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Increased short-range and long-range functional connectivity in first-episode, medication-naive schizophrenia at rest

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ABSTRACT

Objective: Schizophrenia is conceived as a disconnection syndrome and anatomical distance may affect functional connectivity (FC) in schizophrenia patients. However, whether and how anatomical distance affects FC remains unclear in first-episode, medication-naive schizophrenia at rest.
Methods: Forty-nine schizophrenia patients and 50 age-, sex-, and education-matched healthy controls underwent resting-state functional magnetic resonance imaging scanning. Regional FC strength was computed for each voxel in the brain, which was further divided into short-range and long-range FC strength.
Results: The patients exhibited increased short-range positive FC strength in the left superior medial frontal gyrus, and increased long-range positive FC strength in the right angular gyrus and bilateral posterior cingulate cortex (PCC)/precuneus compared with the controls. Further seed-based FC analysis showed that the left superior medial frontal gyrus had increased short-range FC with the right inferior frontal gyrus, while the right angular gyrus and bilateral PCC/precuneus had increased long-range FC with the prefrontal gyrus. No significant correlation was observed between abnormal FC strength and clinical variables in the patient group.
Conclusions: The findings reveal a pattern of increased anatomical distance affecting FC in the patients, with the results of increased short-range positive FC strength in the anterior default-mode network (DMN) and increased long-range positive FC strength in the posterior DMN in schizophrenia, and highlight the importance of the DMN in the neurobiology of schizophrenia.

1. Introduction

Schizophrenia is a complex mental disorder of unclear etiology, with significant heterogeneity of clinical and pathophysiological features (Silveira et al., 2012). A bulk of studies have indicated that the failure of functional connectivity (FC) among brain regions can attribute to schizophrenia symptoms, which support the critical role of dysconnectivity in the neurobiology of schizophrenia (Friston, 1999). For example, a systematical review on the resting-state functional magnetic resonance imaging (fMRI) of schizophrenia has observed decreased FC in both first-episode and chronic schizophrenia, including decreased FC between the frontal gyrus, fronto-temporal gyrus, anterior cingulate cortex (ACC), and other cortical and subcortical areas (Pettersson-Yeo et al., 2011). Furthermore, decreased FC has been reported to be associated with both symptoms (e.g., auditory hallucinations) and cognitive deficits (e.g., working memory) (Lawrie et al., 2002; Meyer-Lindenberg et al., 2005).

Studies focused on the disconnection hypothesis of schizophrenia suggest that abnormality in the function of a single brain region cannot explain the widespread range of deficits seen in this disease (Minzenberg et al., 2009; Ragland et al., 2009). As such, researchers have focused on brain network to understand the sensory, emotional, and cognitive process (Calhoun et al., 2009). One of the consistently examined brain network in schizophrenia is the default-mode network (DMN) (Guo et al., 2014c). The DMN includes the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC)/precuneus, and lateral parietal cortices (Raichle et al., 2001), and recently extends to include the lateral temporal gyrus (Sheline et al., 2009; Guo et al., 2014b) and the cerebellum Crus I and Crus II (Habas et al., 2009; Krienen and Buckner, 2009).

Abnormal DMN connectivity has been repeatedly reported in schizophrenia with mixed results. For example, Whitfield-Gabrieli et al. (2009) observed increased DMN connectivity in schizophrenia patients and their first-degree relatives. Consistent with this study, a number of studies reported DMN hyperconnectivity in schizophrenia (Zhou et al., 2007; Mannell et al., 2010; Salvador et al., 2010; Skudlarski et al., 2010). In contrast, other studies reported either decreased DMN connectivity in schizophrenia (Bluhm et al., 2007; Rotarska-Jagiela et al.,

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2010; Camchong et al., 2011; Jang et al., 2011) or mixed findings of increased and decreased DMN connectivity (Ongur et al., 2010; Mingoia et al., 2012; Guo et al., 2014c). In addition to such factors as different sample size, scanners, and analysis methods, sample heterogeneity may account for the inconsistency of the DMN findings in schizophrenia (Guo et al., 2014c). The participants of most previous studies are chronic and medicated patients (Whitfield-Gabrieli et al., 2009; Wolf et al., 2011), and only a few recruited first-episode, treatment-naive patients (Lui et al., 2009; Guo et al., 2014c). Medication use and long illness duration can confound the fMRI results in schizophrenia (Honea et al., 2005; Cronenwett and Csernansky, 2010; Levitt et al., 2010). Exposure to medication is an important confounding factor for fMRI studies (Davis et al., 2005; Pettersson-Yeo et al., 2011). Moreover, schizophrenia is a progressive mental disorder, and prolonged illness duration has a neurotoxic effect on brain function (Marshall et al., 2005; Perkins et al., 2005). Therefore, it is meaningful to choose first-episode, medication-naive schizophrenia as a starting point for fMRI studies to avoid some important confounders such as medication use and long illness duration, and to provide the naive connectivity information to the neurobiology of schizophrenia.

