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Antidepressant Effects of Electroconvulsive Therapy Correlate With Subgenual Anterior Cingulate Activity and Connectivity in Depression

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Abstract: The mechanisms underlying the effects of electroconvulsive therapy (ECT) in major depressive disorder (MDD) are not fully understood. Resting-state functional magnetic resonance imaging (rs-fMRI) is a new tool to study the effects of brain stimulation interventions, particularly ECT. The authors aim to investigate the mechanisms of ECT in MDD by rs-fMRI.

They used rs-fMRI to measure functional changes in the brain of first-episode, treatment-naive MDD patients (n = 23) immediately before and then following 8 ECT sessions (brief-pulse square-wave apparatus, bitemporal). They also computed voxel-wise amplitude of low-frequency fluctuation (ALFF) as a measure of regional brain activity and selected the left subgenual anterior cingulate cortex (sgACC) to evaluate functional connectivity between the sgACC and other brain regions.

Increased regional brain activity measured by ALFF mainly in the left sgACC following ECT. Functional connectivity of the left sgACC increased in the ipsilateral parahippocampal gyrus, pregenual ACC, contralateral middle temporal pole, and orbitofrontal cortex. Importantly, reduction in depressive symptoms were negatively correlated with increased ALFF in the left sgACC and left hippocampus, and with distant functional connectivity between the left sgACC and contralateral middle temporal pole. That is, across subjects, as depression improved, regional brain activity in sgACC and its functional connectivity increased in the brain.

Eight ECT sessions in MDD patients modulated activity in the sgACC and its networks. The antidepressant effects of ECT were negatively correlated with sgACC brain activity and connectivity. These findings suggest that sgACC-associated prefrontal-limbic structures are associated with the therapeutic effects of ECT in MDD.

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Abbreviations: ALF = Famplitude of low-frequency fluctuation, ECT = electroconvulsive therapy, HAMD = Hamilton Rating Scale for Depression, MDD = major depressive disorder, pgACCpregenual = anterior cingulate cortex, ROIs = region of interests, rs-fMRI = resting-state fMRI, sgACC = subgenual anterior cingulate cortex.

INTRODUCTION

Major depressive disorder (MDD) is a public health burden characterized by recurrent episodes of depression.[1] Various pharmacological and psychotherapeutic treatments are available for MDD. Electroconvulsive therapy (ECT), as a brain stimulation therapy, such as transcranial magnetic stimulation and vagus nerve stimulation, however, is considered the most effective and fastest-acting remission for depressive episodes.[2,3] The clinical treatment and efficacy of ECT in MDD has been well documented. The mechanistic bases for the observed effect are unclear, but could provide valuable insight into the neuropathology of depression,[4] which is now increasingly conceptualized as involving regional brain activity dysfunction and altered connectivity of neural circuits.[5,6]

Changes in local brain perfusion and metabolism in MDD suggest that ECT might alleviate depression via resetting regional brain activity. More precisely, an increase in cerebral blood flow in subcortical regions accompanied by a decrease in cortical midline structures is associated with response to ECT.[7–9] These findings, however, are variable,[10] in part because of the variability of protocols and limited accuracy in characterizing the dynamic changes in cerebral blood flow with positron emission tomography or single photon emission computed tomography.[11–13] The use of advanced resting-state functional magnetic resonance imaging (rs-fMRI) has enabled the examination of spontaneous brain activity with a high degree of reliability[14] in clinical MDD studies,[15–18] whereas the amplitude of low-frequency fluctuations (ALFF) is increasingly being used as biologically meaningful index of neural activity.[19] Characterizing changes in spontaneous neural activity following ECT by rs-fMRI could provide insight into whether ECT in fact resets this activity to alleviate depression.[10]

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It is hypothesized that electric current delivered by ECT can stimulate the formation of neural connections in distant brain areas, a process known as neuroplasticity.[20,21] One study used rs-fMRI and found that the greatest reduction of whole brain connectivity in depressed patients is in the left dorsal lateral prefrontal cortex, which is associated with a therapeutic course of ECT.[22] In contrast, different studies used a seed-based resting-state functional connectivity analysis and found increased anterior cingulate cortex and hippocampal functional connectivity following ECT.[23,24] In all, ECT has been found to normalize resting-state functional network connectivity and interhemispheric connectivity.[25,26] No prior study, however, has examined both regional activity changes in the brain and altered functional connectivity of those regions following ECT.

