RESEARCH ARTICLE

Functional plasticity of the dorsomedial prefrontal cortex in depression reorganized by electroconvulsive therapy: Validation in two independent samples

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Abstract

Previous studies have implied a key role for the prefrontal cortex in the antidepressive effect of electroconvulsive therapy (ECT). However, there is still ubiquitous inconsistency across these studies, partly due to several confounding effects induced by the use of different samples. Studies with independent samples are necessary for validations to minimize confounding effects. In the current study, resting-state magnetic resonance imaging of 84 participants was collected using two scanners and two types of scanning parameters. One sample consisted of 28 patients and 23 healthy controls, and the other sample consisted of 33 patients. The local activity (indexed by the amplitude of low-frequency fluctuations) and functional connectivity were used to examine functional plasticity in the two independent samples before and after ECT. Both samples showed increased local activity of the dorsomedial prefrontal cortex (DMPFC) and enhanced connectivity of the DMPFC with the posterior cingulate cortex (PCC) following ECT. The enhanced connectivity between the DMPFC and PCC was positively associated with clinical improvement for both samples. These findings provide relatively strong evidence to support the functional plasticity of the dorsomedial prefrontal cortex and reorganization by ECT. The functional plasticity of the DMPFC-PCC may underlie the antidepressive effect of ECT.

KEYWORDS

depression, dorsomedial prefrontal cortex, electroconvulsive therapy, posterior cingulate cortex, resting-state functional magnetic resonance imaging

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1 | INTRODUCTION

Depressive disorder is one of the most common psychiatric disorders and a leading cause of significant disability (Ferrari et al., 2013).

Despite advances in pharmacological treatments, about a third of depressive patients still fail to respond to first-line therapies (Rush et al., 2006), which always take two or more weeks to exert antidepressive effects (Katz et al., 2004). Electroconvulsive therapy (ECT) is an alternative antidepressive treatment with a high response rate and rapid onset of beneficial effect in relation to depressive episodes (Husain et al., 2004; Kellner et al., 2012). Although the antidepressive efficacy of ECT is well documented, the precise mechanism of benefit is still unclear. A better understanding of the antidepressant effect of ECT may help obtain an index to optimize clinical treatment.

In simple terms, ECT is a treatment involving induction of seizures through electrodes placed at the surface of the skull. Prefrontal electrode placement is effective in ECT protocols used in clinical practice (Kellner, Tobias, & Wiegand, 2010), suggesting a crucial role of the prefrontal cortex in the antidepressive efficacy of ECT. Indeed, the prefrontal cortex has been regarded as having a key role in mood regulation more generally (Etkin, Buchel, & Gross, 2015). Local dysfunctions of the prefrontal cortex and disrupted prefrontal cooperation with other brain regions have consistently been demonstrated in depressive disorder (Rive et al., 2013; Sheline, Price, Yan, & Mintun, 2010). A substantial number of studies have reported normalized prefrontal local function and cooperation with other regions following successful antidepressive pharmacotherapy (Cheng et al., 2017; Li et al., 2016). Similarly, there are also multiple studies that have demonstrated the modulation of ECT on prefrontal abnormalities in depressed patients using multiple functional neuroimaging tools, including positron emission tomography (PET) (Suwa et al., 2012; Takano et al., 2007), magnetic resonance spectroscopy (Jorgensen et al., 2016; Merkl et al., 2011), and task-related functional magnetic resonance imaging (Beall et al., 2012).

Recently, another functional neuroimaging tool, resting-state functional MRI (RS-fMRI), has enabled the detection of spontaneous brain activity in healthy individuals (Ji, Liao, Chen, Zhang, & Wang, 2017; Ji, Yu, Liao, & Wang, 2017) and patients with neuropsychiatric diseases (Biswal, Yetkin, Haughton, & Hyde, 1995; Zhang & Raichle, 2010). Functional connectivity is one of the most popular approaches to assessing RS-fMRI, and it is capable of detecting the synchronization between regions. Studies assessing the functional connectivity of RS-fMRI have suggested that diverse regional cooperation dysfunctions exist in depression (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). Although infrequently used, the amplitude of low-frequency fluctuations (ALFF) is also used to identify the underlying neural substrates of depression. ALFF is calculated by the square root of the power spectrum (Zang et al., 2007) and has been shown to have a close association with other measures of tonic brain activation, such as PET (Tomasi, Wang, & Volkow, 2013). Consequently, ALFF is usually thought to reflect local spontaneous neural activity at rest (Zang et al., 2007). Abnormal ALFF in depression has been reported in several regions, including the prefrontal cortex and posterior default mode work (predominantly in the posterior cingulate cortex). In addition to being a localized summary measure, ALFF potentially impacts on functional connectivity (Cole, Yang, Murray, Repovs, & Anticevic, 2016). Regions with ALFF abnormality in depression also show dysfunctional inter-regional cooperation. For example, RS-fMRI findings have implicated decreased functional connectivity

