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Decreased interhemispheric resting-state functional connectivity in first-episode, drug-naive major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is shown to have structural and functional abnormalities in specific brain areas and connections by recent neuroimaging studies. However, little is known about the alterations of the interhemispheric resting-state functional connectivity (FC) in patients with MDD. In the present study, we used a newly developed voxel-mirrored homotopic connectivity (VMHC) method to investigate the interhemispheric FC of the whole brain in patients with MDD at rest.
Methods: Twenty-four first-episode, drug-naive patients with MDD and 24 age-, gender-, and education-matched healthy subjects underwent a resting-state functional magnetic resonance imaging (fMRI). An automated VMHC approach was used to analyze the data.
Results: Patients with MDD showed lower VMHC than healthy subjects in the medial prefrontal cortex (MPFC) and the posterior cingulate cortex/precuneus (PCC/PCu), two core regions within default mode network (DMN). Both left and right MPFC showed reduced FC with the other frontal areas and with right anterior cingulate gyrus (ACC), while PCC/PCu exhibited abnormal FC with the frontal areas and thalamus in patient group. Significant positive correlation was observed between VMHC in MPFC and persistent error response of Wisconsin Card Sorting Test (WCST-Pre) in patients. Further ROC analysis revealed that VMHC in the MPFC and PCC/PCu could be used to differentiate the patients from healthy subjects with relatively high sensitivity and specificity.
Conclusions: Our results suggest that decreased VMHC in brain regions within DMN may underlie the pathogenesis of MDD.

1. Introduction

Characterized by persistent and pervasive feelings of sadness, guilt, and worthlessness, major depressive disorder (MDD) will be the second leading cause of global disease burden by the year 2020 (Petersen et al., 2001). As the most common affective disorder and the most important precursor of suicide, MDD is remarkable by a yearly increase in morbidity, a high risk of mortality, and a high rate of medical service utilization (Taki et al., 2005). Despite the progress made over the years in the development of antidepressants, about 60% of patients suffer at least one recurrence (Smith et al., 2009), and the pathogenesis of MDD remains unclear.

Recent imaging techniques make it feasible to explore the structural and functional alterations related to MDD. Numerous positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have accumulated the evidence that MDD is associated with widespread local alterations in many brain regions, such as orbitofrontal cortex (Gilbert et al., 2010; Yao et al., 2009), prefrontal cortex (Frodl et al., 2009; Kennedy et al., 2007), occipital regions (Gilbert et al., 2010), hippocampus (Lui et al., 2009), parahippocampal gyrus (Gilbert et al., 2010), posterior cingulate gyrus (Mah et al., 2007), caudate nucleus (Brody et al., 2001; Norbury et al., 2010), and cerebellum (Guo et al., 2012a,b). Most of the above detected brain regions are bilateral. Moreover, an abnormality of the limbic-cortical networks is supposed to act a key role in the pathogenesis of MDD. For example, alterations in the limbic-cortical networks have been revealed by functional connectivity (FC) studies, such as orbitofrontal

Abbreviations: MDD, major depressive disorder; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; R-fMRI, resting-state fMRI; FC, functional connectivity; ACC, anterior cingulate cortex; VMHC, voxel-mirrored homotopic connectivity; WCST, Wisconsin Card Sorting Test; WCST-Pre, persistent error response of WCST; SCID, Structured Clinical Interview of the DSM-IV; HRSD, Hamilton Rating Scale for Depression; TR/TE, repetition time/echo time; FOV, field of view; ROI, region of interest; ROC, receiver operating characteristic curves; MPFC, medial prefrontal cortex; PCC/PCu, posterior cingulate cortex/precuneus; DMN, default mode network; BOLD, blood oxygen level-dependent; IQ, intelligence quotient.

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cortex–precuneus coupling (Frodl et al., 2009) and pregenual anterior cingulate cortex (ACC)–dorsomedial thalamus coupling (Anand et al., 2009). Most of these observations are summarized to have bilateral abnormalities in the dorsolateral, inferior, and medial prefrontal regions as well as the temporal limbic regions (de Asis et al., 2001). However, depression-related changes in functional interactions between the cerebral hemispheres are rarely explored.

Since the first resting-state fMRI (R-fMRI) study of Biswal et al. (1995), increasing attention has been paid to this approach, which reveals patterns of coherent intrinsic brain activities and provides a method to quantify interhemispheric functional interactions directly. Functional homotopy is designed to quantify the high degree of correlated activity between homotopic interhemispheric counterparts, one of the most salient features of the brain intrinsic functional architecture (Salvador et al., 2005). As mentioned above, the vast majority of large-scale brain regions detected are bilateral by using both task-based and R-fMRI. These findings indicate that functional homotopy may be an essential aspect of brain function. Consistent with this notion, homotopic resting-state FC demonstrates regional alterations related to the brain functional hierarchy (Stark et al., 2008). Particularly, homotopic resting-state FC is disrupted in autism (Anderson et al., 2010) and cocaine addiction (Kelly et al., 2011).