Previous neurophysiological data from depressed patients identified the subgenual anterior cingulate cortex (sgACC) as an area showing the greatest difference in activity with respect to nondepressed control subjects.[27] This brain region is involved in appraisal and expression as well as the regulation of negative emotions.[1,28] Activity in the sgACC may be modulated by serotonergic neurotransmission,[10] antidepressant drugs,[29] and deep-brain stimulation,[30] and is heightened in response to affective stimuli in depressed individuals although levels returned to baseline after ECT treatment.[23]

We hypothesized that the resetting of regional activity and neuroplasticity of distant connectivity in the sgACC underline the effects of ECT in MDD.[23,24] To eliminate the influence of other factors, we evaluated changes in spontaneous whole brain activity and functional connectivity in first-episode, treatment-naïve MDD patients before and after an 8 session course of ECT treatment. To determine whether ECT-induced resetting occurred, we identified regions in which spontaneous, resting-state brain activity was altered. To evaluate whether neuroplasticity is involved in ECT-induced changes in regional brain activity, we assessed changes in distant functional connectivity. Given that the sgACC is critically involved in MDD, it was used as a seed for this analysis. We also assessed the relationship between changes of regional brain activity, distant functional connectivity, and depression severity with respect to ECT. A unique aspect of this study is that we measured both regional brain activity and functional connectivity, which may be a more possible explanation for mechanisms of ECT in MDD than using either one alone.

MATERIALS AND METHODS

Participants

The study protocol was reviewed and approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Electroconvulsive therapy is not always considered as the first treatment for MDD, but the clinical guidelines of the Canadian Network for Mood and Anxiety Treatments recommend that it be considered as such for depression with acute suicidal ideation.[31] Our patients reported acute suicidal ideation in the two weeks before the study. The diagnosis of MDD was confirmed with a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-I/P, Chinese version) [32] and scores $\geq$21 on the 24-item Hamilton Rating Scale for Depression (HAMD).[33] Patients were excluded if they had a history of alcohol or drug abuse, neurologic or other serious diseases, morphologic anomalies in the brain, or had any electronic or metal implants that could interfere with the fMRI scan. Major depressive disorder patients were scanned before 1 day of starting the ECT sessions. All the patients were scanned for the second time at least >24 hours (mean $\pm$ SD: 25.02 ± 0.76 hours) after 8 ECT sessions. We did not control the medicine of subjects during this study, which was decided by their clinician independently. After the first ECT, most patients were given antidepressants over the course of ECT (Table 1). The doses of antidepressants [selective serotonin reuptake inhibitors: mean doses = 31.43 mg/d, serotonin–norepinephrine reuptake inhibitor: mean doses = 112.5 mg/d, and noradrenergic and specific serotonergic antidepressants: mean doses = 36.00 mg/d] were chosen individually by their clinician.

Electroconvulsive Therapy Procedure

Patients underwent modified bitemporal ECT conducted using a brief pulse (pulse width = 0.5 ms)/constant current Thymatron DGx apparatus (Somatics LLC, Lake Bluff, IL) at the Mental Health Center of the First Affiliated Hospital of Chongqing Medical University. The first 3 ECT sessions occurred on consecutive days, and the remaining sessions were conducted every other day with a break during weekends until the patient had undergone at least eight sessions.[8] Electroconvulsive therapy was continued if clinical symptoms of depression had not sufficiently improved after the 8 sessions, as determined by a clinician, for a maximum of 12 ECT sessions. Anesthesia was induced with propofol (1.5–2 mg/kg) and succinylcholine (0.5–1 mg/kg). The initial dose was selected based on patients' sex, age, and weight. Age is the most important factor, and initial percent of energy setting was one-fourth age (100% = 504 mc). We adjusted the percent of energy setting to be an integral multiple of 5 if necessary, based on patients' sex and weight.[34] Seizure threshold was measured at the first ECT session, which was defined as the smallest electrical dose of producing a seizure of at least 25 seconds on the electroencephalogram.[35] If initial dosage failed to elicit a seizure, we used age-adjusted titration to increase 5% output charge of ECT device every time and restimulated the patient after 30 seconds. The total times of stimulating were at most 3 during 1 session, and firstly, we should make sure the levels of muscle relaxation and sedation were still appropriate. If the measurements of seizure threshold still failed, then in the second session, we started stimulating with double the last dose in the first session. To become therapeutic and reduce side effects, the electrical dosage was set at 1.5–2 times seizure threshold in consecutive ECT sessions according to the extent of seizure.[31]

Clinical Assessment

Patients were assessed for depressive symptoms with the 24-item HAMD at 2 time points: within 1 day before the first ECT session (pre-ECT) and the day after completion of 8 ECT sessions (post-ECT).

