Cet al. analyzed some studies that utilized structural and functional MRI techniques to investigate the neural vulnerability to suicidal behavior; the results of this meta-analyses suggested that structural alterations may be trait markers of suicidal vulnerability, and functional alterations may be state markers of suicidal vulnerability; increased sensitivity to negative stimuli and the inability to control maladaptive responses during cognitive processing caused by structural deficits are the two pivotal features of suicidal behavior vulnerability.(27,37,38) In our study, after ECT treatment was accompanied by the elimination of suicidal ideation, the GMVs of the frontal lobe and thalamus increased, and functional connectivity in the frontal lobe was decreased; these findings support the suggestion of van Heeringen Cet al. to some extent.

LIMITATIONS

There are some limitations in our study. First, the patient sample size we analyzed is relatively small. Actually we enrolled 15 patients in total. Due to the influence of the disease, patients generally exhibited poor compliance, which subsequently resulted in the poor MRI data quality and only four patient's data can be used for analysis. Future studies should consider enrolling more patients to validate our findings. Second, the lack of a control group also is another limitation of the current study. Future studies could enroll the patients who receive antidepressants for suicide attempt treatment and compare the specificity of MECT treatment to drug treatment so that the mechanisms of MECT in the elimination of suicide attempts can be better characterized.

CONCLUSION

The structural and functional alterations that occur subsequent to MECT are mainly localized to brain regions that are related to the suicide attempts in the suicidal depressive patients. The brain regions that exhibited structural alterations did not overlap with the brain regions that exhibited functional alterations, which suggests that the structural and functional alterations independently contributed to the efficacy of MECT in the elimination of suicide attempts in patients with suicidal depression.

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Conflicts of Interest

There are no conflicts of interest.

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