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Research paper

# Local functional connectivity density is closely associated with the response of electroconvulsive therapy in major depressive disorder

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## ABSTRACT

*Background:* Electroconvulsive therapy (ECT) has been demonstrated to be an effective treatment of major depressive disorder (MDD). However, the neuroanatomical basis of response to ECT is still largely unknown.
*Methods:* In present study, we used functional connectivity density (FCD) and resting-state functional connectivity (RSFC) to identify the relationship between the changes of resting-state activities and ECT responses in 23 MDD patients before and after ECT. In addition, the identified neural indices as classification characteristics were entered into multivariate pattern analysis using linear support vector machine (SVM) to classify 23 MDD patients before ECT from 25 gender, age and years of education matched healthy controls.
*Results:* We found that the changes of local FCD (lFCD), not long-range FCD, of the left pre-/postcentral gyrus (Pre-/postCG), left superior temporal gyrus (STG), and right STG were significantly correlated with the changes of Hamilton Rating Scale for Depression (HRSD) scores in MDD patients before and after ECT. The subsequent functional connectivity analysis revealed significantly decreased functional connectivity between right STG and right intraparietal sulcus (IPS) in MDD after ECT in spite of no correlation with HRSD scores. Finally, SVM-based classification achieved an accuracy of 72.92% with a sensitivity of 73.91% and a specificity of 72% by leave-one-out cross-validation.
*Conclusions:* Our findings indicated that Pre-/postCG and bilateral STG play an important role in response of ECT in MDD patients, and the lFCD in these areas may serve as a biomarker for predicting ECT response.

## 1. Introduction

Electroconvulsive therapy (ECT) has been widely used for treatment of neuropsychiatric disorders including schizophrenia and depression (Kellner et al., 2012; Lisanby, 2007; Tharyan and Adams, 2005). Compared to other types of treatment, ECT is the optimal choice for therapy of major depressive disorder (MDD), especially for treatment-resistant depressive disorder, given its rapid action (Kellner et al., 2012; Lisanby, 2007). MDD is the leading cause of disability in the worldwide and brings great globally social and economic burden (Ferrari et al., 2013). Although some previous studies revealed structural and functional changes in frontal, parietal, and temporal cortices in MDD patients after ECT (Dukart et al., 2014; Joshi et al., 2016; Abbott et al., 2013; Perrin et al., 2012; Wei et al., 2014), However, the neuroanatomical basis of MDD responding to ECT to alleviate disease symptoms remains unclear.

With the advance in functional magnetic resonance imaging (fMRI), we can non-invasively investigate functional organization in the human brain. The resting-state fMRI, which has been widely used to study functional interaction between spatially distinct regions, primarily

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reflects the spontaneous brain functional activities related to self-initiated behavior (Fox and Raichle, 2007; Raichle et al., 2001). Therefore, resting-state fMRI could better characterize the changes of intrinsic functional connectivity (FC) patterns to understand the neural basis of neuropsychiatric disorders. By measuring the FC, the functional connectivity density (FCD) was recently developed to identify the distribution of hubs in the human brain (Tomasi and Volkow, 2010). A greater FCD value for a particular voxel suggests that the voxel is functionally connected to many other brain voxels and indicates that this voxel takes a more important role in information processing. Moreover, FCD, which can be further divided into the local FCD (lFCD) and long-range FCD (lrFCD) on the basis of the neighboring relationships between brain voxels (Tomasi and Volkow, 2012a), has been widely applied to investigate the neurophysiological basis of neuropsychiatric disorders and cognitive functions (Tomasi and Volkow, 2012b, 2012c; Zhang et al., 2016; Zou et al., 2016).

In the present study, FCD was firstly calculated and applied to identify the brain areas in which the changed FCD values were significantly correlated with the changes of Hamilton Rating Scale for Depression (HRSD) scores in MDD patients before and after ECT. Then, the resting-state FC (RSFC) analyses were used to reveal the changed functional connectivity patterns of the brain areas found in the previous step in MDD patients after ECT. Finally, to validate the reliability of established MRI indices from the FCD and functional connectivity analyses, multivariate pattern analysis using linear support vector machine (SVM) was performed to classify MDD patients from HCs.

## 2. Methods

### 2.1. Participants

The MDD patients receiving ECT treatment were recruited in the Anhui Mental Health Center of the Fourth People's Hospital of Hefei. MDD was diagnosed based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria by a trained senior psychiatrist. All MDD patients are non-psychotic. The patients with substance use disorder, neurological disorders, life threatening somatic disease, pregnancy, other comorbid mental disorders, previous ECT treatment, and MRI-contraindications were excluded in the current study. Finally, a total of 23 participants (11 males, mean age = 38.74 years, standard deviation (SD) = 11.02) were enrolled in the present study. The severity of depression was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). The scale was evaluated 12–24 h before the first ECT and 24–72 h after the last ECT. As a reference group, 25 gender, age, and education matched healthy controls (HC) (12 males, mean age = 39.52 years, SD = 8.07) were used in the present study. All participants were right-handed and provided written informed consent. The study was in accordance with the latest revision of the declaration of Helsinki and experimental procedures and had full ethical approval from the local ethics committees of the Anhui Medical University.

