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Research paper

Alterations in patients with major depressive disorder before and after electroconvulsive therapy measured by fractional amplitude of low-frequency fluctuations (fALFF)

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is an important treatment option for patients with major depressive disorder (MDD). However, the mechanisms of ECT in MDD are still unclear.
Methods: Twenty-four patients with severe MDD and 14 healthy controls were enrolled in this study. Eight ECT sessions were conducted for MDD patients using brief-pulse square-wave signal at bitemporal locations. To investigate the regional cerebral blood flow in MDD patients before and after ECT treatments by resting-state functional magnetic resonance imaging (rs-fMRI), the patients were scanned twice (before the first ECT and after the eighth ECT) for data acquisition. Afterward, we adopted fractional amplitude of low-frequency fluctuations (fALFF) to assess the alterations of regional brain activity.
Results: Compared with healthy controls, the fALFF in the cerebellum lobe, parahippocampal gyrus, fusiform gyrus, anterior cingulate gyrus, and thalamus in MDD patients before ECT (pre-ECT) was significantly increased. In another comparison, the fALFF in the cerebellum anterior lobe, fusiform gyrus, insula, parahippocampal gyrus, middle frontal gyrus, and inferior frontal gyrus in pre-ECT patients was significantly greater than the post-ECT fALFF.
Limitations: Only two rs-fMRI scans were conducted at predefined times: before the first and after the eighth ECT treatment. More scans during the ECT sessions would yield more information. In addition, the sample size in this study was limited. The number of control subjects was relatively small. A larger number of subjects would produce more robust findings.
Conclusions: The fALFF of both healthy controls and post-ECT patients in cerebellum anterior lobe, fusiform gyrus, and parahippocampal gyrus is significantly lower than the fALFF of pre-ECT patients. This finding demonstrates that ECT treatment is effective on these brain areas in MDD patients.

1. Introduction

Major depressive disorder (MDD) is an increasingly common mental disease and is of great concern. To some extent, several common treatments such as cognitive behavioral therapy (Ritchey et al., 2011; Siegle et al., 2006) and antidepressant medication (Sheline et al., 2012) are effective for depressive patients. However, electroconvulsive therapy (ECT) is regarded as the most effective and rapid treatment for depression (Bouckaert et al., 2016; Husain et al., 2004; Kellner et al., 2016a,b), and it is a vital antidepressant treatment selection for most patients with MDD. For patients with severe mental illness, ECT is considered to be psychiatry's "good standard" treatment. Despite its effective outcome, the mechanisms of ECT on MDD are still unclear. It is important to understand the intrinsic mechanisms that may allow further improvements of ECT and reduce its side effects, such as nausea, headache, jaw pain, and muscle ache (Wei et al., 2014).

Previous studies on antidepressant treatment response have reported the effect of gray matter volumes and cortical thickness related

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to improvements in MDD patients (Ota et al., 2015; Sheline et al., 2012). For ECT treatment, certain changes were reported in the structure of brain gray matter in MDD patients. Bouckaert et al. (2016) drew the conclusion that ECT can significantly increase the volume of gray matter. Pirnia et al. (2016) showed that several brain regions, including the bilateral anterior cingulate cortex (ACC); inferior and superior temporal, parahippocampal, entorhinal, and fusiform cortex; and distributed prefrontal areas became thicker after ECT treatment. Ota et al. (2015) reported significant volume increases after ECT in the bilateral medial temporal cortices, inferior temporal cortices, and right anterior cingulate.

Besides assessing structural variations of the brain, functional alterations of brain activity have been measured in MDD patients using advanced imaging techniques. Functional magnetic resonance imaging (fMRI) was employed to explore functional alterations in MDD patients in comparison with healthy controls. Using this technique, Kaiser et al. (2015) demonstrated large-scale network dysfunctions in MDD, including imbalanced connectivity among networks involved in regulating attention to the internal or external world and decreased connectivity among networks involved in regulating or responding to emotion or salience. fMRI has also been found to be a useful tool for measuring the response to antidepressant treatments (Liston et al., 2014; Posner et al., 2013). Beall et al. (2012) adopted task fMRI and found that remission after ECT for MDD was characterized by decreased activation in emotional regulation but increased resting connectivity. Abbott et al. (2013) used resting-state fMRI (rs-fMRI) to investigate the response to ECT for MDD. It was found that successful ECT resulted in an increase in functional network connectivity between two pairs of the network: posterior default mode and the dorsomedial prefrontal cortex (MPFC) as well as posterior default mode and left dorsal lateral prefrontal cortex. Moreover, some data-driven approaches were used to find consistent changes after ECT treatment in MDD patients (Leaver et al., 2016; Perrin et al., 2012). However, there is still a lack of studies on the effectiveness of the ECT response in MDD patients using rs-fMRI (Dichter et al., 2015; Kong et al., 2017).

