Psychiatry Research: Neuroimaging 224 (2014) 218–224

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Decreased default-mode network homogeneity in unaffected siblings of schizophrenia patients at rest

Wenbin Guo [a,*], Feng Liu [b], Dapeng Yao [a], Jiajing Jiang [a], Qinji Su [a], Zhikun Zhang [a], Jian Zhang [a], Liuyu Yu [a], Jinguo Zhai [c], Changqing Xiao [a]

[a] Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, Guangxi, Nanning 530021, China
[b] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan, China
[c] School of Mental Health, Jining Medical University, Shandong, Jining 272067, China

ARTICLE INFO

Article history:
Received 4 October 2013
Received in revised form
3 August 2014
Accepted 24 August 2014
Available online 1 September 2014

Keywords:
Unaffected siblings
Schizophrenia
Network homogeneity
Independent component analysis
Default mode network

ABSTRACT

The dysconnectivity hypothesis proposes that abnormal resting state connectivity within the default-mode network (DMN) plays a key role in schizophrenia. Little is known, however, about alterations of the network homogeneity (NH) of the DMN in unaffected siblings of patients with schizophrenia. Unaffected siblings have unique advantages as subjects of neuroimaging studies independent of the clinical and treatment issues that complicate studies of the patients themselves. In the present study, we investigated NH of the DMN in unaffected siblings of schizophrenia. Participants comprised 46 unaffected siblings of schizophrenia patients and 50 age-, sex-, and education-matched healthy controls who underwent resting state functional magnetic resonance imaging (fMRI). Automated NH and group independent component analysis (ICA) approaches were used to analyze the data. Compared with healthy controls, the unaffected siblings of schizophrenia patients showed decreased DMN homogeneity in the left precuneus. No significantly increased DMN homogeneity was found in the sibling group relative to the control group. Our results suggest that there is decreased NH of the DMN in unaffected siblings of schizophrenia patients and indicate that the alternative perspective of examining the DMN NH in patients' siblings may improve understanding of the nature of schizophrenia.

1. Introduction

A well-known brain network that consistently exhibits coherent intrinsic activity in healthy subjects is the default-mode network (DMN), which includes the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC)/precuneus, and lateral posterior cortices (Raichle et al., 2001). The DMN is implicated in the construction of complex self-referential problems and in negative ruminations. In recent years, the DMN has been extended to include the lateral temporal gyrus (Sheline et al., 2009; Liu et al., 2013). The cerebellar regions have been suggested to "belong" to the dorsal executive, salience, DMN, and sensorimotor networks, respectively (Habas et al., 2009; Krienen and Buckner, 2009; Alalade et al., 2011; Liu et al., 2012b; Guo et al., 2013). Among these regions, the cerebellum Crus I and Crus II were observed to show functional connectivity (FC) with the DMN regions (Habas et al., 2009; Krienen and Buckner, 2009).

Studies in schizophrenia patients have repeatedly reported abnormal resting state connectivity within the DMN, but the results are mixed, with findings of connectivity increases (Zhou et al., 2007; Whitfield-Gabrieli et al., 2009; Mannell et al., 2010; Skudlarski et al., 2010), connectivity decreases (Bluhm et al., 2007; Rotarska-Jagiela et al., 2010; Camchong et al., 2011; Jang et al., 2011), or both (Ongur et al., 2010; Mingoia et al., 2012). One recent study even reported no significant difference between patients and controls (Wolf et al., 2011). There are at least two issues that may account for the discrepancies of the DMN findings in schizophrenia. First, most of the previous studies recruited chronic, medicated patients as their studied populations (e.g., Whitfield-Gabrieli et al., 2009; Wolf et al., 2011), and only a few included first-episode, drug-naive patients (e.g., Lui et al., 2009; Guo et al., 2014d). Findings from schizophrenia patients are often associated with potential confounders, such as medication use, long illness duration and small sample size (Honea et al., 2005; Cronenwett and Csernansky, 2010; Levitt et al., 2010). Schizophrenia has been believed to be a progressive brain disorder (Chan et al., 2011; Asami et al., 2012), and prolonged illness duration appears to have a neurotoxic effect on brain structure and function (Marshall et al., 2005; Perkins et al., 2005). Moreover, exposure to medication

* Corresponding author. Tel.: +86 771 3277200.
E-mail address: guowenbin76@163.com (W. Guo).

http://dx.doi.org/10.1016/j.pscychresns.2014.08.014
0925-4927/

seems to confound significantly the brain structural and functional results in schizophrenia (Lui et al., 2010). It remains unclear to what extent observed progressive deficits may be due to medication use (Zipursky et al., 2013). Unaffected siblings, who share similar genetic and environmental backgrounds with the patients, have an approximately eight-fold higher risk to develop schizophrenia than would be expected in the general population (Picchioni and Murray, 2007). Furthermore, first degree relatives of schizophrenia patients have been reported to show abnormalities in neuropsychological and structural/functional brain domains that are similar to those found in patients (Vink et al., 2006; MacDonald et al., 2009; Mechri et al., 2010; Pettersson-Yeo et al., 2011; van Buuren et al., 2011; Zandbelt et al., 2011; de Leeuw et al., 2013). For example, Jang et al. (2011) observed connectivity abnormalities of the prefrontal regions within the DMN in subjects with a high genetic loading for schizophrenia; the observed abnormalities theoretically reflect psychopathology, such as an inability to allocate resources properly between internal thoughts and external stimuli. Hence, studies on unaffected siblings may have the advantage of assessing brain function before these at-risk individuals can be affected by potential confounders, such as long illness duration and medication use.

