

# Changes in brain network properties in major depressive disorder following electroconvulsive therapy: a combined static and dynamic functional magnetic resonance imaging study

Dayi Liu<sup>1</sup>, Shixiong Tang<sup>2,3</sup>, Zhipeng Wu<sup>1</sup>, Jie Yang<sup>1</sup>, Zhening Liu<sup>1</sup>, Guowei Wu<sup>1</sup>, Adellah Sariah<sup>4</sup>, Xuan Ouyang<sup>1</sup>, Yicheng Long<sup>1</sup>

<sup>1</sup>Department of Psychiatry, The Second Xiangya Hospital, Central South University, National Clinical Research Center for Mental Disorders, Changsha, China; <sup>2</sup>Department of Radiology, The Second Xiangya Hospital, Central South University, Changsha, China; <sup>3</sup>Clinical Research Center for Medical Imaging in Hunan Province, Changsha, China; <sup>4</sup>Department of Mental Health and Psychiatric Nursing, Hubert Kairuki Memorial University, Dar es Salaam, Tanzania

*Contributions:* (I) Conception and design: X Ouyang, Y Long; (II) Administrative support: Z Liu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: D Liu, Y Long; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Xuan Ouyang; Yicheng Long. Department of Psychiatry, The Second Xiangya Hospital, Central South University, Changsha 410011, China. Email: ouyangxuan@csu.edu.cn; yichenglong@csu.edu.cn.

**Background:** Major depressive disorder (MDD) is a common and intractable mood disorder. Electroconvulsive therapy (ECT) is a common means of brain electrical stimulation for the treatment of MDD, but the neurobiological mechanism of its clinical symptom relief effect is still to be explored. This study aims to explore how ECT plays a role in depression remissions by investigating the changes of static and dynamic brain network characteristics in MDD patients before and after ECT.

**Methods:** Resting-state functional magnetic resonance imaging (fMRI) scans were obtained from nine MDD patients twice before and after a full course of ECT, all of whom responded to ECT as defined by at least a 50% reduction from baseline Hamilton Depression Scale (HAMD) scores. Both static and dynamic characteristics of the functional brain network were compared between the pre- and post-ECT scans for all participants, and the correlations between changes in clinical symptoms and altered network metrics were also investigated.

**Results:** The clustering coefficient and local efficiency in static brain networks were increased significantly, while the global flexibility of dynamic brain networks was decreased significantly after ECT. Several regions of interest (ROIs) that changed significantly at the local level were also identified, which involved regions of the cerebellum, hippocampus as well as frontal and temporal cortices. Although not significant, the decrease of HAMD scores were associated with trends of changed network metrics after ECT.

**Conclusions:** Our results suggest that ECT may alleviate the depressive symptoms of MDD by decreasing the randomness of the brain network as reflected by changes in both static and dynamic network properties and that the temporal gyrus, frontal gyrus, hippocampus, and cerebellar regions may play key roles in such mechanisms. These findings have important implications for our understandings of ECT and depression. However, this study is limited by a relatively small sample size and the results should be confirmed in larger samples.

**Keywords:** Electroconvulsive therapy (ECT); depression; brain network; graph theory; dynamic brain network

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## Introduction

Major depressive disorder (MDD), as a common mood disorder, is a kind of severe mental disease from which more than 264 million people worldwide suffer (1). It is well known that MDD is a major cause of disability and a significant risk factor for suicide (2-5), contributing to a growing global burden on the economy and health systems of the society (6).

Electroconvulsive therapy (ECT) provides effective and tolerable treatment to relieve depressive symptoms in patients with MDD (7-9), especially for patients who failed to respond to conventional pharmacotherapies (10,11). Because of such advantages, the use of ECT in psychiatric hospitals has largely increased over the past few years in China, the United States and the rest of the world (12). However, the ECT is not effective for all patients (13), and the underlying mechanisms are still poorly understood. To uncover the physiological markers of ECT response and advance the future treatment optimization, there is an urgent need to know how ECT plays a role in the treatment of MDD.

