Abnormal default-mode network homogeneity in first-episode, drug-naive schizophrenia at rest

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ABSTRACT

Background: Dysconnectivity hypothesis posits that schizophrenia relates to abnormal resting-state connectivity within the default-mode network (DMN) and this aberrant connectivity is considered as contribution of difficulties in self-referential and introspective processing. However, little is known about the alterations of the network homogeneity (NH) of the DMN in schizophrenia. In the present study, we used an automatic NH method to investigate the NH of the DMN in schizophrenia patients at rest.
Methods: Forty-nine first-episode, drug-naive schizophrenia patients and 50 age-, gender-, and education-matched healthy controls underwent a resting-state functional magnetic resonance imaging (fMRI). An automated NH approach was used to analyze the data.
Results: Patients exhibited lower NH than controls in the left medial prefrontal cortex (MPFC) and the right middle temporal gyrus (MTG). Significantly higher NH values in the left posterior cingulate cortex (PCC) and the right cerebellum Crus I were found in the patient group than in the control group. No significant correlation was found between abnormal NH values and Positive and Negative Symptom Scale (PANSS) scores, duration of untreated psychosis (DUP), age or years of education in the patient group.
Conclusions: Our findings suggest that abnormal NH of the DMN exists in first-episode, drug-naive schizophrenia and further highlight the importance of the DMN in the pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is a devastating psychiatric syndrome affecting about one percent of the population worldwide. This chronic illness is characterized by symptoms of the false attribution of perceptual experience to an external stimulus (hallucinations), distorted thought (delusions), reduction in emotion and motivated behavior (negative symptoms), and deficits in cognition and social functioning (Picchioni and Murray, 2007). Effort has been made to elucidate its neural correlates by advanced imaging techniques, such as functional magnetic resonance imaging (fMRI).

Recent evidence suggests that resting-state brain function measured by fMRI is a potentially important tool for the discovery of sensitive markers of the disorder (Broyd et al., 2009). Dysconnectivity hypothesis

of schizophrenia postulates that the disease relates to alterations in neuronal connectivity (Stephan et al., 2009). Resting-state functional connectivity (FC) is profoundly disturbed in schizophrenia (Lynall et al., 2010; Skudlarski et al., 2010), providing a support for the dysconnectivity hypothesis.

Spontaneous neural activity, inferred by resting-state FC, correlates across brain regions and is organized into spatially segregated FC networks (Fox et al., 2005). Among these networks, a consistently examined network is the default-mode network (DMN), which includes the medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC/PCu), and the lateral posterior cortices (Raichle et al., 2001). The DMN routinely shows decreased activity during task-related cognitive process and is regarded as underlying the construction of complex self-referential stimuli, such as mental time travel, perspective taking and theory of mind (Buckner and Carroll, 2007; Molnar-Szakacs and Arzy, 2009). Evidence has been accumulated that the DMN is abnormal in schizophrenia, but the findings are mixed: connectivity increase (Mannell et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009; Zhou et al., 2007), connectivity decrease (Bluhm et al., 2007; Camchong et al., 2011; Jang et al., 2011; Rotarska-Jagiela et al., 2010), or both (Mingoia et al., 2012; Ongur et al., 2010). One study reported no significant difference between patients and controls (Wolf et al., 2011). The mixed findings may be attributed to many factors, including differences in studied populations, sample size, approaches of data analysis, statistical methods, and the potential effects of medication. In the

present study, we recruited patients only with first-episode, drug-naive schizophrenia to reduce such confounds as medication and number of recurrence. In particular, the mixed findings are revealed by an FC method focusing on the correlations of two brain regions. It is unclear which brain region is abnormal when two regions exhibit abnormal FC, although this method offers important information. Some aspects of the intrinsic network organization in the DMN might have been long overlooked. Therefore, the advent of new methods for analyzing imaging data is urgently required.