Image Acquisition

Data were acquired on a 3.0 Tesla MRI system (GE Signa) at the First Affiliated Hospital of Chongqing Medical University. Subjects were instructed to relax with their eyes closed and without moving their heads during the MRI scan while remaining awake (subjects were later asked whether they had fallen asleep). Images were acquired using an echo planar imaging sequence (repetition time: 2000 millisecond; echo time: 30 millisecond; flip angle: 90°; field of view:

TABLE 1. Demographic and Clinical Characteristics of Patients

Demographics	**MDD (n = 23)**		
Age (years)	30.57 ± 9.43		
Sex (Male/Female)	9/14		
Education (years)	11.35 ± 2.92		
Clinical characteristics	MDD (n = 22)		
Age of onset (years)*	26.64 ± 10.87		
Suicidal thought or behavior (%)*	68.18		
Duration of depressive episode (months)*	2.98 ± 6.40		
	Pre-ECT	Post-ECT	*P* Value
HAMD	28.45 ± 4.93	8.23 ± 4.55	<0.0001*
Numbers of patients with antidepressants (%)	21 (95.45%)	21 (95.45%)	
Numbers of Types of Antidepressants			
One type	15 (68.18%)	18 (81.82%)	
Two types	6 (27.27%)	3 (13.64%)	
Antipsychotics	3 (13.64%)	2 (9.09%)	
Types of Antidepressants			
SSRIs	15 (68.18%)	15 (68.18%)	
SNRI	4 (18.18%)	4 (18.18%)	
NaSSA	8 (36.36%)	5 (22.73%)	

ECT = electroconvulsive therapy; HAMD = Hamilton Rating Scale for Depression; MDD = major depressive disorder; NaSSA = Noradrenergic and specific serotonergic antidepressants; SNRI = Serotonin–norepinephrine reuptake inhibitor; SSRIs = Selective serotonin reuptake inhibitors.
The values are illustrated as mean ± SD.
* Paired *t* test.

$240 \times 240\,mm^2$; matrix: 64×64; slice thickness: 5 mm; and 33 axial slices); 200 volumes were collected for a total scan time of 400 seconds. Subsequently, 3D T1-weighted anatomic images were acquired (repetition time: 8.35 millisecond; echo time: 3.27 millisecond; flip angle: 12°; field of view: $240 \times 240\,mm^2$; matrix: 256×256; slice thickness: 1 mm; and 156 sagittal slices).

Image Preprocessing

Images were preprocessed using DPARSF v2.3 software (www.restfmri.net).[36] The first 5 functional images were excluded, and subsequent images were corrected for slice-timing and alignment. Individual 3D T1-weighted anatomic images were coregistered to functional images. The 3D T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid and normalized to Montreal Neurologic Institute space. These transformation parameters were then applied to the functional images. Normalized data were resliced at a resolution of $3 \times 3 \times 3\,mm^3$ and spatially smoothed with a 6-mm full width at half-maximum Gaussian kernel. Several sources of spurious variance (24 head motion parameters and averaged signals from cerebrospinal fluid and white matter, and the global brain signal) were eliminated by multiple linear regression.[37,38] Functional images with linear trends were removed by temporal band-pass filtering (0.01–0.08 Hz).

Amplitude of Low-Frequency Fluctuation Analysis

To determine the spontaneous brain activity pattern of each subject, we computed the ALFF value for each voxel as the average square root of the power spectrum.[19] This value voxel was then normalized to the global mean ALFF value.

Functional Connectivity

We selected a brain region as a seed based on the key role of sgACC in MDD mentioned before, which was exactly one of regions with significant ALFF differences in group comparisons. Thus, the sgACC was defined as a seed (3-mm radius sphere centered at the coordinates of the peak T statistic from group comparisons of ALFF). Resting-state functional connectivity was investigated using a temporal correlation approach,[37] which was carried out between the seed and remaining voxels in the brain. The resulting *r* values were converted using Fisher *r*-to-z transformation to make the distribution more Gaussian.