Whole-brain connectivity analysis based on functional magnetic resonance imaging (fMRI) (14,15) provides the possibility to explore whether and how ECT alters brain function in MDD. For instance, a study including 23 MDD patients and 25 healthy controls has reported significant increases in functional connectivity in the left anterolateral prefrontal cortex and dorsolateral prefrontal cortex after ECT compared with pre-treatment (16). Many recent studies have also suggested that the changes in the functional connectivity of the prefrontal cortex after ECT may be closely correlated with the alleviation of clinical symptoms of MDD (17-19). While the above results significantly deepen our understanding of ECT-related effects in MDD, there is an important limitation that all these studies were performed assuming the patterns of brain connectivity are static. Recent advances in fMRI studies have suggested that functional connectivity patterns are changing dynamically over time, and analysis of dynamic functional connectivity might provide important information on the biological indicators of brain networks in mental illness which is ignored by static fMRI measures (20), such as schizophrenia (21) and bipolar disorder (22). At present, it is believed that combining the dynamic and static functional network metrics could provide more powerful and sensitive classifications when compared to the conventional static functional connectivity-based methods

(23,24). Notably, a number of studies have reported altered dynamic functional connectivity in MDD patients (25-28), bringing the possibility that these measures may be modulated by ECT, which remains to be tested.

The purpose of the present study was to explore the possible neurobiological mechanism of ECT in patients with MDD by using both the static and dynamic brain network properties. Resting-state fMRI data were scanned from MDD patients both before and after ECT and brain network analysis was conducted to (I) investigate the alterations in static and dynamic brain network induced by ECT, and (II) verify whether these alterations would be related to the alleviation of depressive symptoms in MDD patients. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2723>).

## Methods

### *Participants, designs and assessments*

Eleven MDD patients were recruited to the study from The Second Xiangya Hospital, Central South University according to the following inclusion criteria at baseline: (I) being at least 16 years of age; (II) right-handed, Han Chinese ethnicity; (III) diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5); (IV) had at least moderate current depression, as defined by the Hamilton Depression Scale (HAMD) score  $\geq 17$  (29); (V) met the clinical indications for ECT (suicide risk, refractory depression, etc.) (30).

All subjects underwent fMRI scans twice: once at baseline (T0) and once after completing a full course of ECT (T1). ECT was administered 3 times per week on Monday, Wednesday, and Friday with a break of weekends. In line with a previous study by Zeng *et al.* (31), all participants received at least 6 times of ECT sessions; after the 6th ECT session, ECTs were continued if patients' depressive symptoms had not improved sufficiently as decided by experienced clinicians, but up to 8 ECT sessions in total. ECT and EEG monitoring were performed using a spECTrum-5000Q device (First Product Condar Technology Co., LTD, Beijing, China), and the stimulation parameters were set as follows: placing the original bitemporal stimulation, constant current =600–700 mA, pulse frequency =100 Hz, pulse width =1.0–1.2 ms, and stimulus dose adjusted by altering the duration of train. Two patients were lost because of refusing to complete a full course of ECT, and a total of nine patients were included in

the final analysis.

At both time points (T0 and T1), the HAMD was used to measure the severity of current depressive symptoms; the Beck Suicidal Ideation Scale (BSIS) was used to assess the risk of suicide at the nearly 2 weeks (BSIS-2-weeks) and at the worst time of depression (BSIS-worst) (32); the Information (WAIS-I) and Digit Symbol (WAIS-DS) subtests of Wechsler Adult Intelligence Scale (WAIS), Chinese version was used to respectively evaluate two domains of cognitive function, verbal comprehension, and processing speed (33). Response to ECT was defined by at least a 50% reduction from the baseline HAMD scores (13).

The study was approved by the Ethics Committee of Second Xiangya Hospital, Central South University (No. 2016S024) and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Imaging data acquisition and preprocessing*

Resting-state fMRI and three-dimensional T1-weighted (for accurately realigning images) imaging data were collected on a Philips Gyroscan Achieva 3.0 Tesla scanner (First Product Condar Technology Co., LTD) in the axial direction. A gradient-echo echoplanar imaging (EPI) sequence was used to obtain fMRI images with the following parameters: slice thickness = 4 mm, gap = 0 mm, matrix = 64×64, slices = 36, flip angle = 90°, field of view (FOV) = 240×240 mm, repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, and total number of time points = 250. A turbo field echo sequence was used to collect T1-weighted images with the following parameters: TR = 7.5 ms, TE = 3.7 ms, flip angle = 8°, FOV = 240×240 mm, acquisition matrix = 256×200, slice thickness = 1 mm, gap = 0 mm, and number of slices = 180.