between the posterior default mode network and the central executive network (predominantly in the dorsolateral/dorsomedial prefrontal cortex) (Mulders et al., 2015). As an important addition to this work, findings from our previous study suggest that ECT increases the connectivity between the default mode network and the central executive network (Wang et al., 2018). This has been validated by another study that revealed enhanced connectivity between the dorsolateral prefrontal cortex and posterior default mode network following ECT (Abbott et al., 2013).

Although studies demonstrate the reliability and reproducibility of RS-fMRI (Deuker et al., 2009; He et al., 2009), there is ubiquitous inconsistency across studies in depressive patients. For instance, Lui et al. suggest that depressed patients display decreased connectivity between prefrontal cortex and limbic areas (Lui et al., 2011). However, Ye et al. reported increased prefrontal-limbic connectivity in depressed individuals (Ye et al., 2012). These inconsistencies limit the interpretability of existing findings aiming to uncover the neural mechanisms behind depression and the efficacy of antidepressive treatments. These discrepancies may be attributed to several factors, including differences in the scanners used in each study, imaging parameters, sample heterogeneity, and methodological choices adopted in analyses. Therefore, studies with independent samples are necessary to provide stronger evidence and minimize confounding effects.

In the present study, we assessed alterations in brain activity following ECT in two independent samples. Based on the fact that the prefrontal cortex plays a key role in the development of depression and the antidepressive effect of ECT, we assumed that ECT has significant impact on the local activity (ALFF) of the prefrontal cortex. Considering the impact of ALFF alteration on functional connectivity, we further assumed that ECT may also change the connection of the prefrontal cortex with several regions, such as the posterior default mode work, as previous findings suggest. These functional alterations may be associated with the improvement of depressive symptoms.

2 | MATERIALS AND METHODS

2.1 | Participants

Sixty-one patients experiencing a current depressive episode from Anhui Mental Health Center (AMHC) were included in present study and divided into two samples. One sample (33 patients; 25 patients with unipolar depression and 8 with bipolar disorder) was scanned at Anhui Medical University (AHMU) from October 2012 to April 2017. The other sample (28 patients; 23 patients with unipolar depression and 5 with bipolar disorder) was scanned at University of Science and Technology of China (USTC) from February 2017 to May 2018. All patients were diagnosed with having a current depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients were excluded if they met any of the following exclusion criteria: (1) a history of ECT in the last 3 months; (2) age > 65 years; (3) diagnosed with substance misuse, schizoaffective disorder or schizophrenia; (4) past or current neurological illness; (5) head motion exceeding 2 mm in translation or 2° in rotation during

fMRI scanning; (6) other contraindications of MRI scan and ECT administration. We also recruited 23 healthy participants who met the same exclusion criteria as depressive patients except for the diagnosis of depressive disorder. Healthy controls were only scanned at USTC. All participants underwent scanning at two time points (TP): TP1, < 24 hr before the first ECT administration; TP2, after the last ECT administration (72 h apart). Depressive severity was evaluated with the 17-item Hamilton Rating Scale for Depression (HRSD) at both time points. Depressive patients in both samples received antidepressants during the ECT treatment. The categories of medicines used in our sample are presented in Table 1. The medication loads were evaluated with reference to previous research (Redlich et al., 2016) and used as covariate for further analysis. Treatment with benzodiazepines, valproate, and/or lithium was terminated during ECT administration. This study was approved by the Anhui Medical University Ethics Committee, and written informed consent was obtained from all patients.