Statistical Analysis

To determine group-level spontaneous brain activity and functional connectivity patterns, we used Resting-State fMRI Data Analysis Toolkit (REST) v1.8 software (www.restfmri.net)[39] to perform the following analyses: 1-sample *t* test was used specially for functional connectivity via within-group comparisons (within the gray matter mask) for pre- and post-ECT; for longitudinal ALFF between groups comparison, paired *t* test was used between post- and pre-ECT group. The significance threshold was set at $P < 0.05$ (AlphaSim-corrected; combined height threshold $P < 0.01$ and minimum cluster size = 35) (http://afni.nimh.gov/pub/dist/doc/manual/AlphaSim.pdf); whereas for longitudinal comparisons of sgACC functional connectivity, paired *t* test was performed within a mask that was created by combining the regions in both pre- and post-ECT from the 1-sample *t* test results. The significance threshold was set at $P < 0.05$ (AlphaSim-corrected; combined height threshold $P < 0.01$ and minimum cluster size = 24). Correlation analysis were performed to calculate the associations between changes (post- minus pre-ECT) of regional brain activity (or functional connectivity), and

depressive symptoms (post- minus pre-ECT HAMD scores) (n = 22). To this end, we calculated Pearson correlation coefficients between neuroimaging index of region of interests and depressive symptoms improvement across subject. The region of interests was defined as 3-mm radius sphere centered at the peak coordinates of altered regional brain activity (or functional connectivity) from results of the longitudinal comparisons (paired *t* test). As these analyses were exploratory, we used an uncorrected statistical significance level of $P < 0.05$.

RESULTS

Patient Characteristics

There were no subjects who were excluded because of head motion exceeding 3 mm in translation or 3° in rotation during scanning. The mean frame-wise displacement, computed by averaging the frame-wise displacement at each time point for each subject, was the same before and after ECT ($P = 0.7998$). First-episode, medication and physical treatment-naive MDD patients [n = 23; 14 women, all right-handed, age (mean ± SD): 30.57 ± 9.43 years] were recruited from the Inpatient Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University. One patient's clinical data were missed. Among the rest 22 subjects, there was only 1 patient without any medication, the others (n = 21) took at least 1 antidepressant (Table 1).

The mean 24-item HAMD score before ECT was 28.45 ± '4.93, indicating severe depression. After the ECT series, depressive symptoms were significantly improved ($t_{21} = 12.61$, $P < 0.0001$; paired *t* test) (Table 1). Of the 22 patients for whom clinical data were available, 20 (90.91%) were ECT responders whose depressive symptoms were reduced by at least 50% relative to pre-ECT score[40] 11 patients (50%) were in remission—that is, their HAMD scores were ≤7—after the ECT series.

Electroconvulsive Therapy Effects on Regional Brain Activity

On visual inspection, ALFF pattern showed that the default mode network regions had higher ALFF values than other brain regions in both the pre-ECT and pre-ECT groups (Fig. 1A). A comparison of post- and pre-ECT regional brain activity measured by ALFF revealed a significant increase following ECT in the left sgACC, left hippocampus (HIP), bilateral orbitofrontal cortex (OFC), right pregenual (pg)ACC, and right pre-central gyrus. Meanwhile, a significant decrease in ALFF was detected in the middle posterior dorsal (pd)ACC (paired *t* test, $P < 0.05$ AlphaSim corrected; combined height threshold $P < 0.01$ and minimum cluster size = 35 voxels) (Fig. 1B and Table 2). Quantification of each brain region altered ALFF were labeled in Figure 1D.

Electroconvulsive Therapy Effects on Functional Connectivity

Using the sgACC as a seed to calculate functional connectivity with all other voxels in the brain for each subject, sgACC functional connectivity patterns were determined before and after ECT, separately (1-sample *t* test) ($P < 0.05$ AlphaSim-corrected; combined height threshold $P < 0.01$ and minimum cluster size = 24 voxels) (Fig. 2A). The longitudinal comparisons revealed that functional connectivity between left sgACC and ipsilateral parahippocampal gyrus, pgACC, and contralateral middle temporal pole (MTP), OFC increased after ECT (paired *t* test, $P < 0.05$ AlphaSim-corrected; combined height threshold $P < 0.01$ and minimum cluster size = 24 voxels; Figure 2B and Table 3). Quantification of each brain region altered sgACC functional connectivity were labeled in Figure 2D.

Brain Activity and Connectivity and Depression Symptoms

The reduction of HAMD was negatively correlated with the increased regional brain activity in the left sgACC ($r = -0.53$, $P = 0.01$) and left HIP ($r = -0.45$, $P = 0.03$; Fig. 1C). Increased functional connectivity between the sgACC and MTP was also negatively correlated with decreased HAMD following ECT ($r = -0.48$, $P = 0.03$; Fig. 2C). That is, across subjects, the more depressive symptoms improved, the more the regional brain activity and functional connectivity in sgACC increased. There were no significant correlations in the other brain regions.