Imaging data preprocessing was performed using the DPARSF software (<https://rfmri.org/DPARSF>) (34,35) and a standard pipeline whose details can be found elsewhere (26,36). Briefly, the pipeline includes removing the first 10 volumes, slice timing, motion realignment, spatial normalization to the standard brain space, temporal filtering (0.01–0.10 Hz), and regressing out for white matter, cerebrospinal fluid, and global mean signals. To account for head motion, the slice timing for the remaining images was corrected, and images were realigned to the first volume. The mean framewise displacement (FD) (37) was calculated for estimating head motion. All participants had a mean FD < 0.2, rotations < 2° and translations < 2 mm which suggest acceptable head motion, and there were no differences in

mean FD between the before- and after-ECT fMRI scans at the group level ( $P > 0.05$ , paired  $t$ -test).

### *Static and dynamic network metrics*

After data preprocessing, both static and dynamic brain network metrics were calculated with nodes in the network defined by Craddock's clustering 200 regions of interest (ROIs) (38). Static network metrics were computed using the Brain Connectivity Toolbox (BCT) (<http://www.brain-connectivity-toolbox.net/>) (39). The mean time series were extracted from each of the 200 ROIs and then a 200×200 symmetric matrix was created by calculating the Pearson correlation coefficient between each pair of ROIs. Since weak and spurious connections may obscure the topology of stronger meaningful connections, a proportional thresholding processing step is set up to remove spurious edges with lower connection strength from the connectivity matrix by convention (40,41). Multiple sparsity thresholds were set from 10% to 30% with an increment of 1%, to reduce the possibility that results would be biased by a single sparsity level (42,43). All metrics were calculated at all sparsity levels from derived binary networks, including four commonly used global network metrics: characteristic path length ( $L_p$ ), clustering coefficient ( $E_p$ ), global efficiency ( $E_{glob}$ ), and local efficiency ( $E_{loc}$ ); and a local network metric, nodal degree of each ROI (39).

Dynamic brain networks were constructed based on the same 200 ROIs and metric named flexibility (44–48) was computed at both global and local levels to quantify the temporal stability of the brain network. The computation was performed using an open-source MATLAB code package (<https://github.com/GenLouvain/GenLouvain>) (49) and strictly followed a previously published study (46). Briefly, the mean time series of 200 ROIs extracted earlier were firstly divided into a series of time windows with a window length of 40 seconds, which was suggested to be suitable for producing robust results and has been widely used in previous studies (45,46,50). Within each produced time window, a 200×200 connection matrix of the whole brain was calculated using the paired Pearson correlation. Then, the flexibility of constructed dynamic brain network was computed based on the temporal stability of its time-varying community structure, which included flexibility of the whole brain and nodal flexibility for each ROI (46,51). Since the computations of flexibility could produce slightly different results in each operation due to the algorithms, we set the number of operations to 100 and regarded the mean value

as a final result. The value range of flexibility is 0 to 1, and a higher value suggests a more unstable community structure of the dynamic brain network.

### Statistical analyses

All statistical analyses were performed using the SPSS (version 21) software. Paired *t*-tests were used to compare the differences in clinical characteristics and all brain network metrics of patients between two-time points (T0 and T1). For static network metrics, their values were averaged within the sparsity of 10–30% before being fed into the paired *t*-tests. Pearson correlation coefficients were used to further evaluate the correlations between

the changes in clinical symptom severity and changes in network metrics. Significances were set at *P* value less than 0.05, with no multiple comparison corrections performed considering the relatively small sample size.

## Results

### Demographic and clinical characteristics

As shown in *Table 1*, the final analyzed sample consisted of 6 female and 3 male patients, with an average age of  $33.78 \pm 11.01$  years. The mean time interval between T0 and T1 was  $46.11 \pm 49.60$  days, ranging from 14 to 165 days. As shown in *Table 2*, after ECT, the HAMD scores were significantly decreased compared with before the ECT ( $t = 7.517$ ,  $P < 0.001$ ; all subjects had at least a 50% reduction from the baseline HAMD scores), while no significant differences were found in the WAIS-I and WAIS-DS scores ( $t = -0.153$ ,  $P = 0.881$  and  $t = 1.879$ ,  $P = 0.097$ , respectively). Scores of BSIS-2-weeks were decreased significantly after treatment ( $t = 2.477$ ,  $P = 0.038$ ), while there were no significant changes in scores of BSIS-worst ( $t = -1.049$ ,  $P = 0.325$ ).