2.2 | ECT procedure

ECT administrations for all patients were performed at AMHC with a modified bifrontal ECT protocol using a Thymatron System IV Integrated ECT System (Somatics, Lake Bluff, IL). It is usually administered 3 times a week. The initial percent energy was set according to the age-based method. The initial percent energy dial was set based on the age of each participant (e.g., 50% for a 50-year-old patient). The stimulation strength was evenly adjusted with an increment of 5% of the maximum charge (approximately 1,000 millicoulombs) in our treatment strategy. If no seizure activity was detected with the initial stimulation setting, the percent energy was increased until seizure was visually observed. During each ECT procedure, patients were anesthetized with propofol and paralyzed with succinylcholine. More details about the ECT procedure can be found in our previous study (Bai et al., 2017). The ECT procedures were same for two data sets in present study.

2.3 | MRI data acquisition

Structural and functional MRI for each participant was obtained using a 3-T scanner (Signa HDxt, GE Healthcare at AHMU and Discovery GE750w at USTC). During RS-fMRI scanning at both sites, participants were instructed to keep their eyes closed, but not to fall asleep and not specifically try to think of anything in particular. At AHMU, resting-state MRI scans composed of 240 echo-planar imaging volumes with the following parameters: TR = 2,000 ms; TE = 22.5 ms; flip angle = 30°; matrix size = 64 × 64, field of view = 220 × 220 mm; slice thickness = 4 mm; 33 continuous slices (one voxel = 3.4 × 3.4 × 4.6 mm). A T1-weighted anatomical image with 188 slices was also acquired for each patient to further elucidate and discard gross radiological alterations (TR = 8.676 ms; TE = 3.184 ms; inversion time = 800 ms; flip angle = 8°; field of view = 256 × 256 mm; slice thickness = 1 mm; voxel size = 1 × 1 × 1 mm). At USTC, functional images were acquired composed of 217 echo-planar imaging volumes with the following parameters: repetition time = 2,400 ms; echo time = 30 ms; flip angle = 90°; matrix size = 64 × 64, field of view = 192 × 192 mm²; slice thickness = 3 mm; 46 continuous slices

(one voxel = 3 × 3 × 3 mm³). High spatial resolution T1-weighted anatomical images with 188 slices were also acquired in sagittal orientation (TR = 8.16 ms; TE = 3.18 ms; flip angle = 12°; field of view = 256 × 256 mm²; slice thickness = 1 mm; voxel size = 1 × 1 × 1 mm³).

2.4 | MRI processing

RS-fMRI data were preprocessed with the Data Processing Assistant for Resting-State Functional MR Imaging toolkit (Chao-Gan & Yu-Feng, 2010), a software package based on Statistical Parametric Mapping software (www.fil.ion.ucl.ac.uk/spm) and Resting State Functional MR Imaging Toolkit (Song et al., 2011) (<http://www.restfmri.net>). For each participant, we applied the following processing steps: discarding the first 10 volumes to achieve a steady-state, slice timing correction, realignment, coregistering to respective structural images, nuisance regressors with 24 Friston motion parameters, white matter high signal, and cerebrospinal fluid signal as regressors, spatial normalization based on the unified segmentation of structural images, and spatial smoothing (Gaussian kernel = 4 × 4 × 4 mm). Subsequently, motion scrubbing was conducted to remove the time points with high motion (defined as frame-wise displacement >0.5), as well as one time point prior to, and two time points following, each of these high motion time points (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

After preprocessing, the filtered time series was converted to a frequency domain using a fast Fourier transform. The square root of the power for each frequency was calculated to obtain amplitude values. ALFF was calculated as the sum of the amplitude values in the 0.01 to 0.1 Hz low-frequency power range. To reduce the global effects of variability across participants, the ALFF was normalized by the mean within-brain ALFF value for each participant.

The functionally abnormal regions in local activity at both two samples (i.e., the dorsomedial prefrontal cortex, see the Results section) were selected as seed to calculate functional connectivity. For each individual, Pearson's correlation coefficients were computed between the mean time series of seed and time series of each voxel for the rest of the whole brain. To improve the normality, the correlation coefficients was converted to *z* values using Fisher's *r*-to-*z* transformation and the results were displayed as connectivity maps for each participant.