DISCUSSION

We tested the hypothesis that ECT in MDD patients resets regional brain activity and induces neuroplasticity of functional connectivity. We found that: a series of 8 ECT sessions increased regional brain activity (ie, ALFF) in the sgACC; ECT increased functional connectivity between the sgACC and the MTP, HIP, and OFC; and changes in depression symptoms were negatively correlated with increased ALFF in the left sgACC and left HIP, and with distant functional connectivity between the sgACC and contralateral MTP.

Most previous studies have been confounded by differences in time points examined by fMRI and the heterogeneity of the patient pool, some of which had been treated with several types of medication during a long period before ECT and had recurrent depression (see Table 4 for summary), making it difficult to draw accurate conclusions about the effects of ECT alone on brain function.

We used longitudinal treatment (8 ECT sessions) and multiple observational benchmarks to evaluate first-episode, medication, and physical treatment-naive MDD patients. Given that ECT is not always the first treatment choice for depression, previous studies have mostly included treatment-resistant patients who received medication and/or physical treatment for a long period of time before undergoing ECT.[7,9] This likely affected patients' brain states and biased the ECT results. To maintain objectivity in our assessment of the effects of ECT, we recruited treatment-naive subjects. After ECT was initiated, because of ethical considerations we, however, no longer had control over whether or not patients took medication; indeed, most received antidepressants during the course of the study (see Table 1 for more details). Electroconvulsive therapy has more immediate and potent effects than medication during the first 2–3 weeks after the initiation of treatment.[3] In contrast, the therapeutic effects of antidepressants have a delayed onset, which is a major limitation of these drugs. There is no single drug that has been shown to reduce symptoms of depression more quickly than others.[42] Although it cannot be conclusively stated that the changes in cerebral function in our patients resulted exclusively from ECT, we believe that the drugs was not largely responsible.

Most task-based fMRI studies of MDD involve a complex experimental setup.[11,43] In contrast, rs-fMRI facilitates the examination of spontaneous neural activity in the absence of a task or stimulus.[44] Previous rs-fMRI-based cross-sectio nal studies examining regional[16,45] or distant connectivity[17]

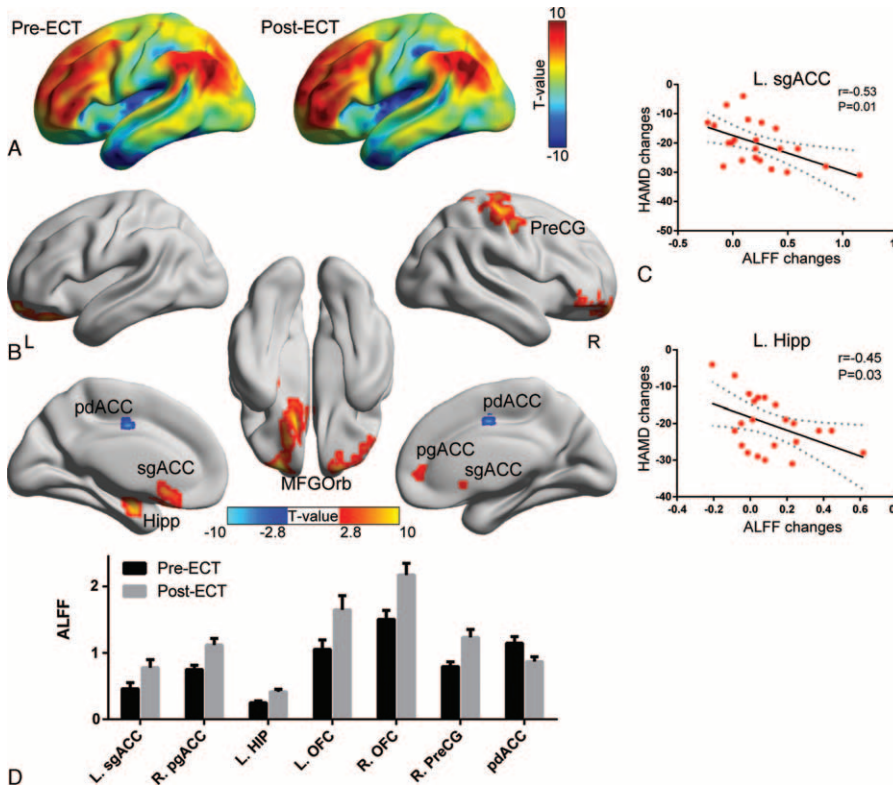

FIGURE 1. Within- and between group comparisons of spontaneous brain activity. A, ALFF maps of pre- and post-electroconvulsive therapy groups were obtained using the uncorrected 1-sample t test. B, A second-level random effects analysis (post- versus pre-electroconvulsive therapy, paired *t* test) revealed significant differences between cortical and subcortical regions, which are shown as inflated surface maps created using BrainNet Viewer (www.nitrc.org/projects/bnv).[41] C, Region of interest-wise clinical analysis results show a significant negative correlation between altered Hamilton Rating Scale for Depression and amplitude of low frequency fluctuation values in the left subgenual anterior cingulate cortex and left hippocampus. Solid and broken lines represent the best-fit line and 95% confidence interval of Pearson correlation, respectively. D, Quantification of data extracted from the coordinates of the peak t statistic from each of the areas labeled in panels (B). For coordinates and statistics, see Table 2. Error bars = SEM.