Network homogeneity (NH), a method suggested by Uddin et al. (2008), is one potential informative approach that would be to offer an unbiased survey of a distributed network of interest, looking for brain regions showing disease-related reduction in network coherence. NH is a voxel-wise measure that provides an assessment of a voxel's correlation with all other voxels within a given network. The mean correlation of a given voxel is defined as the homogeneity. Alternatively, two methods, independent component analysis (ICA) and seed-based region of interest (ROI), are the most widely employed to analyze the resting-state brain networks previously. ICA is a model-free method with the power to assess largely overlapping spatial process. Although ICA has the power to estimate largely overlapping spatial process, it is not clear how best to compare components across subjects and/or between groups (Fox and Raichle, 2007). The seed-based ROI method is utilized to determine the temporal coherence between the timeseries for a given ROI and the timeseries of all other voxels in the brain by using correlation or regression analysis (Biswal et al., 1995). However, the selection and precise placement of ROI seeds can be somewhat arbitrary, and thus have considerable impact on the patterns of FC obtained. In contrast to these two methods, the NH method enables hypothesis-driven interrogation of large-range networks of clinical interest from the viewpoint of assessing the homogeneity of the whole network and therefore combines the advantages of the two previous methods (Uddin et al., 2008). Furthermore, NH is well applied in attention-deficit/hyperactivity disorder (ADHD) (Uddin et al., 2008).

In the present study, NH was utilized to analyze the data from patients with first-episode, drug-naive schizophrenia. Based on previous FC findings of the DMN abnormalities in schizophrenia (Bluhm et al., 2007; Camchong et al., 2011; Jang et al., 2011; Mannell et al., 2010; Mingoia et al., 2012; Ongur et al., 2010; Rotarska-Jagiela et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009; Zhou et al., 2007), we hypothesized that abnormal DMN homogeneity would be observed in the patients compared to the controls. We also explored whether abnormal NH was associated with clinical characteristics in the patients.

2. Methods and materials

2.1. Subjects

Forty-nine young adults with schizophrenia were recruited from the Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. The subjects were from our previous study (Guo et al., 2014). The patients were right-handed, drug-naive, and at their first episode. The duration of untreated psychosis (DUP) for the patients was less than 3 years. Patients were assessed with the Structured Clinical Interview of the DSM-IV (SCID) (First et al., 1997). To reduce 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, although this subtype is not used in the new DSM-V classification system. Exclusion criteria were neurological disorders, severe medical disorders, substance abuse, or electroconvulsive therapy. The symptoms were rated by the Positive and Negative Symptom Scale (PANSS) at the scan time.

Fifty right-handed healthy controls 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. The controls were group matched with the patients in age, sex and educational level.

All subjects gave their written informed consent to participate in the study. The local ethics committee of the First Affiliated Hospital of Guangxi Medical University approved the study.

2.2. Scan acquisition

Imaging was obtained on a Siemens 3 T scanner. Subjects were required to lie still, keep their eyes closed, and remain awake. A prototype quadrature birdcage head coil fitted with foam padding was utilized to limit head motion. 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 (500 s).

2.3. Data preprocessing

Data preprocessing was conducted in Matlab (Mathworks) using Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang, 2010). After the correction 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. Then the images were normalized and resampled to $3 \times 3 \times 3$ mm³. Afterwards, the generated images were temporally bandpass filtered (0.01–0.08 Hz) and linearly detrended.

2.4. DMN identification

As suggested by two recent studies (Guo et al., 2013b; Liu et al., 2012), the group ICA method was implemented to pick out the DMN as a mask from healthy controls. Three main steps, including data reduction, independent component (IC) separation, and back reconstruction, were conducted with the toolbox GIFT (http://mialab.mrn.org/software/#gica). The DMN was selected according to the templates provided by GIFT, which was used as a mask in the following NH analysis.

2.5. NH analysis

NH analysis was performed in Matlab (Mathworks). For each subject, the correlation coefficients were calculated in a given voxel with all other voxels within the DMN mask. The mean correlation coefficient was defined as the homogeneity of the given voxel. The resultant values generated the NH maps, which were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. Finally, the NH maps within the DMN mask were applied for group comparison.

2.6. Statistical analyses

Demographics including age, sex and educational level and imaging data were compared between the patients and the controls. Categorical data were analyzed with Chi-square test and continuous variables were analyzed with two-sample t-test. The NH analysis was implemented with two-sample t-tests via voxel-wise cross-subject statistics in the DMN. The significant level was set at the corrected $p < 0.05$ for multiple comparisons using Gaussian Random Field (GRF) theory (min $z > 1.96$, cluster significance: $p < 0.05$).

In addition, brain regions with abnormal NH were identified as ROIs. Mean NH values of these ROIs were extracted for further correlation analysis between these NH values and the PANSS scores or the DUP in the patient group ($p < 0.05$).