### 2.2. ECT procedures

A modified bi-frontal ECT protocol using a Thymatron System IV Integrated ECT System (Somatics, Lake Bluff, IL, USA) in Anhui Mental Health Center of the Fourth People's Hospital of Hefei was used in the present study. The first three ECT sessions were administered on consecutive days, and the subsequent ECT sessions were conducted every other day with a break over the weekends until patients' reached symptom remission. During ECT, all the MDD patients were anesthetized using propofol. In addition, succinylcholine and atropine were used to relax the musculature and suppress the secretion of glands. And electroencephalography was used to monitor seizure activity. 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 can be evenly adjusted with an increment of 5% of the maximum charge (about 1000 millicoulomb) in our treatment strategy, and the pulse width is 0.5 ms. If no seizure activity was detected with the initial stimulation setting, the percent energy was increased until seizure was visually observed (Wei et al., 2014).

### 2.3. MRI data acquisition

The resting-state functional data was acquired on a clinical 3.0 T MRI system (Signa HDxt, GE Healthcare, Buckinghamshire, UK) using a standard echo planar imaging (EPI) sequence at the First Affiliated Hospital of Anhui Medical University. Patients were scanned 12–24 h before the first ECT and 24–72 h after the last ECT. Healthy controls were also scanned once to determine pre-treatment neural alterations in the patients. Before scanning, participants were instructed to relax and to keep their eyes closed, to remain awake and not to think of anything during the MRI acquisition. The main parameters for resting-state functional images were: repetition time = 2 s, echo time = 22.5 ms, 240 volumes, flip angle = 30°, 33 slices, thickness/gap = 4.0/0.6 mm, voxel size = 3.4 × 3.4 × 4.6 $mm^3$, matrix size = 64 × 64, field of view = 220 × 220 $mm^2$.

### 2.4. Resting-state fMRI data preprocessing

Resting-state fMRI data were preprocessed using SPM8 software (Statistical Parametric Mapping software: http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes were discarded to allow for magnetization equilibrium. The slice timing for the remaining images was corrected and then realigned to the first volume to reduce head motion. A maximum displacement of less than 3 mm and an angular motion of less than 3° were used as the criteria to exclude the participants with high head motion. Under this criterion, all participants were retained for the subsequent analyses. Next, all fMRI images were normalized to the Montreal Neurological Institute (MNI) EPI template and resampled at 3 × 3 × 3 $mm^3$. To calculate the FCD maps, we did not apply spatial smoothing to fMRI images to control the smoothing effect on local correlations (Tomasi and Volkow, 2012b). For the RSFC analysis, the normalized fMRI images were smoothed using a Gaussian kernel of 6 mm FWHM. Finally, the functional images were filtered with a temporal band-path of 0.01–0.1 Hz and six motion parameters, white matter and cerebrospinal fluid signals were regressed out.

### 2.5. FCD calculation

FCD maps including local FCD (lFCD) map and global FCD (gFCD) map for each individual were calculated in a gray matter (GM) mask. The RSFC strength between GM voxels was measured using Pearson correlation coefficient. The number of functional connections of a specific voxel was determined by computing how many voxel-wise connections with correlation coefficient greater than 0.6. This correlation coefficient threshold was selected because the correlation coefficient smaller than 0.4 increases false-positive rates and the coefficient greater than 0.7 results in FCD maps with lower sensitivity because of reduced dynamic range (Tomasi and Volkow, 2010). A great number of previous studies have demonstrated that the value of 0.6 is the most stable threshold to reveal the functional module in the brain (Tomasi and Volkow, 2010, 2012a, 2012b; Zhang et al., 2016; Zou et al., 2016; Tomasi et al., 2016). Thus, in our current study, we also adopted this threshold for calculating the FCD maps. The lFCD at a given voxel $x_0$ was calculated as the local number of connections, $k(x_0)$, between $x_0$ and its neighboring voxels using a 'growing' algorithm. First, we computed the FC between $x_0$ and each voxel ($x_i$) which is directly neighboring with $x_0$, and the FC greater than 0.6 was considered functionally connected to $x_0$. Next, we calculated the FC between $x_0$ and $x_j$ which is directly neighboring with $x_i$ not with $x_0$, and the FC greater than 0.6 was considered functionally connected to $x_0$ as neighbor. This search