features have suggested that in depression, regional brain activity as well as connectivity in various neural circuits are altered[15,18] More specifically, the prefrontal-limbic circuit—including the frontal lobe, cingulate cortex, and parahippocampal gyrus—show aberrant brain activity and connectivity, implying that indications between these regions are involved in the maintenance of adaptation to depression.[1]

Regional brain activity in limbic neural circuits was increased following ECT. It was previously found that serotonin receptor 1A binding was increased in MDD patients receiving

TABLE 2. Brain Regions Showing Changed Amplitude of Low Frequency Fluctuation Between The Post- and Pre-ECT

Brian Region	BA	MNI Coordinates (*x*, *y*, *z*) (mm)	Voxels	T Value
Post-ECT > Pre-ECT				
L. hippocampus	20	(−30, −6, −18)	38	4.32
L. subgenual anterior cingulate cortex	25	(−9, 24, −15)	137	4.60
L. middle orbitofrontal cortex	11	(−21, 57, −15)	43	5.28
R. inferior orbitofrontal cortex	10/11	(48, 39, −15)	221	4.88
R. pregenual anterior cingulate cortex	10/32	(15, 42, 3)	42	5.19
R. precentral gyrus	3/4	(45, −12, 48)	161	5.12
Post-ECT < Pre-ECT				
L. posterior dorsal anterior cingulate cortex	20	(−3, −9, 45)	43	−4.54

ALFF = amplitude of low-frequency fluctuation; BA = Brodmann area; ECT = electroconvulsive therapy; L = left hemisphere; MNI = Montreal Neurologic Institute; R = right hemisphere.
x, *y*, *z*, coordinates of primary peak locations in the MNI space.

