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Decreased resting-state interhemispheric coordination in first-episode, drug-naive paranoid schizophrenia

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ABSTRACT

Background: Dysconnectivity hypothesis posits that schizophrenia relates to abnormalities in neuronal connectivity. However, little is known about the alterations of the interhemispheric resting-state functional connectivity (FC) in patients with paranoid schizophrenia. 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 paranoid schizophrenia at rest.
Methods: Forty-nine first-episode, drug-naive patients with paranoid schizophrenia and 50 age-, gender-, and education-matched healthy subjects underwent a resting-state functional magnetic resonance imaging (fMRI) scans. An automated VMHC approach was used to analyze the data.
Results: Patients exhibited lower VMHC than healthy subjects in the precuneus (PCu), the precentral gyrus, the superior temporal gyrus (STG), the middle occipital gyrus (MOG), and the fusiform gyrus/cerebellum lobule VI. No region showed greater VMHC in the patient group than in the control group. Significantly negative correlation was observed between VMHC in the precentral gyrus and the PANSS positive/total scores, and between VMHC in the STG and the PANSS positive/negative/total scores.
Conclusions: Our results suggest that interhemispheric resting-state FC of VMHC is reduced in paranoid schizophrenia with clinical implications for psychiatric symptomatology thus further contribute to the dysconnectivity hypothesis of schizophrenia.

1. Introduction

Characterized by an extensive collection of impairments, such as impairments in thought, attention, affect, and motor coordination, schizophrenia is a highly heritable, complex psychiatric syndrome with altered brain structure and function (Brown and Thompson, 2010). Evidence has been accumulated that resting-state brain function measured by functional magnetic resonance imaging (fMRI) is a sensitive marker for schizophrenia (Broyd et al., 2009), which provides a potentially important tool to explore the quantitative genetic phenotypes (Biswal et al., 2010). Resting-state functional connectivity (FC) is an interesting method because it measures the correlations between blood oxygen level dependent (BOLD) time series. Furthermore, resting-state FC is predominantly disturbed in schizophrenia (Lynall et al., 2010; Skudlarski et al., 2010), supporting the dysconnectivity hypothesis of schizophrenia (Friston, 1998). Dysconnectivity hypothesis posits that schizophrenia relates to alterations in neuronal connectivity (Stephan et al., 2009), resulting from a combination of genetic and environmental risk factors (Karlsgodt et al., 2008).

According to dysconnectivity hypothesis, there is strong evidence of altered FC in schizophrenia. For example, decreased FC between prefrontal and temporal areas was observed in patients during a working memory task (Meyer-Lindenberg et al., 2001), and FC between auditory regions was altered during an auditory oddball task (Calhoun et al., 2004). This hypothesis is further supported by evidence from structural studies. Rusch et al. (2007) reported that volumetric alterations in specific brain regions, including the dorsal prefrontal cortex, anterior cingulate cortex (ACC), right parahippocampal gyrus, thalamus, cerebellum, and pons are associated with executive dysfunction in schizophrenia.

Recent models have proposed that schizophrenia symptoms may be related to aberrant FC of multiple functional networks. Early studies have focused on one of the resting-state networks, the "default-mode network" (DMN) (Raichle et al., 2001), and indicated DMN dysconnectivity occurs

Abbreviations: fMRI, functional magnetic resonance imaging; FC, functional connectivity; BOLD, blood oxygen level-dependent; ACC, anterior cingulate cortex; DMN, default mode network; R-fMRI, resting-state fMRI; VMHC, voxel-mirrored homotopic connectivity; SCID, Structured Clinical Interview of the DSM-IV; DUP, duration of untreated psychosis; PANSS, Positive and Negative Symptom Scale; TR/TE, repetition time/echo time; FOV, field of view; ROI, region of interest; GRF, Gaussian Random Field; FD, framewise displacement; PCu, precuneus; STG, superior temporal gyrus; MOG, middle occipital gyrus; MNI, Montreal Neurological Institute.

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within the DMN in schizophrenia (Camchong et al., 2011; Ongur et al., 2010). Garrity et al. (2007) observed that the severity of positive symptoms in schizophrenia correlated positively with FC in posterior cingulate and middle temporal regions. In healthy subjects, the DMN shows enhanced baseline activity (Gusnard and Raichle, 2001), and is involved actively in self-referential mental activity (Gusnard et al., 2001) and social cognition (Schilbach et al., 2008). In addition to the DMN, recent studies have shown network dysconnectivity within the frontoparietal network (MacDonald et al., 2005), which can be associated with working memory impairments (Linden, 2007).

