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Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI

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Abstract

The known regional abnormality of the dorsolateral prefrontal cortex (DLPFC) and its role in various neural circuits in schizophrenia has given prominence to its importance in studies on the dysconnection associated with schizophrenia. Abnormal functional connectivities of the DLPFC have been found during various goal-directed tasks; however, the occurrence of the abnormality during rest in patients with schizophrenia has rarely been reported. In the present study, we selected bilateral Brodmann's area 46 as region of interest and analyzed the differences in the DLPFC functional connectivity pattern between 17 patients with first-episode schizophrenia (FES) and 17 matched controls using resting-state fMRI. We found that the bilateral DLPFC showed reduced functional connectivities to the parietal lobe, posterior cingulate cortex, thalamus and striatum in FES patients. We also found enhanced functional connectivity between the left DLPFC and the left mid-posterior temporal lobe and the paralimbic regions in FES patients. Our results suggest that functional dysconnectivity associated with the DLPFC exists in schizophrenia during rest. This may be partially related to disturbance in the intrinsic brain activity.

Keywords: Schizophrenia; fMRI; Dorsolateral prefrontal cortex; Connectivity; Resting state

Schizophrenia is increasingly considered as a disorder of improper functional integration of neural systems, i.e., dysconnection [12,30]. The symptoms of schizophrenia are thought not to be due to a single, regionally specific pathophysiology, but rather to result from abnormal interactions between two or more regions [12]. Based on this opinion, the functional connection of the dorsolateral prefrontal cortex (DLPFC) should be especially emphasized, considering its local abnormalities in anatomy and function [4] and its role in various neural circuits relevant to the anatomical and physiological mechanisms of cognitive dysfunction in schizophrenia [8]. Abundant evidence from functional imaging while engaged in tasks has found dysfunctional connectivities between the DLPFC and widely distributed brain regions, including the temporal lobe [29,30], parietal lobe [17], hippocampal formation [23], thalamus and cerebellum [27].

Recently, brain functional activity and connectivity during rest have increasingly been emphasized, and some investigators even think that the resting brain functional activity may be at least as important as the activity evoked by tasks [26]. During rest, the brain has been suggested to exhibit a functional architecture that includes both "task-negative" and "task-positive" networks [10]. The study of resting-state brain function is especially applicable to the study of schizophrenia because of the practical advantages of resting-state fMRI in terms of ease of clinical application. This includes advantages such as the fact that resting-state fMRI is non-invasive and easy to perform without any complicated task design, and thus can be readily accepted by psychiatric patients including those with schizophrenia. In addition, the mental activity occurring during rest is thought to be possibly relevant to the phenomenology of schizophrenia [21].

Abnormal resting activities of the prefrontal lobe, including the DLPFC, have been observed in schizophrenia [15,21]. However, there are few studies in patients with schizophrenia on the DLPFC functional connectivity during rest. Functional connectivity during rest is often measured by correlation in low frequency fluctuations (LFF) (<0.1 Hz) of the blood oxygen

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level-dependent (BOLD) signal [6]. The low frequency, resting-state interregional correlation has been observed between spatially distinct but functionally related regions [3,13,19], and has been observed to be altered in neuropsychiatric disorders, such as multiple sclerosis [20], Alzheimer's disease [32] and attention deficit hyperactivity disorder [31]. Our previous study, which investigated the distribution of the abnormal resting-state functional connectivities throughout the entire brain in schizophrenia, found abnormal functional connectivities between many regions, including those associated with the prefrontal cortex [18]. However, in that preliminary study, we used a group of non-first-episode schizophrenic patients and computed the functional connectivities of the whole brain which was roughly divided into 116 regions. Thus it could not reveal the precise and detailed connection patterns of the prefrontal cortex. In addition, the effects of medication should also be considered. In the present study, which considered the special role of the DLPFC in schizophrenia, we investigated the resting-state functional connectivity pattern of the DLPFC (Brodmann's area 46, BA46) in a voxel-wise manner in a group of patients with first-episode schizophrenia (FES) using fMRI. Because the patients we studied had a shorter length of illness and limited exposure to antipsychotic medications, the effect of such medications on brain blood flow/metabolism would be expected to be greatly reduced in the present study.

