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Research report

Dissociation of regional activity in the default mode network in first-episode, drug-naive major depressive disorder at rest

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ABSTRACT

Background: Major depressive disorder (MDD) is associated with altered neural activity in the default mode network (DMN). In the present study, we used a fractional amplitude of low-frequency fluctuations (fALFF) approach to directly investigate the features of spontaneous brain activity of the DMN in patients with the first-episode, drug-naive MDD at rest.
Methods: Twenty-four first-episode, drug-naive patients with MDD and 24 age-, gender-, and education-matched healthy subjects participated in the study. The fALFF and independent component analysis (ICA) approaches were utilized to analyze the data.
Results: Patients with MDD exhibited a dissociation pattern of resting-state fALFF in the DMN, with increased fALFF in the left dorsal medial prefrontal cortex (MPFC) and decreased fALFF in the left parahippocampal gyrus (PHG). The increased fALFF values of the left dorsal MPFC were positively correlated to the Hamilton Rating Scale for Depression (HRSD) scores.
Conclusions: Our results first suggested that there was a dissociation pattern of resting-state fALFF in the DMN in patient with MDD, which highlighted the importance of the DMN in the pathogenesis of MDD.

1. Introduction

As a common psychiatric disorder, major depressive disorder (MDD) is characterized by persistent and pervasive feelings of sadness, guilt, and worthlessness (First et al., 1997). Despite the rapid progress made over the years in the development of antidepressive treatments, about 60% of depressed patients suffer at least one recurrence (Smith et al., 2009) and the pathogenesis of MDD remains equivocal.

Evidence has been accumulated that the default mode network (DMN) can serve as a potential biomarker for MDD, and play a critical role in the neural activity mediating MDD (Li et al., 2013). The DMN encompasses a specific set of brain regions including the medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC/PCu), and medial, lateral, and inferior parietal cortex (Raichle et al., 2001). This network has been showed to be involved in self-referential activities (Lemogne et al., 2010), which is aberrant in MDD (Grimm et al., 2009).

To date, few studies have directly explored depression-related alterations in resting-state DMN activity, and inconsistent findings of abnormal neural activity and functional connectivity (FC) of the DMN in MDD have been identified. On the one hand, increased neural activity and FC of the DMN have been reported in MDD. Using independent component analysis (ICA), Greicius et al. (2007) found increased subgenual cingulate and thalamic FC within the DMN but did not observe any decreased FC in depressed patients. Moreover, a positive correlation between the length of the current episode and subgenual cingulate FC was observed in their study. Recently, two spatially independent subnetworks of the DMN were detected in MDD: the anterior subnetwork and the posterior subnetwork. Both subnetworks showed increased FC in the pretreatment MDD (Li et al., 2013). Sheline et al. (2010), Zhou et al. (2010), and Hamilton et al. (2011) also observed increased FC within the DMN in depressed patients. In addition, Hamilton et al. (2011) found that the level of DMN dominance was associated with levels of maladaptive, depressive rumination and adaptive, reflective rumination. On the other hand, a great number of studies found decreased neural activity and FC of the DMN. Bluhm et al. (2009) reported decreased FC between the PCC/PCu and the bilateral caudate in MDD. Previously, the present dataset was analyzed by a voxel-mirrored homotopic connectivity (VMHC) method (Guo et al., 2013a), with the results that the depressed patients had significant lower VMHC in the MPFC and the PCC/PCu. Depression-related reduced FC has also been observed in other studies (Anand et al., 2005; Veer et al., 2010). Interestingly, a study of late-life depression noticed both increased and decreased FC in the brain regions within the DMN (M. Wu et al., 2011). However, the above-mentioned studies have used the FC method

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to analyze the data. There is no study to directly examine the regional activity in the DMN yet.

Obviously, the role of the DMN is far from being clear. Although the inconsistency between the above-mentioned studies may generate from the heterogeneity of studies, such as the different sample size, treatments, and analysis approaches, it should be emphasized that the DMN changes in MDD may present in a complex way, not as sole increases or decreases (Broyd et al., 2009; Northoff et al., 2006). Recently, Zhu et al. (2011) reported a dissociation between the anterior and posterior FC in the resting-state DMN in first-episode, drug-naive patients with MDD. In their study, increased FC in the anterior medial regions and decreased FC in the posterior medial regions were observed in the DMN. However, this study has utilized ICA, an FC method, to analyze their data. Although this method provides useful information, it is unclear which brain region is abnormal when one region exhibits abnormal FC with other brain regions. Hence it is meaningful to measure the regional activity in the DMN to determine whether there is a similar dissociation pattern of regional brain activity in the DMN in MDD.

