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Decreased regional homogeneity in insula and cerebellum: A resting-state fMRI study in patients with major depression and subjects at high risk for major depression

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ABSTRACT

Functional disconnectivity during the resting state has been observed in subjects with major depressive disorder (MDD), and in subjects at high genetic risk for major depression during task performance. It is hypothesized that functional impairments in certain brain areas are present in patients with MDD and in their first-degree relatives. To test this hypothesis, an analysis of regional homogeneity (ReHo) of the whole brain was performed on 45 subjects. Compared with the control group, subjects with MDD and those at high risk for MDD exhibited significantly decreased ReHo in the right insula and in the left cerebellum. These abnormalities may play an important role in the pathophysiology of depression.

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1. Introduction

Major depressive disorder (MDD) is characterized by cognitive impairments, functional disability and mortality, and affects 7%~11% of the general population. The pathophysiology of depression is unclear. Neurobiological diagnostic markers are not currently established, and the diagnosis of depression is dependent on clinical signs and symptoms.

It is proposed that functional magnetic resonance imaging (fMRI) can provide new insights into the pathophysiology of depression, because of its advantage in not requiring exposure to radioactive tracers. A large number of fMRI studies have focused on cognitive and emotional tasks. Previous fMRI findings have suggested that the brain regions affected in MDD primarily lie in the prefrontal–amygdalar–pallidostriatal–mediothalamic mood regulating circuit (MRC) (Anand et al., 2005b, 2007). This network is involved in the regulation of mood, cognition and behavior, and is considered a contributor in the pathophysiology of MDD. However, the results of these studies are not consistent. For example, some contradictory findings have emerged regarding abnormalities in the prefrontal cortex associated with cognitive and emotion processing. Some studies have reported hypofrontality in MDD subjects compared with controls (Lee et al., 2008; Mitterschiffthaler et al., 2003; Elliott et al., 2002) whereas other research has conversely identified hyperfrontality in MDD (Walter et al., 2007; Fitzgerald et al., 2008; Fu et al., 2004). Several fMRI studies based on tasks using emotional stimuli found that hypoactivation of the cingulate was correlated with depression (Malhi et al., 2004; Anand et al., 2005a). In addition, hypoactivation of the amygdala has been found to play a key role in the neural substrate of negatively biased automatic emotion processing (Dannlowski et al., 2007; Hamilton and Gotlib, 2008). It is certainly difficult for the results obtained from the large variety of task-states to be repeated, because of the complicated designs of these studies.

Recently, resting-state fMRI has attracted more attention as a new branch of this field of study. Low-frequency fluctuations (LFF; <0.08 Hz) of fMRI signals are considered to be related to spontaneous neuronal activity in resting state and were found to be highly synchronous in healthy subjects (Biswal et al., 1995; Cordes et al., 2000). These resting-state fMRI studies have suggested that patients with many psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), schizophrenia and depression (Zhou et al., 2007; Tian et al., 2006; Greicius et al., 2007) exhibit decreased LFF synchrony in particular brain regions.

More recently, the regional homogeneity (ReHo) method (Zang et al., 2004) was used to analyze the similarities of intra-regional time series across the whole brain. Kendall's coefficient of concordance (KCC) was used to measure the similarity of the time series of one voxel with those of its nearest neighbors in a voxel-wise analysis.

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ReHo reflects the temporal synchrony of the regional blood oxygen level-dependent (BOLD) signal, which may be potentially helpful to understanding the pathophysiology of psychiatric disorder. This method has been used to explore regional neural activity patterns in healthy volunteers and psychiatric patients in the resting state. Decreased ReHo among remote brain areas has been reported in schizophrenia and ADHD (Liu et al., 2006; Zhu et al., 2005).

Genetic factors play an important role in the pathology of depression. Some fMRI studies have demonstrated that subjects at high genetic risk for depression exhibit impaired modulation of some regions, such as the amygdala and the anterior cingulate cortex during task performance (Wolfensberger et al., 2008; Mannie et al., 2008).

We hypothesize that abnormal ReHo will be discovered in certain regions in patients with MDD, and in their first-degree relatives. These abnormalities may be a stable trait marker for the diagnosis of MDD. To test this hypothesis, the present study compared the ReHo of the whole brain among patients with MDD, their first-degree relatives, and healthy controls.

2. Methods

2.1. Subjects

Fifteen patients with MDD (seven females, eight males) were recruited from the inpatient and outpatient units at the Mental Health Department, First Hospital of Shanxi Medical University. These patients met the DSM-IV criteria for MDD. Confirmation of the diagnosis was made by clinical psychiatrists for all patients, using a Chinese version of the Modified Structured Clinical Interview for DSM-IV, patient version (SCIDI/P, First et al., 1995). All patients were in their first episodes of illness, had never been on medication, and had no history of neurological or systemic illness, head injury or any other relevant medical or additional psychiatric disease.

Fifteen first-degree relatives (eight females, seven males) were recruited from the patients' families. Fifteen healthy, paid volunteers (seven females, eight males) were recruited by advertisements. The first-degree relatives and healthy controls were interviewed using the Structured Clinical Interview for DSM-IV, nonpatient edition (SCIDI/NP). None of them had a current or past history of depression or other major physical or neurological illness, or substance abuse.