Two methods, independent component analysis (ICA) and seed-based regions of interest (ROIs), have been used to assess resting brain networks in functional magnetic resonance imaging (fMRI) studies. ICA is a model-free approach with the power to estimate largely overlapping spatial processes. It is unclear, however, how best to compare components across subjects and/or between groups with this approach (Fox and Raichle, 2007). Seed-based ROI methods are applied to determine the temporal coherence between the time series for a given voxel or ROI and the time series of all other voxels in the brain (Biswal et al., 1995). This method is limited by the requirement to select an a priori ROI that may be somewhat arbitrary. For instance, three studies in the first degree relatives of schizophrenia patients reported reduced connectivity within the PCC (Jang et al., 2011) or no abnormal connectivity within the midline regions of the DMN by using different seeds (Repovs et al., 2011; Liu et al., 2012c). Clearly, the selection of different ROIs, based on different hypotheses, may lead to different results in studies of first degree relatives. Hence, the development of other unbiased approaches to analyze imaging data is urgently needed.

Here, we employed a network homogeneity (NH) method (Uddin et al., 2008) to analyze resting state data in unaffected siblings of schizophrenia patients, an approach that provides an unbiased way to investigate a given network without the requirement to specify in advance where the network abnormalities might be located. The NH method is designed to assess the homogeneity of the whole network, an aspect of intrinsic network organization that has been long overlooked. NH is a voxel-wise measure of a voxel's correlation with all other voxels within a given network. The mean correlation of a given voxel is defined as the NH value of this voxel. Clinically, the NH method has been used in attention-deficit/hyperactivity disorder (ADHD) (Uddin et al., 2008), schizophrenia (Guo et al., 2014d), and depression (Guo et al., 2014b). It provides an alternative approach for assessing the homogeneity of specific network (here, homogeneity is defined as the similarity of the time series of a given voxel to those of the other voxels of the specific network), and offers an unbiased survey of the DMN. Previously, we examined voxel-mirrored homotopic connectivity in the present sibling sample with the results of decreased interhemispheric connectivity in the angular gyrus, although the examination of the DMN was not the primary goal of that study (Guo et al., 2014a). Based on our previous findings (Guo et al., 2014a, 2014c) and studies of DMN abnormalities in the first degree relatives of schizophrenia patients (Jang et al., 2011; van Buuren et al., 2012), we hypothesized that reduced DMN homogeneity would be observed in the unaffected siblings of schizophrenia patients relative to the controls.

2. Methods

2.1. Subjects

Participants comprised 46 unaffected siblings of schizophrenia patients and 50 healthy controls. All were right-handed and group-matched in age, sex and educational level. They were assessed with the Structured Clinical Interview for DSM-IV (SCID), non-patient version (First et al., 1997). Exclusion criteria were neurological or psychiatric disorders, severe medical disorders, substance abuse, or any contraindications for MRI. All subjects were unrelated to each other, and healthy controls that had a first-degree relative suffering from a psychotic disorder were excluded.

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

2.2. Scan acquisition

Scanning was conducted on a Siemens 3-T scanner. Participants were instructed to lie still with their eyes closed and remain awake. A prototype quadrature birdcage head coil fitted with foam padding was applied 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 field of view, 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 Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang, 2010). For each subject, the 250 volumes were realigned to the first image to correct head motion and a mean functional image was correspondingly obtained. All subjects had less than 2 mm of translation in x, y, or z and 2° of rotation in each axis. Then the images were normalized and resampled to $3 \times 3 \times 3$ mm^3. The generated images were temporally band-pass-filtered (0.01–0.08 Hz) and linearly detrended to reduce the effect of low-frequency drifts and physiological high-frequency noise.

2.4. DMN identification

The group ICA method was performed for each of the 46 siblings and 50 controls as described in a previous study (Liu et al., 2012a). The analyses included three steps using the toolbox GIFT (http://mialab.mrn.org/software/#gica): data reduction, independent component (IC) separation, and back reconstruction. The DMN components were picked out for each group according to the templates provided by GIFT (Raichle et al., 2001; Sheline et al., 2009). Then the DMN components were overlaid to produce a DMN mask in the following NH analysis.

2.5. NH analysis

NH analysis was conducted in Matlab (Mathworks). For each subject, the correlation coefficients were obtained in a given voxel with all other voxels within the DMN mask. The mean coefficient of the given voxel was defined as the homogeneity of this voxel, and then converted to z values by using z-transformation to improve the normal distribution as described in a previous study (Buckner et al., 2009). The resultant z values generated the NH maps, which were smoothed with a Gaussian kernel of 8-mm full-width at half-maximum. Afterwards, the NH maps were used for further analyses.

2.6. Statistical analysis

Demographic information, including age, sex and educational level, and imaging data were calculated between the siblings and the controls. Categorical data were compared with the Chi-square test and continuous variables were compared with the two-sample t-test. To test for regional group differences in NH, individual-level NH maps were entered into a group-level voxelwise t-test analysis using one-sample t-tests. Then, the NH maps were analyzed with two-sample t-tests via voxel-wise cross-subject statistics within the DMN mask. The significance level was set at corrected $p < 0.01$ corrected for multiple comparisons using Gaussian Random Field (GRF) theory (min $z > 2.5758$, cluster significance: $p < 0.01$).