Here, we employed the fractional amplitude of low-frequency fluctuations (fALFF) approach (Zou et al., 2008) to directly compare the regional activity in the DMN between patients with MDD and healthy subjects. Compared to the FC method, fALFF is designed to identify the regional intensity of spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals. The regional intensity of BOLD signals varies according to spontaneous fluctuations of blood flow to the area. Therefore, increased fALFF might be related to a neural hyperactivity in the area or vice versa (Biswal et al., 1995; Lui et al., 2009).

In the present study, we aimed to explore the differences of fALFF in the DMN between patients with the first-episode, drug-naive MDD and healthy subjects. Based on the previous study (Zhu et al., 2011), we hypothesized that there was a dissociation pattern of resting-state fALFF between the anterior and posterior parts of the DMN in the depressed patients. We also hypothesized that the identified regions with abnormal fALFF would be correlated to the clinical variables and the executive function.

2. Methods and materials

2.1. Subjects

Twenty-five first-episode, drug-naive patients were consecutively recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. The subjects were from our previous studies (Guo et al., 2013a, 2013b). Depression episode was diagnosed according to the Structured Clinical Interview of the DSM-IV (SCID) (First et al., 1997). The depression severity was assessed by using a 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). The executive function was measured by Wisconsin Card Sorting Test (WCST) (48 cards) (Greve et al., 2005). Inclusion criteria of the patients included (1) first episode and drug naive; (2) currently experiencing an episode of depression with HRSD total score ≥ 18; and (3) the illness duration ≤ 1 year. Exclusion criteria were (1) other Axis I psychiatric disorders such as schizophrenia, schizoaffective disorder, bipolar disorders, anxiety disorders, or severe Axis II personality disorders or mental retardation, assessed with SCID; (2) a history of organic brain disorders, neurological disorders, cardiovascular diseases or other serious physical illness provided by personal history or laboratory analysis; and (3) any contradictions to undertake an MRI scan.

Twenty-five right-handed healthy subjects were recruited from the community in the same period. They were interviewed for a current or life time diagnosis of any Axis I or II disorder by using SCID Non-Patient Edition and SCID Axis II Personality Disorders. None of them had a history of neuropsychiatric illness, brain injury, or serious physical illness.

All subjects were given information about the procedures and signed a written informed consent. The study was approved by the local ethics committee.

2.2. Image acquisition

Images were obtained on a Siemens 3T scanner. Participants were required to remain motionless, keep their eyes closed and not perform specific cognitive exercise. The following parameters were applied for functional imaging: repetition time/echo time (TR/TE)= 2000/30 ms, 30 slices, 64×64 matrix, 90° flip angle, 24 cm FOV, 4 mm slice thickness, 0.4 mm gap, and 250 volumes (500 s).

2.3. Data preprocessing

Data preprocessing was conducted in Matlab (Mathworks) using the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang, 2010). The images were corrected for the acquisition delay between slices. The head motion was corrected by estimating the values for translation (mm) and rotation (degree) for each subject. Participants should have no more than 2 mm maximum displacement in x, y, or z and 2° of angular motion during the image acquisition. Then the images were normalized to the standard SPM8 echoplanar imaging template, resampled to $3 \times 3 \times 3$ mm^3. The resulting data were temporally band-pass filtered (0.01–0.08 Hz) and linear detrended.

2.4. DMN identification

The group ICA was performed to select the DMN as a mask by using the toolbox GIFT (http://mialab.mrn.org/software/#gica). There were three main steps of group ICA: data reduction, independent component (IC) separation, and back reconstruction. The number of ICs was estimated by using the minimum description length (MDL) criteria. The common ICs were acquired over the healthy subjects after IC separation using the Infomax algorithm, and back reconstruction of the ICs was conducted based on the above results. The ICs of the DMN were selected according to the templates offered by GIFT.

2.5. FALFF analysis

FALFF analysis was performed by using DPARSF (Yan and Zang, 2010). The time series of each voxel was transformed to the frequency domain using a Fast Fourier Transform and the power spectrum was acquired. The square root was calculated at each frequency of the power spectrum and the mean square root was obtained across 0.01–0.08 Hz at each voxel. The sum of amplitude across 0.01–0.08 Hz was divided across the whole frequency range. Finally, the fALFF of each voxel was divided by the global average fALFF within a brain mask for a standardization purpose (Zou et al., 2008).

2.6. Statistical analysis

When appropriate, demographic and clinical data were compared by using two-sample t-test and Chi-square test. The fALFF analyses were performed with the independent two-sample t-tests via voxel-wise cross-subject statistics in the regions within the DMN with a significance threshold of $p < 0.005$ for multiple comparisons using Gaussian Random Field (GRF) theory (min $z > 2.807$, cluster significance: $p < 0.005$). Linear correlations were calculated between the mean fALFF values across all voxels in the brain regions with abnormal fALFF in the patient group and clinical or psychometric variables.