### Changes in static network metrics

At global level, the  $E_{loc}$  and  $E_p$  were significantly increased ( $t = -2.861$ ,  $P = 0.021$  and  $t = -2.450$ ,  $P = 0.039$ , respectively; shown in *Figure 1*) after the ECT, while the  $E_{glob}$  and  $L_p$  were not significantly changed ( $t = 2.211$ ,  $P = 0.058$  and  $t = -2.190$ ,  $P = 0.060$ , respectively; shown in *Figure 1*). At a local level, nodal degrees of several ROIs located in the cerebellum were found to be significantly changed after ECT; significantly decreased nodal degrees were also found in two separate regions of the temporal gyrus and olfactory cortex (see more details in *Table 3* and *Figure 2*).

**Table 1** Demography and clinical characteristics of the participants at baseline

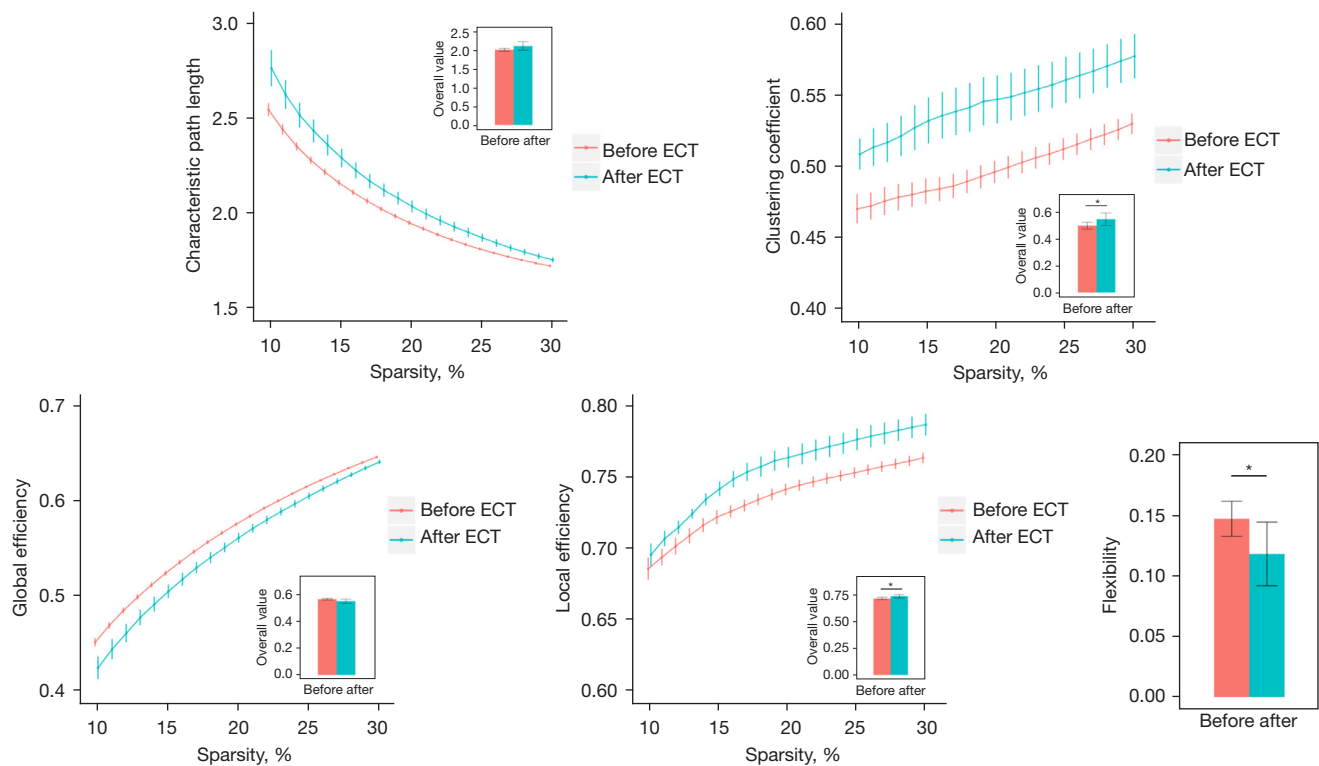
Demographics	Descriptive statistics
N	9
Age (mean $\pm$ SD)	$33.78 \pm 11.01$
Gender (male/female)	3/6
Handedness (right/left)	9/0
Months of illness duration (mean $\pm$ SD)	$64.67 \pm 46.38$
Years of education (mean $\pm$ SD)	$11.83 \pm 2.83$
Age of first onset (mean $\pm$ SD)	$29.50 \pm 11.20$
Medications	
Antidepressant	9/0
Antipsychotic	3/6
Benzodiazepine	4/5
Other	1/8