2.5 | Statistical analysis

For the functional images at both sites, we conducted a paired *t* test to detect the ECT effect on brain function (ALFF and functional connectivity) with Data Processing & Analysis for (Resting-State) Brain Imaging software. Age, sex, number of ECT sessions, medicine load, and whole brain volume effects were eliminated by being used as covariates in the analyses. All statistical maps were corrected with Gaussian Random Field method at threshold of voxel $p < .001$, cluster $p < .05$. For the data in USTC site, the mean value of significantly different regions was extracted to perform two-factor repeated-measure analysis of variance (ANOVA), group (depression and controls) repeated over time point (pre-ECT and post-ECT). For significant interaction effects, post hoc comparisons were conducted to detect group difference at TP1 (two-sample *t* test) and ECT effects for

TABLE 1 Demographic and clinical information

	Patients in USTC (mean $\pm$ SD)	Patients in AHMU (mean $\pm$ SD)	Controls in USTC (mean $\pm$ SD)
Sample size (n)	28	33	23
Age (years)	35.25 $\pm$ 11.48	35.97 $\pm$ 11.11	37.83 $\pm$ 11.34
Gender (female/male)	22/6	18/15	19/4
Diagnosis (unipolar/bipolar, n)	23/5	25/8	NA
Number of ECT sessions	8.71 $\pm$ 1.80	8.03 $\pm$ 1.91	NA
Interval of two scan (days)	21.36 $\pm$ 4.24	18.45 $\pm$ 4.87	20.09 $\pm$ 1.24
HRSD at TP1	21.54 $\pm$ 4.73	22.42 $\pm$ 4.12	1.78 $\pm$ 2.15
HRSD at TP2	8.36 $\pm$ 5.62	5.24 $\pm$ 5.09	1.35 $\pm$ 2.01
Medicine category			
SSRIs (patients number)	18	22	0
SNRIs	11	11	0
SARIs	2	2	0
NaSSAs	8	2	0
NDRIs	0	1	0
NRIs	0	1	0
TCA	1	0	0
Antipsychotics	13	17	0
Anticonvulsants ^a	3	9	0
Nonbenzodiazepine hypnotic	10	5	0
Anti-anxiety ^b	0	4	0

Abbreviations: USTC, University of Science and Technology of China; AHMU, Anhui Medical University; ECT, electroconvulsive therapy; HRSD, Hamilton rating scale of depression; TP1, time point 1; TP2, time point 2; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SARIs, serotonin antagonist/reuptake inhibitors; NaSSAs, norepinephrine and specificity serotonergic antidepressants; NDRIs, norepinephrine-dopamine reuptake inhibitors; NRIs, selective norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

^aAnticonvulsants mainly include benzodiazepines and valproate, used for insomnia or bipolar disorder and terminated during ECT administration.

^bThe anti-anxiety here includes buspirone and tandospirone.

depressive patients and time effect for healthy controls (paired *t* test). The significance level was defined as two-tailed $p < .05$ for an interaction effect and $p < .017$ (0.05/3) for post hoc analyses. Considering the evidence that bipolar and unipolar depression differ from one another, we conducted a supplementary analysis for unipolar depression with ROI-level paired *t* test for the site at AHMU ($n = 23$) and USTC ($n = 25$).

Further, exploratory Pearson correlation analyses were conducted between the change of brain function (ALFF, functional connectivity) and clinical response, represented by percentage of HRSD changes, that is, (HRSD at T2 – HRSD at T1)/HRSD at T1. In consideration of the strong impact of singular value on correlations analysis, we excluded the singular data defined as outside three standard deviations of the mean. Finally, one patient in AHMU was excluded when performing correlation analysis because of the singular data on HRSD. Besides, correlation analyses were conducted between the change of brain function and the number of ECT sessions. All significance levels were defined as two-tailed $p < .05$.