All subjects were right-handed and gave written, informed consent prior to taking part in the study. This study was approved by the Ethical Committee for Medicine of First Hospital of Shanxi Medical University, China.

2.2. MR imaging

Images were acquired using a SIEMENS TRIO 3-Tesla scanner. Foam pads were used to limit head motion and reduce scanner noise. During the resting state, subjects were instructed not to concentrate on anything in particular, but to just relax with their eyes closed and move as little as possible. The scanning sessions included the following: (i) T1-weighted axial image: repetition time/echo time (TR/TE) = 580/18 ms; thickness/gap = 4/0 mm; matrix: 256×144; field of view (FOV) = 256×192 mm; (ii) three-dimensional T1-weighted whole-brain images: 3D-FLASH sequence, TR/TE = 14/4.92 ms, 120 slices, thickness/gap = 1.5/0.3 mm, FOV = 230×230 mm, matrix = 256×192, flip angle = 25°; (iii) the resting-state fMRI image: echo planar imaging (EPI) pulse sequence, 33 slices; TR/TE = 2000/30 ms; thickness/gap = 4/0 mm; matrix = 64×64; FOV = 192×192 mm; flip angle = 90°; 110 volumes.

2.3. Data analysis

Image preprocessing was conducted using statistical parametric mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). The first 10 volumes of each functional time series were discarded because of instability of the initial MRI signal and adaptation of participants to the circumstance, leaving 100 volumes in total. The remaining fMRI images were corrected for the acquisition delay between slices and for the head motion. Motion time courses were obtained by estimating the values for translation (mm) and rotation (degrees) for each subject. One participant who had more than 2 mm maximum displacement in x, y, or z and 2°of angular motion during the whole fMRI scan was excluded in this study. After slice acquisition correction and head-motion correction, the fMRI images were normalized to the standard SPM2 echoplanar imaging template, re-sampled to 3-mm cubic voxels. The resulting fMRI data were temporally band-pass filtered (0.01–0.08 Hz) to reduce low-frequency drift and physiological high frequency respiratory and cardiac noise for further ReHo analysis. One patient was excluded in the analysis because of excessive motion.

This resulted in usable resting-state fMRI data of 14 MDD patients, 15 first-degree relatives and 15 normal controls. For the visualization results, the individual high-resolution three-dimensional anatomical image was also normalized to the standard SPM2 template. By averaging all individual normalized anatomical images, we obtained a mean normalized anatomical image across the participants. The voxels outside the mean brain image were excluded to create a mask. Only the voxels within the mask were included in further analysis. Regional homogeneity analysis was performed for each participant by calculating the KCC of the time series of a given voxel with those of its nearest neighbors (26 voxels) in a voxel-wise analysis. The KCC can be computed by the following formula:

$$W = \frac{\sum (R_i)^2 - n\left(\overline{R}\right)^2}{\frac{1}{12}K^2(n^3 - n)}$$

where W is the KCC of a given voxels, ranging from 0 to 1; R_i is the sum rank of the ith time point; $\overline{R} = \frac{(n+1)\times K}{2}$ is the mean of the R_is; K is the number of time series within a measured cluster ($K = 27$, one given voxel plus the number of its neighbors) and n is the number of ranks. The KCC program was coded in REST software (http://resting-fmri.sourceforge.net) by the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China. Group statistical analysis was performed using SPM2. The resulting fMRI data were then spatially smoothed with a Gaussian kernel of $4\times4\times4$ mm^3 full-width at half-maximum.

The resulting contrast images were entered into second level (random effects) analyses for between-group comparisons. These used a one-way ANOVA for the three groups and a random-effect two-sample t-test was performed on the individual ReHo maps in a voxel-by-voxel fashion. The resulting statistical map was set at a combined threshold of $P = 0.001$ (uncorrected) and a minimum continuous cluster number of 10.

3. Results

Subject characteristics were analyzed by one-way ANOVA. The three groups were matched for age (mean ± SD) (29.13 ± 13.55 years for MDD group; 37.93 ± 10.42 years for relatives; 30.20 ± 12.31 years for normal controls; $F_{(2,41)} = 2.34$, $P = 0.11$), educational level (mean ± SD) (12.47 ± 2.78 years for MDD group; 13.13 ± 2.77 years for relatives; 13.47 ± 3.23 years for normal controls; $F_{(2,41)} = 1.33$, $P = 0.28$), and gender ($\chi^2 = 1.04$, $df = 2$, $P = 0.79$). Mean duration of illness was (mean ± SD) 1.1 ± 0.3 years and mean total score of $HAMD_{24}$ is (mean ± SD) 32.6 ± 6.5 in the MDD group. There was no significant difference in head motion between the three groups, or between of the two-group pairs (mean ± SD) (max translation: MDD: 0.575 ± 0.221, relatives: 0.633 ± 0.280, control: 0.509 ± 0.252, $F_{(2,41)} = 0.91$, $P = 0.41$; MDD vs relatives: $t = 0.74$, $df = 27$, $P = 0.47$, MDD vs. control: $t = 0.63$, $df = 27$, $P = 0.54$, relatives vs. control: $t = 1.28$, $df = 28$, $P = 0.21$; max rotation: MDD: 0.0101 ± 0.004, control: 0.011 ± 0.006, relative: 0.009 ± 0.005, $F_{(2,41)} =$

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