SD, standard deviation.

**Table 2** Comparisons on clinical characteristics before and after ECT

Measures	Before ECT (mean $\pm$ SD)	After ECT (mean $\pm$ SD)	Comparisons
HAMD scores	$21.33 \pm 4.53$	$7.67 \pm 6.18$	$t = 7.517$ , $P < 0.001$
WAIS-DS scores	$69.56 \pm 18.94$	$63.67 \pm 15.56$	$t = 1.879$ , $P = 0.097$
WAIS-I scores	$16.28 \pm 6.51$	$16.56 \pm 7.28$	$t = -0.153$ , $P = 0.881$
BSIS-2 weeks scores	$16.56 \pm 8.43$	$10.67 \pm 4.18$	$t = 2.477$ , $P = 0.038$
BSIS-worst scores	$18.67 \pm 9.73$	$22.11 \pm 8.07$	$t = -1.049$ , $P = 0.325$

ECT, electroconvulsive therapy; SD, standard deviation; HAMD, Hamilton Depression Scale; WAIS-DS, Digit Symbol subtest of Wechsler Adult Intelligence Scale; WAIS-I, Information subtest of Wechsler Adult Intelligence Scale; BSIS, Beck Suicidal Ideation Scale.



**Figure 1** Alterations in each brain network metric after ECT. \*, indicates a significant difference with  $P < 0.05$ . ECT, electroconvulsive therapy.

### Changes in dynamic network metrics

As shown in *Figure 1*, brain network flexibility at the global level was significantly decreased after ECT ( $t = 2.334$ ,  $P = 0.048$ ). At the local level, the flexibility of 19 ROIs was found to be significantly changed (mostly decreased) after ECT; these ROIs mainly involved the cerebellum and hippocampus areas, as well as frontal and temporal cortices (*Table 3* and *Figure 2*).

### Correlations with clinical improvements

No significant correlations were found between the changes in brain network metrics and changes in clinical characteristics (all  $P > 0.05$ ); nevertheless, the decreases in HAMD scores were associated with trends of changes in all network metrics after the ECT (*Figure 3*).

### Supplementary analysis

In order to exclude the influence of the selection of threshold (sparsity) range on the results, we further

compared the difference in all static network metrics before and after ECT in the threshold range from 10% to 40% and from 10% to 50%, respectively. The results showed that within each threshold range, both  $E_{loc}$  and  $E_p$  remained significantly increased (10% to 40%:  $t = -2.742$ ,  $P = 0.025$  and  $t = -2.453$ ,  $P = 0.040$  for  $E_{loc}$  and  $E_p$ , respectively; 10% to 50%:  $t = -2.659$ ,  $P = 0.029$  and  $t = -2.431$ ,  $P = 0.041$  for  $E_{loc}$  and  $E_p$ , respectively) after ECT, while  $E_{glob}$  and  $L_p$  remained not significantly different.

### Discussion

To the best of our knowledge, the current research is the first one to explore the mechanism of ECT in MDD by combining both static and dynamic brain network analyses. Overall, our research illustrated that ECT significantly alters both the static and dynamic properties of brain networks in MDD patients.