3 | RESULTS

3.1 | Demographic and clinical results

In the sample at USTC, no significant difference was observed between the depressive patients and healthy controls in age ($t = 0.80$,

$p = .43$), gender ($\chi^2 = 0.13$, $p = .72$) or interval between the two time points ($t = 1.51$, $p = .14$). There were also no significant differences in age ($t = 0.25$, $p = .81$), gender ($\chi^2 = 3.87$, $p = .049$), or ECT sessions ($t = 1.43$, $p = .16$) between patients at USTC and AHMU. Compared with the sample at USTC, there was a shorter interval between the two time points at AHMU ($t = 2.46$, $p = .02$). HRSD score significantly declined following ECT treatment in patients at both USTC ($t = 14.03$, $p < .001$) and AHMU ($t = 14.70$, $p < .001$). No significant change in HRSD score was found for healthy controls between the two time points ($t = 0.91$, $p = .37$; see Table 1). For head motion indexed by the frame-wise displacement (Jenkinson, Bannister, Brady, & Smith, 2002), there was no significant difference between the two time points for data sets acquired at AHMU ($t = -1.01$, $p = .32$) or USTC ($t = -1.65$, $p = .11$ for patients and $t = -1.47$, $p = .16$ for controls).

3.2 | ALFF contrasts

In the sample at USTC, ECT increased the ALFF in the DMPFC (see Figure 1a, Supporting Information Table S1). Patients at AHMU also presented with higher ALFF in the DMPFC at TP2 than TP1 (see Figure 1b). In addition, patients after ECT at AHMU also exhibited increased ALFF in the right inferior/middle temporal gyrus and left postcentral gyrus extending to the precuneus, as well as decreased ALFF in the right superior temporal gyrus/insula, middle/superior temporal gyrus, left cerebellum, precuneus/posterior cingulate gyrus,

FIGURE 1 Modulatory effect of ECT on ALFF value of two samples with Gaussian random field (GRF) correction (voxel $p < .001$, cluster $p < .05$). Both samples showed enhanced ALFF in DMPFC (red arrow). Bar charts in the right row show mean ALFF value in DMPFC. Bars show the mean; error bars show the SE. ECT, electroconvulsive therapy; ALFF, amplitude of low-frequency fluctuations; DMPFC, dorsomedial prefrontal cortex; USTC, University of Science and Technology of China; AHMU, Anhui Medical University; TP1, time point 1; TP2, time point 2. *** $p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Modulatory effect of ECT on RSFC value of DMPFC of two samples with Gaussian random field (GRF) correction (voxel $p < .001$, cluster $p < .05$). Both samples showed enhanced RSFC of DMPFC in PCC (red arrow). Bar charts in the right row show z value of RSFC between DMPFC and PCC. Bars show the mean; error bars show the SE. ECT, electroconvulsive therapy; RSFC, resting-state functional connectivity; DMPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; USTC, University of Science and Technology of China; AHMU, Anhui Medical University; TP1, time point 1; TP2, time point 2. *** $p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

calcarine, and dorsal anterior cingulate gyrus (see Supporting Information Table S2).

3.3 | Functional connectivity contrasts based on the seed of DMPFC

In the sample at USTC, ECT increased the functional connectivity of the DMPFC with posterior cingulate cortex (PCC), as well as right inferior parietal lobule (see Figure 2a and Supporting Information Table S1). Patients at AHMU also presented with increased DMPFC-PCC connectivity at TP2 compared with TP1 (see Figure 2b and Supporting Information Table S3). In addition, compared with TP1, patients at TP2 exhibited increased functional connectivity of the DMPFC with the bilateral orbitofrontal cortex, bilateral temporo-parietal junction, left inferior/middle temporal gyrus and adjacent DMPFC (see Supporting Information Table S3).

3.4 | ROI-based comparisons in the data set from USTC

The mean value of ALFF in the DMPFC and DMPFC-PCC RSFC was extracted to perform two-factor repeated-measure analysis of variance (ANOVA), by group (depression and controls) repeated over time point (pre-ECT and post-ECT). For ALFF in the DMPFC, there was a significant interaction effect between group and time point ($F = 28.51$, $p < .001$). Post hoc analysis showed significantly decreased ALFF of the DMPFC in depressed patients compared to controls at TP1 ($t = 4.05$, $p < .001$), but increased ALFF of the DMPFC in depressed patients at TP2 than TP1 ($t = 5.15$, $p < .001$). There was no significant difference for controls between the two time points ($t = 2.38$, $p = .027$) (see Supporting Information Figure S1, part A). For the DMPFC-PCC RSFC, there was significant interaction effect between group and time point ($F = 18.19$, $p < .001$). Post hoc analysis showed significantly decreased DMPFC-PCC RSFC in depressed patients compared to controls at TP1 ($t = 2.50$, $p = .016$), but increased DMPFC-PCC RSFC in depressed patients at TP2 compared to TP1 ($t = 4.98$, $p < .001$). There was no significant difference for controls between two time points ($t = 1.22$, $p = .23$) (see Supporting Information Figure S1, part B).