As a conspicuous aspect of the brain functional architecture, homotopic resting-state FC may offer a sensitive index of the depression-related changes. Here, a recently validated approach, voxel-mirrored homotopic connectivity (VMHC) (Zuo et al., 2010), was employed to examine interhemispheric resting-state FC in MDD directly. VMHC quantified the resting-state FC between each voxel in one hemisphere and its corresponding voxel in the opposite hemisphere. We compared VMHC between the patients with MDD and controls to evaluate the spatial heterogeneity of interhemispheric connectivity alterations in MDD. Based on previous studies to date, we hypothesized that patients with MDD would show reduced VMHC. Given evidence for frontal lobe dysfunction associated with MDD (Frodl et al., 2009; Gilbert et al., 2010; Kennedy et al., 2007; Yao et al., 2009), we expected the frontal regions to be particularly affected. We also explored whether, within patients with MDD, VMHC was related to clinical characteristics and executive function using Wisconsin Card Sorting Test (WCST).

2. Methods and materials

2.1. Subjects

A total of 50 aged from 18 to 43 years old, right-handed subjects were recruited, including 25 first-episode, drug-naive patients with MDD and 25 age-, gender-, and education-matched healthy subjects. Patients were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. The first-episode depression was diagnosed according to the Structured Clinical Interview of the DSM-IV (SCID) (First et al., 1997). All healthy subjects 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. The severity of depression was assessed by using a 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). Executive function was evaluated by WCST (48 cards) (Greve et al., 2005). Inclusion criteria of the patients were 1) first episode and drug naive; 2) currently experiencing an episode of depression with HRSD total score $\geq$18; and 3) the illness duration $\leq$1 year. Exclusion criteria included 1) other Axis I psychiatric disorders such as schizophrenia, schizoaffective disorder, bipolar 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 4) any contradictions to undergo an MRI.

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

2.2. Image acquisition

Imaging was conducted on a Siemens 3T scanner. A prototype quadrature birdcage head coil fitted with foam padding was applied to minimize head motion. Subjects were instructed to remain motionless, keep their eyes closed and not think of anything in particular. The following parameters were used 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 section thickness, 0.4 mm gap, and 250 volumes (500 s).

2.3. Data preprocessing

Data preprocessing was performed in Matlab (Mathworks) using the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The images were corrected for slice timing and head motion. The subjects should have no more than 2 mm maximum displacement in x, y, or z and 2° of angular motion during the scan. Then the images were normalized to the standard SPM8 echoplanar imaging template, and each voxel was resampled to $3\times3\times3$ mm^3. The processed images were smoothed with an isotropic Gaussian kernel (full-width at half-maximum = 8 mm). Finally, the resulting data were further temporally bandpass filtered (0.01–0.08 Hz) and linearly detrended to reduce the effect of low-frequency drifts and physiological high-frequency noise. Several sources of spurious covariates along with their temporal derivatives were then removed from the data by using linear regression. These variances included six head motion parameters obtained by rigid body correction, the whole-brain averaged signal, the signal from a ventricular region of interest (ROI), and the signal from a region centered in the white matter (Fox et al., 2005a).

2.4. Interhemispheric correlation

VMHC was performed with software REST (http://resting-fmri.sourceforge.net). Individual VMHC maps were generated by computing the Pearson correlation (Fisher *z*-transformed) between a given voxel and a corresponding voxel in the opposite hemisphere. The details of VMHC obtainment has been expounded in a previous study (Zuo et al., 2010).

Individual-level VMHC maps were entered into a group-level voxelwise *t* test analysis to determine regional group differences in VMHC. The resulting statistical map was set at $p<0.05$ (corrected for False Discovery Rate). Once significant group differences were observed in any brain regions, we further evaluated the relationships between these VMHC values and the HRSD score, the illness duration or the WCST in patient group. Multiple linear correlation analyses were performed ($p<0.05$).

Brain areas exhibiting significant differences between groups were identified as masks. Mean VMHC values were extracted for further receiver operating characteristic curves (ROC) analysis.

2.5. Seed-based FC

Seed-based FC was conducted using a temporal correlation approach (Fox et al., 2005b). Regions showing significantly altered VMHC were defined as seed ROIs. The time series of each ROI was preprocessed as follows: first, six head motion parameters, the averaged signals from CSF and white matter, and the global brain signal were regressed (Fox et al., 2005b); second, to reduce the effects of low-frequency drifts and high frequency noise, the time series were band filtered (0.01–0.08 Hz) and linearly detrended. The residual