In respect of static brain network properties, our results suggested that at the global level, both the  $E_{loc}$  and  $E_p$  were significantly increased after ECT (*Figure 1*), which is highly consistent with the results in several previous studies

**Table 3** The ROIs with significant alteration in nodal degree and flexibility after ECT

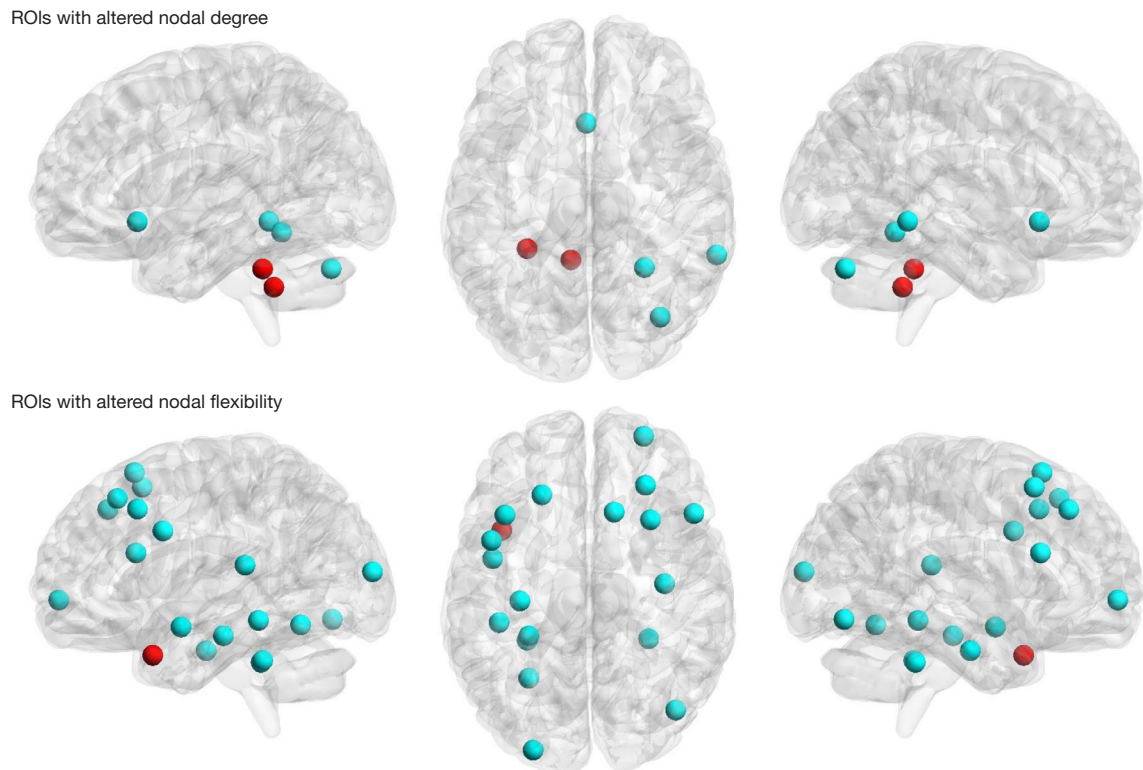
Center of mass (MNI coordinate, x; y; z)	ROI label	Before ECT	After ECT	<i>t</i>	P
<b>Nodal degree</b>					
62.9; -43.0; -7.8	Right middle, inferior temporal gyrus	0.00059	-0.15587	2.349	0.047
-7.3; -45.4; -39.5	Left cerebellum	-0.10308	0.00731	-3.747	0.006
-28.4; -40.0; -30.7	Left cerebellum	0.00313	0.02049	-2.521	0.036
35.7; -73.0; -30.6	Right cerebellum peduncle	-0.00548	-0.03143	4.748	0.001
0.1; 20.4; -8.0	Bilateral olfactory cortex	0.01789	-0.00023	2.854	0.021
28.1; -49.1; -13.0	Right fusiform gyrus	-0.01549	-0.02977	2.459	0.039
<b>Nodal flexibility</b>					
27.7; 58.2; -1.6	Right middle frontal gyrus	0.17040	0.10212	3.444	0.009
43.2; -73.6; -10.9	Right inferior occipital gyrus	0.14333	0.07050	3.326	0.012
-45.6; 8.0; 31.7	Left precentral gyrus	0.15020	0.09393	3.029	0.016
30.1; -39.3; -31.6	Right cerebellum	0.16646	0.09293	3.321	0.011
-39.1; 20.3; 42.2	Left middle frontal gyrus	0.11838	0.04889	3.666	0.006
-40.6; 12.9; -28.2	Left superior and middle temporal gyrus	0.13253	0.16030	-3.315	0.011
37.8; -12.8; -26.0	Right fusiform gyrus	0.16222	0.09980	2.677	0.028
-28.4; -40.0; -30.7	Left cerebellum	0.19717	0.13162	2.350	0.047
28.6; 34.6; 42.0	Right superior, middle frontal gyrus	0.13374	0.08061	2.451	0.040
-27.6; -38.0; -11.4	Left fusiform gyrus	0.16838	0.11929	3.392	0.009
31.0; 18.0; 52.7	Right superior, middle frontal gyrus	0.13455	0.07242	2.486	0.038
-45.0; -0.7; -14.6	Left middle, superior temporal gyrus	0.16495	0.09545	3.923	0.004
-25.5; -92.9; 12.0	Left middle occipital gyrus	0.16253	0.09071	2.547	0.034
-31.9; -21.1; -18.8	Left hippocampus	0.16283	0.09051	4.007	0.004
51.9; 21.0; 21.1	Right triangle inferior frontal gyrus	0.15838	0.08778	2.641	0.030
13.5; 21.7; 59.8	Right superior frontal gyrus	0.16455	0.08859	2.549	0.034
-27.6; -58.3; -13.6	Left fusiform gyrus	0.15455	0.09010	2.339	0.047
-21.3; 30.0; 47.3	Left superior, middle frontal gyrus	0.09980	0.04515	2.727	0.026
-41.9; -31.5; 15.2	Left superior temporal gyrus	0.15434	0.08535	2.326	0.048