3.5 | ROI-based comparisons for unipolar depression in the two data sets

The mean ALFF in the DMPFC was increased following ECT for unipolar depression in the data sets from AHMU ($t = 4.55$, $p < .001$) and USTC ($t = 4.20$, $p < .001$) (see Supporting Information Figure S2). The mean DMPFC-PCC connectivity in unipolar depression was also increased following ECT for the data sets from AHMU ($t = 4.72$, $p < .001$) and USTC ($t = 4.00$, $p < .001$) (see Supporting Information Figure S3).

3.6 | Correlation analyses

The increased DMPFC-PCC functional connectivity was positively correlated with clinical response for both samples at USTC ($r = 0.384$, $p = .043$) and AHMU ($r = 0.456$, $p = .009$; see Figure 3). There was no significant relationship between ALFF change with clinical response for the sample at

FIGURE 3 The scatter plot and linear fit show the relationship between the improvement of depressive symptoms and differences in connectivity between DMPFC and PCC among all patients for both samples. The red point was regarded as singular data (defined as outside three standard deviations of the mean) and was not included correlation analysis. ECT, electroconvulsive therapy; RSFC, resting-state functional connectivity; DMPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; HDRS, Hamilton rating scale of depression, USTC, University of Science and Technology of China; AHMU, Anhui Medical University; TP1, time point 1; TP2, time point 2 [Color figure can be viewed at wileyonlinelibrary.com]

USTC ($r = 0.165$, $p = .403$) or AHMU ($r = 0.177$, $p = .325$). The correlation was not significant between the number of ECT sessions and the alterations of DMPFC ALFF ($r = -0.11$, $p = .58$ for the USTC site and $r = -0.05$, $p = .77$ for the AHMU site), or DMPFC-PCC RSFC ($r = -0.08$, $p = .70$ for the USTC site and $r = -0.17$, $p = .33$ for the AHMU site).

4 | DISCUSSION

Compared with previous studies, the main novelty of this study is the validation using two independent samples to investigate the regulating effect of ECT on brain function. As the prefrontal cortex plays a key role in depressive development and antidepressive effect of ECT, we hypothesized that functional plasticity of the prefrontal cortex induced by ECT is crucial for the improvement of depressive symptoms. Indeed, our results showed that ECT increased local activity in the DMPFC and increased connectivity between the DMPFC and PCC for both data sets. Furthermore, there was a positive correlation between increased DMPFC-PCC RSFC and improvement of depressive symptoms for both data sets.

The DMPFC is a region implicated in many cognitive and emotional processes. For example, during emotional attention processing, the DMPFC shows stronger activity when participants view positive compared with negative pictures (Berpohl et al., 2006). Furthermore, the DMPFC is crucial for the inhibition of negative affect (Phan et al., 2005). The DMPFC is also a key node of the central executive network (CEN), which is involved in several cognitive functions including attention, executive control, and working memory (Bressler & Menon, 2010). Many neuroimaging studies have implicated the dysfunctional of the CEN in depression. This dysfunction is associated with deficient cognitive control and difficulties with emotion recognition in depression (Stange et al., 2017). More importantly,

normalized function of the CEN by antidepressive treatment contributes to the remission of depressive symptoms (Yoshimura et al., 2014). Shiota et al. have demonstrated that depressed individuals display increased activation in the DMPFC during other perspective self-referential processing for positive words after cognitive-behavioral therapy (Shiota et al., 2017). Increased activation in the DMPFC is positively correlated with the improvement of depressive symptoms. Similar results have also been found following pharmacotherapy in a study using RS-fMRI (Abdallah et al., 2016). In line with previous findings, our results suggested lower low-frequency fluctuation of the DMPFC in depressive patients at baseline and increased low-frequency fluctuation in the DMPFC after ECT.

