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Decreased resting-state interhemispheric functional connectivity in unaffected siblings of schizophrenia patients

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ABSTRACT

Background: Neuroimaging studies in unaffected siblings of schizophrenia patients can provide clues to the pathophysiology for the development of schizophrenia. However, little is known about the alterations of the interhemispheric resting-state functional connectivity (FC) in siblings, although the dysconnectivity hypothesis is prevailing in schizophrenia for years. In the present study, we used a newly validated voxel-mirrored homotopic connectivity (VMHC) method to identify whether aberrant interhemispheric FC was present in unaffected siblings at increased risk of developing schizophrenia at rest.
Methods: Forty-six unaffected siblings of schizophrenia patients and 50 age-, sex-, and education-matched healthy controls underwent a resting-state functional magnetic resonance imaging (fMRI). Automated VMHC was used to analyze the data.
Results: The sibling group had lower VMHC than the control group in the angular gyrus (AG) and the lingual gyrus/cerebellum lobule VI. No region exhibited higher VMHC in the sibling group than in the control group. There was no significant sex difference of the VMHC values between male siblings and female siblings or between male controls and female controls, although evidence has been accumulated that size and shape of the corpus callosum, and functional homotopy differ between men and women.
Conclusions: Our results first suggest that interhemispheric resting-state FC of VMHC is disrupted in unaffected siblings of schizophrenia patients, and add a new clue of abnormal interhemispheric resting-state FC to the pathophysiology for the development of schizophrenia.

1. Introduction

The two human hemispheres interact with each other by the brain's commissural system, such as the corpus callosum, anterior commissure, posterior commissure, interthalamic adhesions, and cerebellar commissures (Hoptman and Davidson, 1994). Disconnection phenomena on divided sensory spatial field tasks have been observed in patients with forebrain commissures sectioned (Nebes, 1972). In addition, the split brain patients showed impaired sustained attention and other cognitive processes (Dimond, 1979a,b). Evidence has been accumulated that there is an advantage to bihemispheric processing (Belger and Banich, 1992). Relatively few behavioral data have been observed that healthy subjects exhibit an advantage to processing information presented bilaterally compared to the same amount of information presented initially to one hemisphere alone (Belger and Banich, 1992). This bilateral advantage indicates that it would be more efficient for the two hemispheres to interact than for one hemisphere to process all information.

However, the bilateral advantage seen in healthy subjects is absent in schizophrenia patients (Barnett et al., 2007). The deficit in interhemispheric interaction is reported in schizophrenia by using event related potential (ERP) method (Mohr et al., 2008) and electroencephalographic (EEG) measures (Morrison-Stewart et al., 1996), with the results of a reduction in the "bilateral redundancy gain". Focusing on the extent of callosal deficits in schizophrenia, a great number of diffusion tensor imaging (DTI) studies have observed decreased fractional anisotropy (FA) in the corpus callosum in schizophrenia (Kubicki et al., 2008; Guo et al., 2012), suggesting interhemispheric hypoconnectivity in schizophrenia patients (Knochel et al., 2012).

Recently, resting-state functional connectivity (FC), which is designed to analyze intrinsic neural activity of gray matter regions (Fox and Raichle, 2007), provides a novel approach for assessing inter- as well as intrahemispheric FC in schizophrenia. Using this method, schizophrenia patients exhibit predominantly deficits in resting-state FC (Lynall et al., 2010; Skudlarski et al., 2010), supporting the dysconnectivity hypothesis of schizophrenia (Friston, 1998). Despite the evidence of interhemispheric interaction deficits and the dysconnectivity hypothesis in schizophrenia, only a few studies make an effort to examine FC between homotopic brain regions in schizophrenia using a voxel-mirrored homotopic connectivity (VMHC) method (Hoptman et al., 2012; Guo et al., 2014). VMHC, suggested by Zuo et al. (2010), is a recently validated method to assess the resting-state FC between the time series for each voxel in one hemisphere and that of its homotopic voxel from the opposite hemisphere. This method has been well applied in clinical studies,

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including depression (Guo et al., 2013a,b; Wang et al., 2013), schizophrenia (Hoptman et al., 2012; Guo et al., 2014), autism (Anderson et al., 2010) and cocaine addiction (Kelly et al., 2011), indicating that VMHC is sensitive to abnormal interhemispheric FC in pathophysiology. The only two existing studies in schizophrenia using VMHC, including our previous study, have shown deficits in interhemispheric coordination in schizophrenia, with the results of reduced VMHC in the default-mode network (DMN), sensorimotor regions and cerebellum (Hoptman et al., 2012; Guo et al., 2014). However, no study is engaged in examining interhemispheric coordination in first-degree relatives of schizophrenia patients, including unaffected siblings.

Sharing considerable genetic backgrounds with the patients, the unaffected siblings of schizophrenia patients are at an increased genetic risk to develop the disease. Considering that schizophrenia is a highly heritable, complex psychiatric syndrome, studies on the unaffected siblings can provide insight into the pathophysiology of schizophrenia independently of the clinical and treatment issues that complicate studies of patients themselves (Jang et al., 2011).