Because Biswal et al. (1995) adopted rs-fMRI to investigate human brain function, considerable studies have been conducted to reveal intrinsic spontaneous brain activity. Most researchers examined spontaneous low-frequency oscillations at the frequency band of 0.01–0.08 Hz. Meanwhile, many studies have presented different measures of the nature of rs-fMRI. Among them, the amplitude of low-frequency fluctuations (ALFF) is a reliable measure of whole-brain rs-fMRI signals (Kong et al., 2017; Zou et al., 2008). The ALFF has been widely adopted because it directly correlates to the intensity of spontaneous neural activity in the resting state with regard to energy metabolism (Qi et al., 2012; Yu-Feng et al., 2007). Moreover, Zou et al. (2008) proposed that fractional ALFF (fALFF) reduces the effects of physiological noise. The fALFF represents the ratio of the power spectrum of low-frequency (0.01–0.08 Hz) to that of the entire frequency range. Using the fALFF, one can measure functional abnormalities in patients with affective disorders by rs-fMRI signals. As a whole-brain data-driven method with high test-retest reliability, the fALFF has been selected for carrying out many studies in patients with MDD (Guo et al., 2013b; Lai and Wu, 2015; Liu et al., 2013a; Wang et al., 2012). Some significant alterations have been reported in MDD patients in some brain regions, such as the limbic system and the cerebellum. Because ECT is an effective antidepressant treatment for MDD, there should be some significant alterations in specific brain regions in MDD patients before and after ECT. Thus, we adopted rs-fMRI and fALFF to assess brain function alterations and illustrate the effectiveness of ECT treatment.

2. Materials and methods

2.1. Participants

Inpatients (14 women and 10 men, aged 31.33 ± 10.79, range 18–55 years) who had been diagnosed with major depression were recruited from the Mental Health Center, the First Affiliated Hospital of Chongqing Medical University. Healthy controls (10 women and 4 men, aged 33.29 ± 10.36, range 20–56 years) were also selected to take part in this study. Ethical approval was acquired from the Local Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and this study was carried out in accordance with the Declaration of Helsinki. Two psychiatrists conducted the diagnoses and structured clinical interviews for all participant patients who had a unipolar depressive episode as determined by Diagnostic and Statistical Manual (DSM)-IV criteria for MDD (First et al., 2002) and the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1967). All the patients were under severe depression and actively seeking effective treatment. Before ECT, they underwent physical examination, electroencephalogram, electrocardiogram, blood test, and X-ray. Moreover, they were excluded from the study if they had received ECT, mood stabilizers, antidepressants, or antipsychotics within the past 1 month.

Additional inclusion criteria for the MDD patients were (1) agreement to receive ECT (consent provided either by the patient or, in certain cases, a direct relative), (2) aged between 16 and 60 years, (3) HAMD scores greater than 21, and (4) no contraindication to ECT treatments. Exclusion criteria for all subjects included (1) contraindication to MRI scan, (2) neurological disorders, (3) severe somatic disease, (4) substance abuse, (5) pregnancy, (6) lactation, or (7) depression caused by or combined with somatic disease and other psychiatric disorders (Cao et al., 2018). Healthy controls had no personal or family history of any psychiatric disorder.

2.2. ECT procedure

ECT was performed using the Thymatron DGx system (Somatics LLC, Lake Bluff, IL, USA) at the Mental Health Center, the First Affiliated Hospital of Chongqing Medical University. Over the course of 3 weeks, all 24 patients underwent 8 sessions of ECT treatment, including 3 sessions per week (Monday, Wednesday, and Friday mornings) for the first 2 weeks and 2 sessions (Monday and Friday mornings) during the third week. All patients were restricted from water and food intake beginning at midnight before ECT. The time and frequency of ECT treatment were the same for all patients. They were administered the HAMD rating scale, MRI scan, and fMRI scan before the first ECT and after the eighth ECT. During this period, antipsychotics and antidepressants were not used.

The intensity of electric stimulation was individually adjusted based on seizure response and adverse effects experienced during the ECT process, if any. The energy setting percentage was adjusted by integral multiples of 5. During the first ECT session, the seizure threshold was measured by the smallest electrical dose that produced a seizure of at least 25 seconds on the electroencephalogram (Abrams, 2002). If the initial dosage failed to elicit a seizure, the age-adjusted titration was adopted to increase by 5% the output charge of the ECT device every time, and the patient was restimulated after 30 seconds. Electric stimulation was conducted at most 3 times during an ECT session. If the seizure threshold was not achieved in the first session, stimulation with twice the last dose in the next session was performed. The electrical dosage was set at 1.5–2 times the seizure threshold in consecutive ECT sessions according to the extent of the seizure (Kennedy et al., 2009). The patients were administered anesthesia with succinylcholine (0.5–1.0 mg/kg) and sodium thiopental (3.0–5.0 mg/kg) during the ECT procedure.

ECT was continued if clinical symptoms of depression had not sufficiently improved after 8 sessions, as determined by a clinician, for a