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Research report

The patterns of fractional amplitude of low-frequency fluctuations in depression patients: The dissociation between temporal regions and fronto-parietal regions

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Objective: This study surveyed the characteristics of the indicator for the fluctuations of default brain activity, fractional amplitude of low-frequency fluctuations (fALFF), in patients with pure major depressive disorder (MDD).
Methods: Forty-four patients with MDD and 27 normal controls were enrolled in our study. All the participants received the resting-state functional magnetic resonance imaging (rs-fMRI) scans, which were pre-processed by the REST toolbox (resting-state functional MRI data analysis toolbox). The group-related differences of the fALFF between patients and controls were explored by performing comparisons of the fALFF values obtained from rs-fMRI data. The fALFF outputs of patients and controls were compared with global brain volume, age and gender as covariates. In addition, the correlations between the clinical variables (such as depression severity, anxiety severity, illness duration) and fALFF values were also estimated in each group and across both groups.
Results: The patients with MDD had significantly higher fALFF values than the controls, for the left temporal subgyral region. In the contrary, the patients had lower values of fALFF than controls, for the right frontal subcallosal gyrus and right parietal postcentral gyrus. In addition, the fALFF values were negatively correlated with the depression severity in the left temporal subgyral region.
Conclusion: MDD patients had dissociable alterations in the fALFF values of the fronto-parietal and temporal regions. The pattern of fALFF alterations might be unique for depression patients with later onset-age of young adult phase.

1. Introduction

It is an interesting issue to research the alterations in the brain function of major depressive disorder (MDD). Several hypotheses have been mentioned in the underlying neurophysiology of patients with MDD, such as fronto-limbic network (Alexopoulos et al., 2012; de Kwaasteniet et al., 2013; Lai et al., 2010; van Tol et al., 2010). The fronto-limbic findings might be compatible with initial "limbic–cortical–striatal–pallidal–thalamic tract" hypothetic model for MDD (Sheline, 2000). In the recent years, a modified MDD model has been proposed and the network involves the regions with resting-state brain activity, such as ventromedial prefrontal cortex, anterior cingulate and lateral parietal cortex. The results support that fronto-limbic network plays a role in the pathophysiology for MDD (Sheline et al., 2009). The fronto-cingulate dysfunction hypothesis also specified the importance of fontal cortex to regulate amygdala activity in MDD (Pizzagalli, 2011). In addition to the fronto-limbic network, the fronto-parietal network is important for the treatment effects, the cognitive dysfunction and rumination in the patients with MDD (Brzezicka, 2013; Kosel et al., 2003). The faulty circuit theory also indicated the important roles of frontal-, temporal- and parietal-cortex in the functional impairment in MDD (Insel, 2010). These literatures provided us a clue of the pathophysiology for MDD.

Among the several modalities for exploring the alterations in brain activities, the resting-state functional magnetic resonance imaging (rs-fMRI) is a well-established method to investigate the resting-state brain activity. The rs-fMRI includes many parameters, which can be applied in the study of neurophysiology for the mental disorders. Among these parameters, the fractional amplitude of low frequency fluctuations (fALFF) is a measure with more focus on neuronal fluctuations, which can be assessed by the amplitude of low-frequency fluctuations. The fALFF is fraction of amplitude of low-frequency fluctuations (ALFF) in a given frequency band to the ALFF

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over entire frequency range detectable in the given signal. ALFF measures the absolute strength or intensity of low frequency oscillations (power spectrum density). It usually represents intensity of spontaneous BOLD fluctuations, which might represent neuronal activities. In brief, ALFF measures the absolute strength or intensity of low-frequency oscillations, whereas fALFF represents the relative contribution of low-frequency oscillations within a specific frequency band to the whole detectable frequency range. For instance, root mean square of low-frequency fluctuations in white matter was lower than that in gray matter by about 60%, which suggested that ALFF might be specific to gray matter metabolism (Biswal et al., 1995). It is based on previous reports mentioning spontaneous fluctuations within default mode network, resting activation map in the visual cortex and the mean power spectral density of intrinsic low-frequency fluctuations changes during working memory task (Fransson, 2006). The power spectrum of a signal is based on the discrete Fourier transform and squared magnitude of the Fourier coefficient. Zang et al. (2007) developed the concept for the ALFF, which is an index for the amplitude of low-frequency fluctuations . It is estimated by the square root of power spectrum integrated into the low frequency range and regional intensity of spontaneous blood oxygen level dependent fluctuations. However, ALFF is sensitive to environmental and physiological noises. Therefore, Zou et al. (2008) proposed the modified method, fALFF, to reduce the influences of physiological noise . It may effectively suppress the non-specific signals and significantly improve the specificity and sensitivity of detecting regional brain spontaneous fluctuations. fALFF represents relative contribution of low frequency oscillations within a specific frequency band to whole detectable frequency range (Zou et al., 2008). For the psychological meanings, the decreased or increased fALFF values will suggest the decreases or increases in the temporal synchronization (Lui et al., 2009). The alterations in fALFF of the brain network have been found in several neuropsychiatric illnesses, such as mild cognitive impairment (Han et al., 2012), panic disorder (PD) (Lai and Wu, 2012), depression (Guo et al., 2013b; Wang et al., 2012) and schizophrenia (He et al., 2013). Among the studies of the fALFF in depression, a report shows the dissociation pattern of the fALFF in the fronto-temporal region. The report suggested a pattern of increased fALFF values in the frontal region and decreased fALFF values in the temporal parahippocampal gyrus of first-episode medication-naïve patients (Guo et al., 2013b). However, the number of patients was small, which would limit the interpretation of the results.

