Archival Report

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Modulation of Intrinsic Brain Activity by Electroconvulsive Therapy in Major Depression

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ABSTRACT

BACKGROUND: One of the most effective interventions for intractable major depressive episodes is electroconvulsive therapy (ECT). Because ECT is also relatively fast acting, longitudinal study of its neurobiological effects offers critical insight into the mechanisms underlying depression and antidepressant response. Here, we assessed modulation of intrinsic brain activity in corticolimbic networks associated with ECT and clinical response.

METHODS: We measured resting-state functional connectivity (RSFC) in patients with treatment-resistant depression ($n = 30$) using functional magnetic resonance imaging acquired before and after completing a treatment series with right unilateral ECT. Using independent component analysis, we assessed changes in RSFC with 1) symptom improvement and 2) ECT, regardless of treatment outcome in patients, with reference to healthy control subjects ($n = 32$, also scanned twice).

RESULTS: After ECT, consistent changes in RSFC within targeted depression-relevant functional networks were observed in the dorsal anterior cingulate cortex (ACC), mediodorsal thalamus (mdTh), hippocampus, and right anterior temporal, medial parietal, and posterior cingulate cortices in all patients. In a separate analysis, changes in depressive symptoms were associated with RSFC changes in the dorsal ACC, mdTh, putamen, medial prefrontal cortex, and lateral parietal cortex. RSFC of these regions did not change in healthy control subjects.

CONCLUSIONS: Neuroplasticity underlying clinical change was in part separable from changes associated with the effects of ECT observed in all patients. However, both ECT and clinical change were associated with RSFC modulation in dorsal ACC, mdTh, and hippocampus, which may indicate that these regions underlie the mechanisms of clinical outcome in ECT and may be effective targets for future neurostimulation therapies.

Keywords: Anterior cingulate, Connectivity, Depression, ECT, fMRI, Thalamus

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Current theories describe major depression as a brain network disorder, manifesting as hyperactivity in ventral limbic structures together with dysregulation by hypoactive dorsal anterior cingulate cortex (ACC), lateral prefrontal cortex (PFC), and/or related structures (1–4). However, the interrelationships among these structures as related to treatment and clinical response to treatment have yet to be empirically determined. Electroconvulsive therapy (ECT) is an effective intervention for patients with major depressive episodes (MDEs) and occurs by eliciting controlled transient seizures every 2 to 3 days over 2 to 4 weeks, sometimes followed by maintenance sessions (5). Because both response rates (50% to 80%) and response times (≤1 month) are better for ECT than for other currently available treatments (6–8), longitudinal neuroimaging research of ECT-induced treatment response offers a pivotal opportunity to improve our understanding of the role of corticolimbic networks in depression and antidepressant response to treatment.

Previous studies have demonstrated that ECT elicits changes in specific brain regions as impacted by electrode placement (9,10). Some of the brain structures affected by ECT, including the ACC (11–13) and hippocampus (14,15), are also frequently implicated in the pathophysiology of major depression by other studies. However, not all patients respond to ECT; for example, just over half (55% to 65%) experience remission when using right-unilateral ECT with optimal parameters (16,17). Therefore, brain networks affected by ECT-induced seizures in all patients may differ or only partially overlap with networks supporting improved depressive symptoms in patients that respond to ECT. To date, very few neuroimaging studies address the contributions of ECT-induced seizures and symptom improvement to structural or functional neuroplasticity, relying instead on post hoc analyses of symptoms in regions already showing ECT effects (11,18) or restricting analyses to treatment responders (12,19,20). Therefore, some ECT-related effects reported previously may not underlie clinical outcome but instead reflect nonspecific physiological effects of ECT unrelated to depressive symptoms. ECT research is further complicated by the challenges in recruiting a sufficiently large and homogeneous study sample, as ECT is typically reserved for more severe or treatment-resistant depression and may be avoided due to its potential cognitive side effects and lingering stigma. Thus, neuroimaging research has yet to form a coherent understanding of the neurobiology of ECT.

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In the current study, we used functional magnetic resonance imaging to examine changes in resting state functional connectivity (RSFC) associated both with ECT itself (ΔECT) and with changes in depressive symptoms during ECT (ΔMD). We measured RSFC during functional magnetic resonance imaging scans in patients before right-unilateral ECT and after 2 to 4 weeks of index treatments and in healthy volunteers assessed 2 to 4 weeks apart to quantify normative values and variance. We used independent component analysis to define resting-state networks (RSNs), which comprise brain regions that share temporally coherent (i.e., correlated) intrinsic brain activity while participants are at rest. In particular, we targeted well-characterized RSNs (21–24) overlapping medial frontolimbic and temporal regions previously implicated in depression and ECT response, specifically medial prefrontal cortex (mPFC), ACC, and associated fronto-thalamo-striatal networks and hippocampus. However, because we hypothesized that ΔECT and ΔMD effects would be unlikely to be captured by a single RSN, we measured RSFC changes both 1) within each RSN and 2) overlapping across RSNs in partial conjunction analyses.