Furthermore, an interesting phenomenon is noticed that schizophrenia is related to abnormal functional lateralization in the frontal, temporal, parietal, and occipital areas (Barnett and Kirk, 2005; Bertolino et al., 2004). An increasing number of studies indicate that schizophrenia may be associated with an alteration in the development of left hemisphere dominance for language (Artiges et al., 2000; Dollfus et al., 2005). Reversed hemispheric asymmetry has been reported during the processing of sensory information in schizophrenia (Heckers et al., 2002). Bilateral functional asymmetry disparity has also been revealed in positive and negative schizophrenia (Ke et al., 2010). Given that laterally presented cognitive tasks in healthy subjects indicate an advantage to bihemispheric processing (Belger and Banich, 1992), abnormal functional lateralization could interfere with interhemispheric interaction in schizophrenia. It would not be surprising if interhemispheric interaction deficits played a key role in the pathophysiology of schizophrenia. Therefore, it would be meaningful to examine the interhemispheric coordination in schizophrenia.

Resting-state fMRI (R-fMRI), which represents the patterns of coherent spontaneous fluctuations of BOLD signals, offers a novel approach for examining the interhemispheric interaction (Wang et al., 2013). Functional homotopy, a basic principle of the brain's intrinsic functional architecture (Salvador et al., 2005), is defined as the high degree of synchrony in spontaneous activity between geometrically corresponding interhemispheric regions. As a conspicuous feature of the brain functional architecture, homotopic resting-state FC may provide a sensitive parameter of the schizophrenia-related alterations.

Here, we directly examined homotopic resting-state FC in patients with first-episode, drug-naive paranoid schizophrenia using a recently validated approach, voxel-mirrored homotopic connectivity (VMHC) (Zuo et al., 2010). VMHC quantified the resting-state FC between each voxel in one hemisphere and its mirrored voxel in the opposite hemisphere. This method has been well conducted in depression by our group recently (Guo et al., 2013a, 2013b). By using VMHC, decreased interhemispheric coordination in sensorimotor regions has been demonstrated in schizophrenia and schizoaffective disorder (Hoptman et al., 2012). However, the findings from schizophrenia and schizoaffective disorder in their study may not be generalized to patients with schizophrenia. Also, the effect of medication could not be ignored in their study. To minimize the effect of such confounding factors, only first-episode, drug-naive patients with paranoid schizophrenia were recruited in the present study. Given the extensive evidence of functional disconnections and functional asymmetry disparity in schizophrenia, we hypothesized that the patients would have reduced VMHC. Based on previous studies (Camchong et al., 2011; Hoptman et al., 2012; Ongur et al., 2010), the brain regions within the DMN and the sensorimotor regions were expected to be particularly affected. We also explored whether VMHC was related to clinical characteristics in the patients.

2. Methods and materials

2.1. Subjects

Forty-nine right-handed, young adults with schizophrenia were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. To limit the heterogeneity of symptom manifestations and potentially underlying pathology, only patients who met diagnostic criteria for paranoid schizophrenia according to the DSM-IV were included in the study. Patients were evaluated by the Structured Clinical Interview of the DSM-IV (SCID) (First et al., 1997). Exclusion criteria included neurological disorders, severe medical disorders, substance abuse, or electroconvulsive therapy. The patients were at their first episode and drug-naive. The duration of untreated psychosis (DUP) for the patients was less than 3 years. Current psychopathology was assessed using the Positive and Negative Symptom Scale (PANSS) at the scan time. The patients were successfully followed after the scan for a minimum of 6 months and confirmed the diagnosis of paranoid schizophrenia.

Fifty right-handed healthy subjects were recruited from the community. None of them had a history of severe medical or neuropsychiatric illness or a family history of severe medical or neuropsychiatric illness in their first-degree relatives, and all were matched with the patient group in age, gender and education level.

The local ethics committee of the First Affiliated Hospital of Guangxi Medical University approved the study. Written informed consent was obtained from all participants.

2.2. Scan acquisition

Scans were performed on a 3.0 T MRI scanner (Siemens Magnetom, Trio Tim). To minimize head movement, a prototype quadrature birdcage head coil fitted with foam padding was used. Participants were instructed to lie motionless, keep their eyes closed, and remain awake. 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 slice thickness, 0.4 mm gap, and 250 volumes. For each subject, the fMRI scanning lasted 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). Functional images were corrected for slice timing and head motion. Participants were examined with no more than 2 mm maximum displacement in x, y, or z and 2° of angular motion. Then the images were normalized and resampled to $3 \times 3 \times 3$ mm^3. The generated images were processed using spatial smoothing with an 8 mm FWHM Gaussian kernel, temporally bandpass filtering (0.01–0.08 Hz) and linearly detrended removal. Several sources of spurious covariates along with their temporal derivatives were then removed from the data by using linear regression, 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, it is controversial to remove the global signal in the preprocessed resting-state FC data (Fox et al., 2005; Murphy et al., 2009; Saad et al., 2012). Thus, the global signal was not regressed out in the present study. Finally, the residual time series for each participant was registered to a symmetric Montreal Neurological Institute (MNI) template and was utilized to calculate the homotopic resting-state FC.

2.4. Interhemispheric correlation

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