Therefore we designed this study with larger sample of first-episode medication-naïve patients with MDD to decrease the bias of sample size. We would use the fALFF technique to analyze the rs-fMRI data of the MDD patients. According to the previous literature, we hypothesized that the fALFF would be altered in the fronto-limbic–fronto-parietal regions and the alterations might show a dissociation pattern with increased fALFF in the frontal region and decreased fALFF in the temporal region.

2. Materials and methods

2.1. Participants

The selection criteria for patients were as follows: (1) first-episode, medication-naïve patients with only MDD diagnosis (without other co-morbid diagnosis in psychiatry) (DSM-IV criteria) as assessed by the Structured Clinical Interview for DSM-IV; (2) no co-morbid psychiatric illnesses or medical illnesses; (3) severity of MDD was at least moderate: measured by Clinician Global Impression of Severity >4, Hamilton Rating Scales for Depression 17 items (HDRS) score >20, Hamilton Rating Scales for Anxiety (HARS) score <5; (4) no previous cognitive behavioral therapy or other psychotherapies; (5) medication-naïve (6) no abuse of or dependence on alcohol or other substances; and (7) no past history of claustrophobia or discomfort while receiving RFMRI scanning. The healthy controls had no psychiatric illnesses or significant medical illnesses. All participants signed the inform consent approved by the Institute of Review Board, Buddhist Tzu Chi Hospital, Taipei Branch. At the time of the scanning, none of the participants in the control group received psychotropic treatment of any kind. Handedness was determined by using the Edinburgh Inventory of Handedness (Oldfield, 1971). There were 44 patients with MDD and 27 healthy controls enrolled in current study.

2.2. RFMRI data acquisition and pulse sequence

Echo planar imaging (EPI) sequences were acquired in 20 axial slices (TR=2000 ms, TE=40 ms, flip angle $=90^{\circ}$, field of view= 24 cm; 5 mm thickness and 1 mm gap). The sequence duration was 300 s for each subject, 150 time points were acquired (voxel dimension: $64\times\ 64\times 20$) at baseline in patients and controls (3 T Siemens scanner housed at MR center of National Yang Ming University). All the patients and controls were asked to relax and close their eyes and they were instructed to move as little as possible during scanning. All the patients and controls reported that they were fully awake during MRI scanning.

2.3. fALFF analysis

EPI data was first preprocessed by DPARSF (Data Processing Assistant and Resting-State FMRI, version 2.2; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China.) (Chao-Gan and Yu-Feng, 2010) working with the statistical parametric mapping 8 (SPM8) on the Matlab platform. The first 10 time points were removed in consideration of the instability of initial MRI signal and patient's difficulty in adapting to MRI acquisition circumstance. The subsequent images were sliced timing with 20th slice as the reference slice, realigned and normalized to standard MNI spaces using EPI templates; and re-sampled with $3\times 3\times 3\ mm^3$, smoothing with Full Width at Half Maximum (FWHM) $4\times 4\times 4$ kernel, to detrend and filter data with residual signals within 0.01–0.08 Hz to discard the bias from high-frequency physiological noise and low-frequency drift. As all subjects' head movements were less than 0.5 mm in translation and one degree in rotation (through obtaining the motion time courses of all subjects), no subject was excluded due to observed excessive motions. The effects of "micro-movements" and the nuisance correlation caused by head motion were removed by checking covariates in nuisance regressors in DPARSF (Power et al., 2012; Yan et al., 2013a). The individual covariates of motion included Friston-24 parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) and group covariates of motion included framewise displacement motion regression model (Yan et al., 2013b). The final output data after DPARSF preprocessing was then processed by REST (Resting State FMRI Data Analysis Toolkit, version 1.4; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China.) (Song et al., 2011). We estimated fALFF and ALFF by using the REST software. Briefly, for a given voxel, the filtered residual and resting state time series were transformed into the frequency domain using the fast Fourier transform (FFT). Since the power is proportional to [amplitude]^2 at a given frequency, the power spectrum obtained by FFT was square rooted to obtain amplitude. The average squared root was termed ALFF at a given voxel. A ratio of the amplitude averaged across 0.01–0.08 Hz to that of the entire frequency range (0–0.25 Hz) and was computed at each voxel to obtain the fALFF, creating an amplitude map for the whole brain, which was then normalized by the following formula:

normalized fALFF=(fALFF − ALFF − global fALFF)/(standard deviation of global mean power spectrum density).