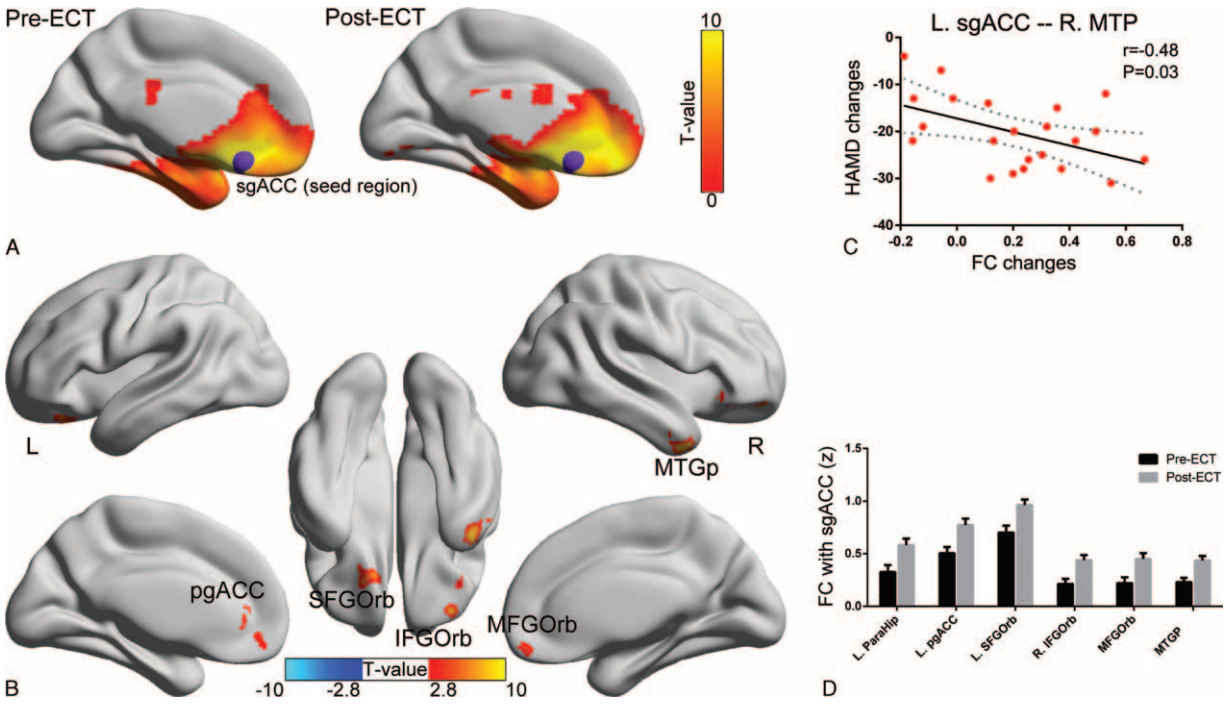

FIGURE 2. Within- and between group comparisons of left sgACC functional connectivity. A, Functional connectivity patterns of the left sgACC (violet sphere) in pre- and post-electroconvulsive therapy groups were determined with the uncorrected 1-sample *t* test ($P < 0.05$). B, A second-level random effects analysis (post- versus pre-electroconvulsive therapy, paired *t* test) revealed significant differences ($P < 0.05$, AlphaSim-corrected; combined height threshold $P < 0.01$ and minimum cluster size = 24 voxels) that are presented as inflated surface maps created using BrainNet Viewer (www.nitrc.org/projects/bnv).[41] C, Altered functional connectivity between the left sgACC and right middle temporal pole was negatively correlated with Hamilton Rating Scale for Depression changes. Solid and broken lines represent the best-fit line and 95% confidence interval of Pearson correlation, respectively. D, Quantification of data extracted from the coordinates of the peak t statistic from each of the areas labeled in panels (B). For coordinates and statistics, see Table 3. Error bars = SEM, sgACC = subgenual anterior cingulate cortex.

ECT, suggesting that this treatment has the same mode of action as selective serotonin reuptake inhibitors.[10] Major depressive disorder patients show reduced spontaneous brain activity in the (para)limbic circuits,[46,47] consistent with the deficits in prefrontal-limbic emotional processing observed in MDD.[48] The normalization of spontaneous brain activity and concomitant alleviation of depressive symptoms following ECT suggest that ECT resets regional brain activity to protect against depression.[10]

The sgACC showed increased ALFF following ECT. It was previously demonstrated that gray matter volume in the ACC was abnormally reduced in MDD, and a reduction in sgACC-resting cerebral blood flow and metabolism has been detected in MDD patients by positron emission tomography studies.[27,49,50] Others, however, have reported increased metabolic activity in the sgACC in primary[30,51] or secondary depression.[52] This has not been consistently observed in rs-fMRI[18,45,46,53] or task-related fMRI.[44] Moreover, increased regional brain activity in the ventral ACC has been reported in patients with MDD.[54–56] A major drawback of previous studies is that they did not identify the precise location within the ACC that shows functional abnormalities. We found that

TABLE 3. Brain Regions Showing Functional Connectivity Differences Between the Post- and Pre-ECT

Brian Region	BA	MNI Coordinates (*x*, *y*, *z*) (mm)	Voxels	T Value
Post-ECT > Pre-ECT				
R. middle temporal gyrus, pole	21	(45, 9, −36)	105	5.36
R. middle orbitofrontal cortex	11	(33, 51, −15)	24	4.87
R. inferior orbitofrontal cortex	11/47	(36, 30, −9)	50	3.68
L. superior orbitofrontal cortex	11	(−12, 30, −21)	48	4.54
L. parahippocampal gyrus	28	(−21, 6, −24)	25	4.11
L. pregenual anterior cingulate cortex	11/32	(−9, 39, 3)	84	3.92

BA = Brodmann area; ECT = electroconvulsive therapy; L = left hemisphere; MNI = Montreal Neurologic Institute; R = right hemisphere. *x*, *y*, *z*, coordinates of primary peak locations in the MNI space.

TABLE 4. Resting-State Functional Magnetic Resonance Imaging Studies Assessing Changes in Brain Function Induced by Electroconvulsive Therapy Treatment in Major Depressive Disorder

Author, Year	No. Patients (Depression Subtype)	Medication	ECT: No. Sessions, Type of Stimulation	Primary Analysis Method
Perrin et al, 2012[22]	9 (MDD, treatment resistant)	Partially	Mean: 8; bitemporal	FCS + seed-FC (left DLPFC)
Beall et al, 2012[23]	6 (MDD, treatment resistant)	Yes	Mean ± SD: 9 ± 4; Bitemporal	ROI to ROI FC
Abbott et al, 2013[26]	12 (MDD, treatment resistant	Yes	mean ± SD: 11 ± 3; unilateral/bitemporal	FNC
Abbott et al, 2014[24]	19 (MDD, treatment resistant)	Yes	Mean ± SD: 11 ± 3; unilateral/bitemporal	Seed-FC (left and right hippocampus)
Wei et al, 2014[25]	11 (MDD, treatment resistant)	Partially	Mean ± SD: 7 ± 2; bifrontal	VMHC
Our study	23 (MDD, treatment-naïve)	Partially	8 (fixed)	ALFF + seed-FC (sgACC)