METHODS AND MATERIALS

Participants

Thirty patients (16 female patients, age mean/SD = 40.90/12.45 years) and 32 demographically similar healthy control subjects (16 female subjects, age mean/SD = 39.66/12.54 years) gave informed consent to participate in this study, which was approved by the University of California Los Angeles Institutional Review Board. All patients were characterized as treatment refractory and were experiencing a DSM-IV-TR defined MDE; 24 were diagnosed with major depressive disorder and 6 were diagnosed with bipolar disorder, compatible with recent support for reframing mental disorders in terms of shared symptomatology and neurobiology rather than binary diagnoses (25). Depressive symptoms were assessed in patients using the Hamilton Depression Rating Scale (HAMD) and duration of illness measured from first MDE was variable. Additional participant information is given in Table 1, and inclusion/exclusion criteria and additional clinical information are provided in Supplement 1.

Electroconvulsive Therapy and Research Sessions

Patients volunteered for this research study before initiating a clinically prescribed course of ECT at the University of California Los Angeles Resnick Neuropsychiatric Hospital. Right-unilateral ECT was administered using standard protocols (Supplementary Methods in Supplement 1) after patients were tapered off all psychotropic medications for a minimum of 48 to 72 hours and for the duration of the 2- to 4-week index series. Research sessions included inventories to assess depressive symptoms and magnetic resonance imaging scanning 1) at baseline before starting ECT (MD1), 2) before the third treatment (MD2), and 3) after 2 to 4 weeks of treatment (MD3) when clinical decisions indicated transition to a maintenance therapy. Control subjects were also scanned twice, approximately 2 to 4 weeks apart (CO1 and CO3). Research sessions occurred in the morning before patients' ECT sessions; therefore, any changes in functional connectivity measured could be considered lasting or cumulative effects of prior treatments.

Image Acquisition and Preprocessing

Using a 3T MAGNETOM Allegra MRI scanner (Siemens, Erlangen, Germany), functional images were acquired: repetition time = 2.0 seconds, echo time = 30 milliseconds, flip angle = 70°, 34 axial slices, 3.4 × 3.4 × 5 mm^3 resolution, 180 volumes. A high-resolution T1-weighted anatomic scan (magnetization prepared rapid acquisition gradient-echo) was also collected at each session. Preprocessing and normalization procedures are described in detail in the Supplementary Methods in Supplement 1.

Statistical Analyses

Independent component analyses were executed in FSL (FMRIB, Oxford, UK) (Supplementary Methods in Supplement 1) and established cross-subject RSNs. Eight canonical RSNs that 1) cover medial corticolimbic areas previously implicated in depression and emotional processing and 2) have been reliably demonstrated in healthy control subjects in previous research (21–24) were targeted as networks of interest. Two approaches were taken for group-level statistics: one model measured changes in RSFC resulting from ECT (ΔECT), and the other measured changes in RSFC associated with changes in depressive symptoms (ΔMD).

ΔECT Analysis. We constructed linear mixed-effects models implemented in R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria), with subject as a random factor and the hypothesized ΔECT effect as a fixed factor, that modeled a change in patients and no change in control subjects (i.e., MD1 ≠ MD3 = CO1 = CO3 or MD3 ≠ MD1 = CO1 = CO3).

Table 1. Participant Characteristics

					HAMD Scores		
	Sex	Age	Age at 1st MDE	Total ECT Sessions	1	2	3
MDE Patients (n = 30)	14 male,16 female	40.9 (12.5)	24.5 (12.5)	9.4 (3.3)	26.3 (5.8)	20.4 (6.4)	9.3 (5.5)
Healthy Control Subjects (n = 32)	16 male,16 female	39.7 (12.6)	na	na	na	na	na
t or X^2 (p Value)[a]	.0 (1.0)	.39 (.70)	na	na	na	5.6 (<.0001)	10.7 (<.0001)

ECT, electroconvulsive therapy; HAMD, Hamilton Depression Rating Scale; MDE, major depressive episode; na, not applicable.
[a]Chi-squared (χ^2) test was applied to sex data, unpaired t test compared age data, and paired t tests compared changes in HAMD score from baseline with ECT.