First-degree relatives of schizophrenia patients, including unaffected siblings, exhibit various abnormalities of neuropsychological and of brain structural and functional domains that are also seen in patients (MacDonald et al., 2009; Pettersson-Yeo et al., 2011; van Buuren et al., 2011). For example, the first-degree relatives often have a pattern of cognitive deficits similar to those observed in the patients, such as deficits in set shifting, inhibition of prepotent response, and working memory (Johnstone et al., 2002; Brewer et al., 2005; Snitz et al., 2006). Brain abnormalities in neuroimaging findings, such as decreased cortical thickness in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and superior temporal gyrus, have been reported in first-degree relatives of schizophrenia patients (Goghari et al., 2007; Gogtay et al., 2007). Alterations of resting-state FC, which are predominantly disturbed in schizophrenia (Lynall et al., 2010; Skudlarski et al., 2010), have also been found in the first-degree relatives (Jang et al., 2011). Among the FC networks, the DMN dysfunction is most consistently involved in the first-degree relatives (Jang et al., 2011; van Buuren et al., 2012). However, it remains unknown whether the unaffected siblings have abnormal interhemispheric resting-state FC.

In this study, we examined the whole-brain homotopic FC in the unaffected siblings of schizophrenia patients compared to similar individuals with no family history of any mental illness using the VMHC method. Based on previous studies (Ongur et al., 2010; Camchong et al., 2011; Hoptman et al., 2012; Guo et al., 2014), we hypothesized that the unaffected siblings would have reduced VMHC, and the brain regions within the DMN and the sensorimotor areas were expected to be particularly affected.

2. Methods and materials

2.1. Subjects

Forty-six unaffected siblings of schizophrenia patients and fifty healthy controls participated in the study. The Structural Clinical Interview for DSM-IV (SCID), non-patient version (First et al., 1997) was utilized in assessing psychiatric disorders in all participants. Schizophrenia patients were evaluated with SCID, patient version (First et al., 1997), and met the DSM-IV diagnostic criteria for schizophrenia. Exclusion criteria included neurological or psychiatric disorders, severe medical disorders, substance abuse, or any contraindications for MRI. All participants were unrelated to each other and healthy controls who had a first-degree relative suffering from a psychotic disorder were excluded. All participants were right-handed and the groups were matched in age, sex ratio and education level.

The ethics committee of the First Affiliated Hospital of Guangxi Medical University approved the study. All participants gave written informed consent.

2.2. Scan acquisition

Imaging was conducted on a Siemens 3 T scanner. A prototype quadrature birdcage head coil fitted with foam padding was used to minimize head motion. Participants were instructed to lie still with their eyes closed and not to fall asleep. Afterwards, all participants indicated that they remained awake. 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 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. All subjects should have no more than 2 mm maximum displacement in x, y, or z and 2° of angular motion. Afterwards, the functional images were normalized and resampled to $3 \times 3 \times 3$ mm^3. Then the images were spatial smoothed with an 8 mm FWHM Gaussian kernel, temporally bandpass filtered (0.01–0.08 Hz) and linearly detrended to reduce the effect of low-frequency drifts and physiological high-frequency noise. Finally, linear regression was applied to remove several sources of spurious covariates along with their temporal derivatives, including six head motion parameters obtained by rigid body correction, the signal from a ventricular region of interest (ROI), and the signal from a region centered in the white matter (Fox et al., 2005). Of note, the global signal was not regressed out in the present data for the reason that it is still a controversy of removing the global signal in the preprocessing of resting-state FC data (Fox et al., 2005; Murphy et al., 2009; Saad et al., 2012).

2.4. Interhemispheric correlation

VMHC was computed with software REST (Song et al., 2011). For each subject, the homotopic resting-state FC was calculated as the Pearson correlation coefficient between each voxel's residual time series and that of its mirrored interhemispheric counterpart. The correlation coefficients were then Fisher *z*-transformed to improve the normality. The resultant values generated the VMHC maps.

Individual level VMHC maps were group compared with a voxel-wise two-sample *t*-test analysis. Significance was assessed using Gaussian Random Field (GRF) theory with a threshold of $p < 0.005$ (min $z > 2.807$, cluster significance: $p < 0.005$, corrected). Given that resting-state FC could be affected by micromotions from volume to volume (Power et al., 2012), we computed the framewise displacement (FD) values for each subject. The mean FD was applied as a covariate in the group comparisons of VMHC.

Since there was a trend towards a significant difference in the sex ratio between groups ($p = 0.09$), we further divided the groups into 4 groups, including male siblings, female siblings, male controls and female controls, and investigated whether there was sex difference in VMHC in both the siblings and the controls given strong evidence that size and shape of the corpus callosum (Scheller-Gilkey and Lewine, 1999; Panizzon et al., 2003), and functional homotopy differ between men and women (Scheller-Gilkey and Lewine, 1999). The mean FD values were also applied as a covariate in the group comparisons and the significant level was set at $p < 0.005$ (GRF corrected).

3. Results

3.1. Characteristics of the participants

The characteristics of the participants in each group were present in Table 1. There were no difference in age (*t*-test $t = -0.76$, df = 94, $p = 0.45$), sex ratio (chi-square test $x^2 = 2.80$, df = 1, $p = 0.09$),