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Modulation of Limbic and Prefrontal Connectivity by Electroconvulsive Therapy in Treatment-resistant Depression: A Preliminary Study

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ABSTRACT

Background: Although current models of depression suggest that a sequential modulation of limbic and prefrontal connectivity is needed for illness recovery, neuroimaging studies of electroconvulsive therapy (ECT) have focused on assessing functional connectivity (FC) before and after an ECT course, without characterizing functional changes occurring at early treatment phases.
Objective: To assess sequential changes in limbic and prefrontal FC during the course of ECT and their impact on clinical response.
Methods: Longitudinal intralimbic and limbic–prefrontal networks connectivity study. We assessed 15 patients with treatment-resistant depression at four different time-points throughout the entire course of an ECT protocol and 10 healthy participants at two functional neuroimaging examinations. Furthermore, a path analysis to test direct and indirect predictive effects of limbic and prefrontal FC changes on clinical response measured with the Hamilton Rating Scale for Depression was also performed.
Results: An early significant intralimbic FC decrease significantly predicted a later increase in limbic–prefrontal FC, which in turn significantly predicted clinical improvement at the end of an ECT course.
Conclusions: Our data support that treatment response involves sequential changes in FC within regions of the intralimbic and limbic–prefrontal networks. This approach may help in identifying potential early biomarkers of treatment response.

Introduction

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders and a leading cause of disability worldwide [1]. Despite advances in the understanding of its pathophysiology, pharmacological treatments are only partially effective. Indeed, an estimated 30% of patients with MDD continue to suffer from refractory symptoms leading to marked functional impairment [2]. Electroconvulsive therapy (ECT) is a well-established alternative for patients with treatment-resistant depression [3]. Although different meta-analyses of randomized controlled trials have consistently confirmed the antidepressant effectiveness of ECT for treatment-resistant depression [4–6], its specific mechanism of action still remains unclear.

Previous research has consistently reported that dysregulation of the limbic and prefrontal connectivity is crucial in the development of the depressive phenotype, and the restoration of the neurophysiological limbic and prefrontal balance leads to illness

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recovery [7–10]. Functional connectivity (FC), as assessed with Functional Magnetic Resonance Imaging (fMRI), can suitably assess changes in the coordinated pattern of activity of limbic and prefrontal regions. Nevertheless, the modulatory effect of ECT on brain FC has only been studied in a few previous reports. These studies have revealed that the modulation of FC patterns of different regions within the prefrontal cortex (PFC), such as the dorso-lateral prefrontal cortex (DLPFC), is crucial in order to achieve therapeutic response with ECT [11–13]. However, it is worth noting that symptom recovery with other treatments involves not only prefrontal regions, but also limbic regions such as the amygdala and the subgenual anterior cingulate cortex (SgACC) [14,15].

In this context, it has been suggested that activity within the limbic and prefrontal networks may progressively change during symptom recovery. Specifically, while early effects of antidepressant treatment are observed at the limbic level, secondary or late treatment effects are observed in the PFC [7,16]. Nevertheless, neuroimaging studies of ECT have exclusively assessed brain function before and after treatment [11–13], but have not aimed to characterize functional changes occurring at early treatment phases. The measurement of such early-effects may have significant clinical utility as an outcome predictor [17], and may help to unveil the mechanism of action of current antidepressant treatments, including ECT.

The results of these previous studies led us to hypothesize that a complex interaction between early intralimbic and late limbic–prefrontal ECT-induced FC changes will impact on clinical improvement of patients with MDD. Therefore, in order to better characterize how changes in limbic and prefrontal connectivity underpin ECT efficacy, here we assessed a group of treatment-resistant depression patients at four different time-points throughout the entire course of an ECT protocol (i.e., pre-treatment, after one ECT session, after nine ECT sessions, and 15 days after ECT completion). The specific aims of the study were: (1) to assess changes in intralimbic (i.e., amygdala–SgACC) and limbic–prefrontal FC (i.e., amygdala–DLPFC) throughout the course of ECT, and (2) to test a model of sequential change in limbic and prefrontal FC across ECT sessions and their impact on clinical response by means of path analysis.