ROIs, regions of interest; ECT, electroconvulsive therapy; MNI, Montreal Neurological Institute.

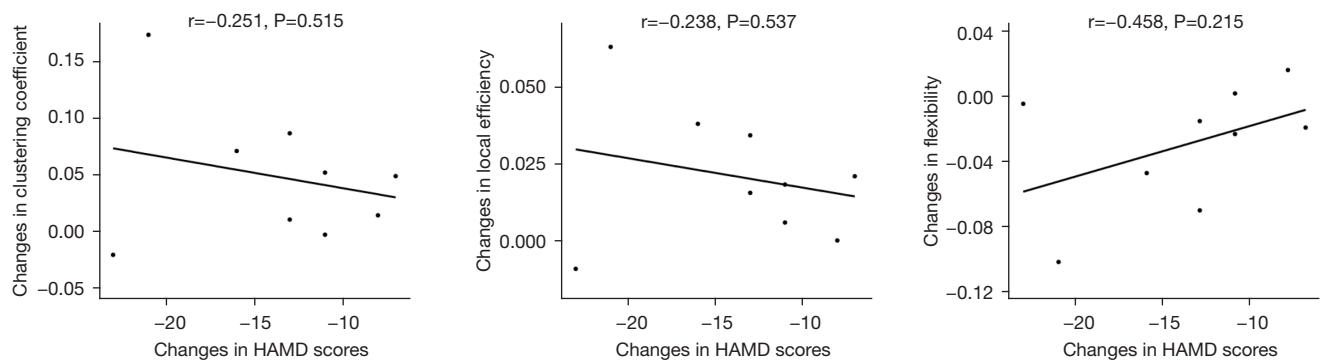
(52-54). For example, a recent study including 17 patients with depression has reported that the  $E_p$  of the brain network was significantly increased after ECT (53). Compared with healthy subjects, MDD patients are generally thought to have a shift toward randomization in their brain networks, reflecting a less optimal topological organization which may be due to overactivated connections in the network (55). The increases in  $E_{loc}$  and  $E_p$  reflect

that the brain network is more regularized with enhanced information transfer efficiency between nodes and less energy costs (56). Thus, it could be hypothesized that ECT may have effects to decrease the randomness of brain network as reflected by elevated levels of  $E_{loc}$  and  $E_p$ , which has been reported in a series of previous studies (52-54) and confirmed in the present study again.

Beyond static network properties, our study revealed



**Figure 2** The ROIs with altered nodal degree/nodal flexibility after ECT. Red: increased; blue: decreased. ROIs, regions of interest; ECT, electroconvulsive therapy.