A well-organized human brain depends on both short-range and long-range FC. Long-range FC operates at a higher time- and metabolic-cost (Bullmore and Sporns, 2012; Liang et al., 2013). By contrast, short-range FC operates at a lower time- and metabolic-cost and predominates with increased FC strength (Salvador et al., 2005). However, a well-organized brain will not penalize all long-range FC that will lead to inefficient communication (Vertes et al., 2012). The brain will be beneficial from the preferential long-range FC for information transfer (Sepulcre et al., 2010). Recent evidence shows that anatomical distance can affect FC in schizophrenia patients and their siblings (Guo et al., 2014a; Wang et al., 2014). Guo et al. (2014a) reported a disproportionate reduction in the number of long-range connections in medicated schizophrenia, affecting the subcortical, interhemispheric, and the salience network connections. Wang et al. (2014) observed reduced short-range and long-range FC in minimally treated chronic schizophrenia. Both studies provide important information of disrupted short-range and long-range FCs in schizophrenia. However, it is unclear to what extent the findings of these two studies are due to medication use or long illness duration, and whether and how the short-range and long-range FCs are disturbed in a more representative sample of first-episode, medication-naive schizophrenia patients remains unknown.

Here, we constructed whole-brain FCs by assessing temporal correlations of each pair of brain voxels in a relatively large sample of first-episode, medication-naive schizophrenia patients to limit the effect of such potential confounding factors as medication use, long illness duration and small sample size. Specifically, we divided the connections into short-range and long-range FCs according to their anatomical distance (Achard et al., 2006; He et al., 2007). We hypothesized that both short-range and long-range FCs were reduced in patients based on the general issue that FCs were decreased overall in schizophrenia (Karlsgodt et al., 2008), and that schizophrenia patients showed decreased short-range and long-range FCs (Guo et al., 2014a; Wang et al., 2014), particularly in the FCs within the DMN which was one of the most examined networks (Whitfield-Gabrieli et al., 2009; Guo et al., 2014c). Finally, we examined the correlations between FC strength (FCS) and clinical variables.

2. Materials and methods

2.1. Participants

Fifty-six right-handed schizophrenia patients were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. The clinical diagnosis was made by the consensus of two experienced psychiatrists using the Structural Clinical Interview for DSM-IV (SCID), patient version (First et al., 1997). The patients with other Axis-I or Axis-II comorbidity disorders were excluded. To minimize the heterogeneity of symptom manifestations and potentially underlying pathophysiology, only patients who met diagnostic criteria for paranoid schizophrenia according to DSM-IV were enrolled in this study. The patients aged from 16 to 30 years and obtained more than 9 years of formal education. All patients were at their first episode and medication naive. The duration of untreated psychosis (DUP) of the patients was less than 3 years. Clinical symptoms were rated by Positive and Negative Symptom Scale (PANSS) at the scan time. All patients had no history of other major psychiatric disorders, neurological disorders, severe medical disorders, and substance abuse.

Fifty-four right-handed healthy controls were recruited from the community. They were screened with SCID, nonpatient version (First et al., 1997) and were chose to match the patient group for sex, age, and educational level. The age of the controls ranged from 16 to 30 years and obtained more than 9 years of formal education. None of the controls had any diagnosis of psychiatric disorders, neurological disorders, severe medical disorders, or substance abuse. The controls who had a first-degree relative with a history of any psychiatric disorders were also excluded.

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

2.2. Imaging acquisition

Imaging was acquired on a Siemens 3 T scanner. Each participant was instructed to remain awake and close their eyes while lying quietly. A resting-state fMRI scan was performed using a gradient-echo echo-planar imaging (EPI) sequence with the following parameters: 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 using Data Processing Assistant for Resting-State fMRI (Yan and Zang, 2010) in Matlab (Mathworks). Briefly, the imaging data were corrected for within-scan acquisition time differences among slices and realigned to the first volume to correct for head movement. Participants with more than 2 mm of maximal translation of x, y, or z and 2° of maximal rotation were excluded from the analyses (4 patients and 3 controls). The obtained data were spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to $3 \times 3 \times 3$ mm^3. The images were subsequently smoothed with an 8 mm full width at half maximum Gaussian kernel, bandpass filtered (0.01 - 0.08 Hz), and linearly detrended. Several nuisance signals, along with their temporal derivatives, including six head motion parameters obtained by rigid body correction, the signal from a ventricular ROI, and the signal from a region centered in white matter, were regressed out from the data (Fox et al., 2005; Liu et al., 2015). However, the global mean signal was not regressed out for the reason that it is suggested to be saved in analyzing the FC data (Hahamy et al., 2014).

2.4. Short-range and long-range FCS analysis

Whole-brain resting-state FC analysis was performed on the preprocessed data. Pearson's correlation coefficients were computed between the time series of all pairs of gray matter voxels within a gray matter mask, and a whole-brain FC matrix was obtained for each participant (Liu et al., 2014). Individual correlation matrices were then transformed into a z-score matrix using Fisher z-transformation to improve normality. The regional FCS of a voxel was computed as the sum of the connections (z values) between a given voxel and all other voxels. To examine the effects of anatomical distance on FC analysis, we divided