ALFF = amplitude of low-frequency fluctuation; DLPFC = dorsolateral prefrontal cortex; ECT = electroconvulsive therapy; FC = functional connectivity; FCS = functional connectivity strength; FNC = functional network connectivity; L = left hemisphere; MDD = major depressive disorder; R = right hemisphere; ROI = region of interest; sgACC = subgenual anterior cingulate cortex; VMHC = voxel-mirrored homotopic connectivity.

regional activity was increased in the ventro-rostral ACC (sgACC and pgACC) and decreased in the pdACC. The ACC includes several subregions that overlap anatomically but differ in terms of function.[28] In mood disorders, sgACC activity is often associated with the severity of depressive symptoms,[57] whereas pgACC activity is linked to treatment outcome.[58] Dorsal regions of the pgACC, however, respond to diverse types of emotional or autonomic stimuli[59] These findings can partly explain the diverse functional changes observed in the ACC in MDD patients, and suggest that the ACC plays a significant role in the autonomic regulation of emotion.

The regional function of the ACC may be highly variable in MDD, which is regarded as a heterogeneous disease. The sgACC hyperactivation has been observed in treatment-resistant patients and is associated with negative emotional states.[60] Amplitude of low-frequency fluctuation of the ACC may be higher or lower in MDD patients than in healthy controls, and results for treatment-resistant versus treatment-responsive patients have been inconsistent.[55] Future studies should examine MDD subtypes in a large population to clarify functional changes in each region of the ACC.

Our study showed that the sgACC is functionally connected to the entorhinal cortex, temporal lobe, medial prefrontal cortex, and other limbic structures, consistent with previously reported resting-state functional connectivity patterns in MDD.[61,62] These regions constitute the so-called affective network responsible for emotional processing, which is altered in MDD,[63,64] that is, functional connectivity is decreased in the sgACC-based neural network-mediating emotion processing.[64] There, however, have been no studies describing changes in sgACC-based connectivity pattern with respect to the effects of ECT on MDD. A prior rs-fMRI study suggested that transcranial magnetic stimulation normalized depression-related subgenual hyperconnectivity in the default mode network (eg, pgACC) for alleviating depression.[65] We observed increased functional connectivity between sgACC and pgACC following ECT. This opposite finding would rely on the difference of seed location and different ways of brain stimulation. Here, the sgACC-based neural network and an association between sgACC–MTP connectivity and a reduction in depressive symptoms after ECT likely acts via modulation of neural plasticity.[20]

Based on regional activity and distant connectivity, the sgACC, pgACC, HIP/PGH, and OFC comprise a core prefrontal-limbic structure. We propose an integrated model in which ECT induces resetting of and neuroplasticity within this structure in MDD.[21] These novel findings increase our understanding of the mechanisms underlying the therapeutic effects of ECT and reveal a core circuit for future clinical intervention.

This study had several methodological limitations. First, patients were scanned twice (before and after ECT) within a predefined time window, but a higher number of scans (between ECT sessions) could potentially reveal more detailed changes in each patient.[66] In addition, simultaneous antidepressant will synergize ECT treatment, which may have impacted both the regional cerebral blood flow[7] and remote functional connectivity [24] results. Third, although ECT is highly efficient for treating depression, ECT-associated cognitive side effects have not been considered here, but they should be evaluated in future studies.[67] Finally, based on spontaneous brain activity, we chose sgACC as a seed for functional connectivity analysis rather than performing a whole-brain analysis. Connectome-based neuroimaging studies will provide new ways of conceptualizing the mechanisms of ECT in MDD.[17]

Concomitant changes in regional brain activity and distant functional connectivity reflect an integration of the resetting and neuroplastic effects of ECT that alleviate depressive episodes. The current work is the first report of ECT, inducing an increase in local activity and connectivity in sgACC-related core limbic structures in the context of a clinical response (ie, a decrease in depressive symptoms). Our findings provide evidence that sgACC-associated prefrontal-limbic structures play a key role in the biologic mechanisms underlying the therapeutic effects of ECT in MDD.

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