**Figure 3** Associations between the decrease in HAMD scores and alterations in each brain network metric after ECT. HAMD, Hamilton Depression Scale; ECT, electroconvulsive therapy.

that an important dynamic brain network metric named flexibility was significantly decreased, which suggests a significantly decreased temporal variability (increased temporal stability) of brain network after the ECT in MDD patients (*Figure 1*). Previous hypotheses (21) suggest that an increase in brain network flexibility may imply excessive

brain activity, which may lead to a decrease in network remodeling and a further decrease in the ability to adapt to the environment (57). Such an increase in brain network flexibility has been reported in multiple psychiatric diseases such as schizophrenia (58) and autism (59). Although not fully consistent, a number of previous dynamic fMRI studies

have shown that the temporal variability of FC in the brain network is significantly increased in MDD patients compared to normal subjects, which is correlated with their clinical symptoms (26,60,61). Similar to what was found in static brain networks, such an alteration may also indicate a more randomized brain network organization attributed to increased aberrant brain connections (26). Therefore, ECT may make the brain network more regularized and stable over time, which may explain why ECT can alleviate the depressive symptoms in MDD patients in the context of a dynamic brain network for the first time.

At the local level, several ROIs with significant changes after ECT were found in both the static and dynamic networks, which mainly involve the cerebellum, hippocampus, frontal gyrus, and temporal gyrus (*Table 3* and *Figure 2*). These regions may thus play key roles in the effects of ECT on depressive symptoms in MDD. Previous studies have found that frontal and temporal cortices play important roles in the development of MDD (62); the disrupted functions of the cerebellum and hippocampus were also repeatedly reported in patients with MDD (55,63,64), which are consistent with our results. It is also noteworthy that in this study, more ROIs with significant local-level alterations were revealed by the dynamic brain network analysis method compared to static network metrics (*Table 3* and *Figure 2*); such results may partly support the opinion that the dynamic network model may provide a more sensitive tool for detecting the brain dysfunctions than conventional static network model (23,24).

In this study, we failed to find any significant correlation between the relief in clinical symptoms and changes in brain network metrics. Nevertheless, the decreases in HAMD scores were associated with trends of changes in all network metrics after the ECT (*Figure 3*). Future explorations with a larger sample and a higher statistical power may be needed to confirm such associations.

The current research mainly has the following limitations for future research reference. Firstly, as mentioned above, the sample size of this study is small. Further studies are needed to verify our results in a larger sample with higher statistical power and reliability. Secondly, we only analyzed changes in brain network connectivity before and after ECT and were unable to further analyze long-term dynamic changes after the acute treatment period (65). In addition, because few participants were discharged from the hospital after completing the ECT course, the interval of the second scan was delayed

for a part of the time, which may lead to unstable results. Future researches with a longer follow-up period, if undertaken, will provide more insight into the prognostic benefits of ECT for MDD. Thirdly, problems regarding the lack of control group (46,65), possible impacts of the heterogeneity of different subtypes of depression (such as patients with/without somatic or psychotic symptoms) (66), different ECT regimens (67) and varied time intervals between the two assessments have not been effectively addressed in this research, which may be investigated in future research. Lastly, while we focused on the flexibility in this study, there are some other dynamic brain network measures (68,69) which can be further investigated.

## Conclusions

Briefly, this study explores the neurobiological mechanism by which ECT may play its role in relieving depressive symptoms in MDD by investigating the changes in both static and dynamic brain network properties after ECT. We found that the clustering coefficient and local efficiency in static brain networks were increased, while the flexibility of the dynamic brain network was decreased after ECT. Several ROIs that changed significantly at the local level were also identified, which involved regions of the cerebellum, hippocampus as well as frontal and temporal cortices. Moreover, although not significant, the decrease of HAMD scores were associated with trends of changes in all network metrics after ECT. Our results suggest that ECT may alleviate the depressive symptoms of MDD by decreasing the randomness of brain network as reflected by changes in both static and dynamic network metrics, which might extend our knowledge of mechanisms underlying ECT for the clinical treatments of MDD. However, this study is limited by a relatively small sample size and the results should be confirmed in larger samples.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-2723>

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*Data Sharing Statement:* Available at <https://dx.doi.org/10.21037/apm-21-2723>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-2723>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Second Xiangya Hospital, Central South University (No. 2016S024) and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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