Our results also indicate a modulatory effect of ECT on DMPFC-PCC connectivity in depressive individuals. The PCC is the posterior part of the default mode network (DMN) (Whitfield-Gabrieli & Ford, 2012), a network associated with processes frequently employed during rest such as rumination, which is associated with depression (Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner, Andrews-Hanna, & Schacter, 2008). Although most reports suggest DMN hyperconnectivity in depression (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Li et al., 2013), more than a few studies have also shown declined intranetwork and internetwork connectivity of the DMN in depressive individuals, especially in the posterior DMN (Li et al., 2016; Zhu et al., 2012). Recent studies have revealed that the connectivity between the CEN and the posterior DMN is decreased in depressive patients and participants at risk of depression (Manoliu et al., 2013; Rzepa & McCabe, 2016). Aberrant CEN-DMN connectivity is thought to be correlated with maladaptive rumination in depression (Hamilton et al., 2011; Manoliu et al., 2013). Indeed, the PCC has been implicated in self-referential processing, which underlies maladaptive rumination in depression (Nejad, Fossati, & Lemogne, 2013). Previous research has confirmed that abnormal

DMPFC-PCC connectivity in depressive individuals is associated with disturbed self-referential processing (Davey, Breakspear, Pujol, & Harrison, 2017). In line with previous results, our results revealed low levels of DMPFC-PCC connectivity in depressive patients at baseline. More significantly, our current study also shows increased DMPFC-PCC connectivity in depressive patients following ECT administration, and a significant association between increased DMPFC-PCC connectivity and improvement of depressive symptoms. Similarly, increased DMPFC-PCC connectivity following ECT has been demonstrated in a study using the method of independent component analysis (Abbott et al., 2013).

It must be noted that there is a discrepancy between our current results and previous findings. Sheline et al. report increased functional connectivity of the DMPFC for three networks: the cognitive control network, DMN, and affective network (Sheline et al., 2010). The discrepancy may be attributed to several factors, including sample heterogeneity, analytical strategy and scanning parameters. Furthermore, the DMPFC in Sheline et al.'s study was positioned more rostrally than ours. Subregions of the DMPFC serve distinct facets of advanced human cognition (Eickhoff, Laird, Fox, Bzdok, & Hensel, 2016). Hence, subregional heterogeneity of the DMPFC may be another potential factor contributing to the discrepancy in findings.

Several limitations of our study are worthy of discussion. First, in addition to similar regions observed between two data sets, there are many disparate regions showing significant effects of ECT at AHMU compared with USTC. Sample size and sample heterogeneity are potential factors in explaining this inconsistency. On the other hand, these disparate regions may be susceptible to confounding factors and not a dependable substrate underlying the antidepressive effect of ECT. Given this realization, we did not explore the relationship between clinical improvement and function alteration of the disparate regions. Second, like most studies on ECT, we did not use a placebo-controlled design for ethical reasons. However, after controlling for medicines, our study still identified local activity and connectional changes in depression. Furthermore, the connectional changes were associated with improvement of depressive symptoms. These observations may ameliorate this concern. Third, the sample size of both data sets was relatively small. However, both data sets included unipolar and bipolar depression patients, which have been suggested to differ from one another. In consideration of this limitation, we performed supplementary analysis for unipolar depression at the ROI-level but not the voxel level. Further research with larger samples of unipolar depression patients is needed to confirm our current findings. Finally, all patients included in the present study were administrated with drugs in addition to ECT, although medicine load was used as a covariate during statistical analysis, we still cannot eliminate the effects of drugs on our findings.

5 | CONCLUSIONS

In conclusion, we used two independent samples to explore the modulation of ECT on brain function. Our results revealed that ECT increased the ALFF of the DMPFC, and DMPFC-PCC functional connectivity for both samples. The increased DMPFC-PCC connectivity was correlated with clinical response for both samples. These results provide relatively strong evidence suggesting that DMPFC-PCC cooperation may be a potential substrate for ECT in performing an

antidepressive effect. In addition to elucidating the mechanisms underlying ECT, these findings may also help to improve antidepressive treatment strategies, such as repetitive transcranial magnetic stimulation targeted at modulating DMPFC-PCC cooperation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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