Materials and methods

Participants

Fifteen inpatients with severe treatment-resistant MDD were recruited from the Mood Disorders Inpatient Unit of Bellvitge University Hospital, Barcelona. Psychiatric diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version [18], following Diagnostic and Statistical Manual of Mental Disorders [19] criteria. Diagnostic assessments and clinical outcome measurements were obtained by a senior psychiatrist with extensive experience in mood disorders and the use of these metrics. All patients underwent a clinical assessment prior to ECT, including physical examination, routine blood sampling, EKG and chest x-ray. The concurrent pharmacological regimen of patients with MDD is described in Table S1.

The comparison sample included 10 healthy participants of comparable age, gender and years of education in relation to patients with MDD. In order to rule out the possibility of current or lifetime psychiatric disorders and the use of psychotropic medication, subjects from the comparison group were underwent a medical anamnesis and the Structured Clinical Interview for DSM-IV Axis I Disorders non-patient version [20].

For both groups, exclusion criteria included: (1) the presence or past history of severe medical, neurological or psychiatric disorders (other than MDD in patients), (2) anxiety comorbidity was not considered an exclusion criterion provided that MDD was the main diagnosis and the primary reason for seeking assistance, (3) contraindication to functional Magnetic Resonance Imaging (fMRI) scanning or abnormal MRI upon visual inspection and (4) a history of ECT during the previous 12 months.

After receiving the approval from the ethical committee of clinical research (CEIC) of Bellvitge University Hospital all participants gave written informed consent to participate in this study, which was performed in accordance with the Declaration of Helsinki.

Electroconvulsive therapy

ECT was administered using a Thymatron System IV device (Somatics, LLC). Anesthesia was induced with intravenous thiopental (2–2.5 mg/kg) and succinylcholine (0.5 mg/kg) was used for paralysis. Patients were preoxygenated and then manually ventilated during the duration of anesthesia. All patients were treated with bifrontotemporal ECT. Initial electrical dose was determined by the *half-age method* [21] and subsequent dosing was determined according to seizure adequacy.

Study protocol

The protocol was designed to characterize longitudinal ECT-induced changes in limbic and prefrontal functional connectivity at different time-points, thus covering the entire course of treatment. Patients with MDD were scanned four times: 24–48 hours before the first ECT session (fMRI1 – baseline), 24–48 hours after the first ECT session (fMRI2 – early ECT effects), 24–48 hours after the ninth ECT session (fMRI3 – intermediate ECT effects), and 2 weeks after the completion of ECT course (fMRI4 – long-lasting ECT effects). Comparison participants were scanned two times, five weeks apart. Moreover, all patients underwent a weekly clinical assessment using the Hamilton Rating Scale for Depression (HRSD) [22].

Image acquisition and preprocessing

Resting-state images were acquired with a 3-T scanner (Phillips Achieva, Best, The Netherlands), equipped with an 8-channel SENSE head coil and a single-shot echoplanar imaging (EPI) software. Imaging parameters were as follows: repetition time = 2000 ms; echo time = 35 ms; pulse angle = 90°; field of view 230 × 230 mm; matrix size = 96 × 96 pixels; in-plane resolution = 1.8 × 1.8 mm^2; slice thickness = 4 mm; interslice gap = 1 mm. Twenty-two interleaved slices parallel to the anterior–posterior commissure line were acquired in descending direction to cover the whole brain. For each subject, a single 6-minute continuous functional sequence was acquired, generating 180 whole-brain EPI volumes. The first four (additional) images in each run were discarded to allow the magnetization to reach equilibrium. We also acquired a high-resolution T 1-weighted anatomical image for each subject with 160 slices (repetition time = 8.2 ms; echo time = 3.8 ms; flip angle = 8°; field of view 240 × 240 pixels; in-plane resolution = 0.94 × 0.94 mm^2; slice thickness = 1 mm) to discard gross radiological alterations.

Imaging data were processed on a Microsoft Windows platform using technical computing software (MATLAB 7.8; The MathWorksInc, Natick, Mass) and Statistical Parametric Mapping (SPM8; The Welcome Department of Imaging Neuroscience, London, UK). After an initial pre-alignment step to the first image of the time-series, motion correction was performed by aligning (within subject) each time-series to the mean image using a least-squares minimization and a 6-parameter (rigid body) spatial transformation. These realigned functional sequences were then coregistered and normalized to the standard Montreal Neurological Institute (MNI)