Seventeen FES patients (5 females, 12 males) were recruited from the Institute of Mental Health, Second Xiangya Hospital and met the following criteria: (a) Diagnostic and Statistical Manual-IV criteria for schizophrenia; (b) duration of illness less than 2 years and an allowed exposure to antipsychotic treatment of less than 2 weeks in the year preceding study entry or 6 weeks life time exposure [9]; (c) right-handed; (d) no history of neurological or systemic illness, head injury, and drug or alcohol abuse. At the time of scanning, all patients were receiving atypical antipsychotic medications, except for four, which were on no medication. And the symptoms of these patients were assessed by trained and experienced psychiatrists using the Positive and Negative Symptom Scale (mean 85.9 ± 21.5). Seventeen healthy, paid volunteers (5 females, 12 males) were recruited by advertisements and met the same (c) and (d) criteria as the patients (see above). The two groups were matched for age (25.7 ± 5.6 years for normal controls; 22.9 ± 6.0 years for schizophrenia; $P = 0.18$), gender and educational level (13.6 ± 3.3 years for normal controls; 12.6 ± 2.2 years for schizophrenia; $P = 0.18$). Subjects included 15 new subjects (9 patients, 6 controls) and 19 subjects (8 patients, 11 controls) in common with our previous study [18]. All subjects gave written, informed consent prior to taking part in the study, which was approved by the Medical Research Ethics Committee of the Second Xiangya Hospital, Central South University.

Imaging was performed on a 1.5-T GE scanner. Foam pads were used to limit head motion and reduce scanner noise. Three-dimensional T1-weighted images were acquired in a sagittal orientation employing a 3D-SPGR sequence (TR/TE = 12.1/4.2 ms, flip angle = 15°, in-plane resolution of 256×256, 1.8 mm slice thickness). The fMRI scanning was carried out in darkness, and the participants were explicitly instructed to keep their eyes closed, relax, and move as little as possible. Functional images were collected using a gradient echo Echo Planar Imaging (EPI) sequence sensitive to BOLD contrast (TR/TE = 2000/40 ms, flip angle = 90°, FOV = 24 cm). Whole-brain volumes were acquired with 20 contiguous 5-mm thick transverse slices, with a 1 mm gap and 3.75 mm × 3.75 mm in-plane resolution. For each participant, the fMRI scanning lasted for 6 min allowing 180 volumes to be obtained.

Image preprocessing was performed using a statistical parametric mapping software package (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). The first 10 volumes of each functional time series were discarded and the rest of the images were corrected for the acquisition delay between slices and for head motion. Motion time courses were obtained by estimating the values for translation and rotation for each of the 170 consecutive volumes. The participants in this study had less than 1 mm maximum displacement in x, y or z and less than 1° of angular motion about each axis. Because correlation analysis is sensitive to gross head motion effects, we further characterized the peak displacements as a measure of head motion for each subject [16,19], and no significant difference in the peak displacements of head motion was found between the groups by a random effect two-sample t-test (0.31 ± 0.20 mm for normal controls; 0.36 ± 0.18 mm for schizophrenia; $P = 0.45$). To further reduce the effects of confounding factors, six motion parameters, linear drift and the mean time series of all voxels in the whole brain were removed from the data through linear regression after the fMRI images were normalized to the standard EPI template and smoothed with a Gaussian kernel of 4 mm × 4 mm × 4 mm full-width at half maximum. Then the fMRI data were temporally band-pass filtered (0.01–0.08 Hz). A mask was then created by taking the intersections of the normalized T1-weighted high-resolution images of all subjects, which were stripped using the software BrainSuite2 (http://brainsuite.usc.edu). Only the voxels within the mask were further processed. In addition, to visualize the statistical results, a mean anatomical image was obtained by averaging these normalized high-resolution anatomical images across all subjects.

The DLPFC generally refers to BA46 and the ventral part of BA9, and sometimes also includes BA10. This region is relatively unitary in function but is difficult to anatomically delimit. In order to define the ROI as precisely as possible, we chose bilateral BA46 as ROIs using the software WFU_PickAtlas (www.ansir.wfubmc.edu) [22], which has been used in a previous study [28]. In brief, the right ROI was generated by intersecting the following three parts: BA46 in the TD (Talairach Daemon) Brodmann area atlas, the right middle frontal gyrus in the TD AAL (Automated anatomical labeling) atlas and the gray matter in the TD Type atlas. The left ROI was generated in the same way. The generated bilateral ROIs were respectively intersected with the mask to create the final right and left ROIs.

Functional connectivity analysis was performed for the right and left DLPFC. A seed reference time series for each ROI was obtained by averaging the fMRI time series of all voxels within the ROI. Correlation analysis was carried out between the seed reference and the rest of the whole brain in a voxel-wise manner.