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.

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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
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 25.7 ± 85.9). 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.
Then, the correlation coefficients were transformed to z-values using the Fisher r-to-z transformation to improve normality.

Within the normal group, individual z-values were entered into a random effect one-sample t-test in a voxel-wise manner to determine the brain regions showing significantly positive or negative correlation to the right or left DLPFC. A stringent threshold of $P < 0.005$ (corrected for multiple comparisons by false discovery rate) and a minimum cluster size of 540 mm$^3$ were used in order to obtain the connection maps within the group. Between groups, the z-values were entered into a random effect two-sample t-test in a voxel-wise manner to determine the brain regions that show significant differences in positive or negative correlation to the right DLPFC. A combined threshold of $P < 0.005$ (corrected for multiple comparisons by false discovery rate) and a minimum cluster size of 540 mm$^3$ (20 resampled voxels) were used in order to obtain the connection maps within the group. Between groups, the z-values were entered into a random effect two-sample t-test in a voxel-wise manner to determine the brain regions that show significant differences in positive or negative correlation to the right DLPFC. A combined threshold of $P < 0.005$ (corrected for multiple comparisons by false discovery rate) and a minimum cluster size of 540 mm$^3$ was equal to the corrected threshold of $P < 0.002$, determined by AlphaSim (B.D. Ward, http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). The differences identified by the above statistical method were further limited to the regions showing correlation with the right DLPFC in at least one group at the combined threshold of $P < 0.01$ and a cluster size of at least 405 mm$^3$. Exactly the same statistical analysis between groups was performed on the connection maps of the left DLPFC. Statistical parametric maps were superimposed on transverse sections of the average neuroanatomical landmarks.

In normal controls, the regions significantly positively correlated with the right ROI were similar to those in the “task-positive network”, and the regions significantly negatively correlated with the right DLPFC were similar to those in the “task-negative network” (Fig. 1A). The left DLPFC showed a similar functional connectivity pattern in normal controls (Fig. 1B).

Compared to the normal group, the bilateral IPL (BA40) (left: peak Talairach coordinates: $(-30, -51, 36)$, peak $t$: 3.94; cluster size: 459 mm$^3$; right: peak Talairach coordinates: $(42, -36, 35)$, peak $t$: 3.21; cluster size: 432 mm$^3$) and left intraparietal sulcus (IPS, BA7) (peak Talairach coordinates: $(-27, -65, 39)$, peak $t$: 3.84; cluster size: 432 mm$^3$) showed reduced positive correlation with the right DLPFC (Fig. 2A), and the PCC extending to the cuneus (BA18/31) (left: peak Talairach coordinates: $(15, -72, 17)$, peak $t$: $-3.95$; cluster size: 2403 mm$^3$; right: peak Talairach coordinates: $(18, -60, 17)$, peak $t$: $-3.87$; cluster size: 999 mm$^3$) and its adjacent lingual gyrus (LG, BA18/19) (left: peak Talairach coordinates: $(18, -61, -2)$, peak $t$: $-3.56$; cluster size: 864 mm$^3$; right: peak Talairach coordinates: $(21, -55, -2)$, peak $t$: $-3.79$; cluster size: 1458 mm$^3$) showed reduced negative correlation (i.e. closer to zero) with the right DLPFC in the FES group (Fig. 2B). Comparing the left DLPFC connectivity pattern of the controls with those of the patients, the similar regions showed reduced positive (right supramarginal gyrus, BA40, peak Talairach coordinates: $(39, -42, 33)$, peak $t$: 3.65; cluster size: 1242 mm$^3$) or negative (left precuneus/superior parietal lobule (BA7), peak Talairach coordinates: $(24, -47, 52)$, peak $t$: $-4.2$; cluster size: 1026 mm$^3$) correlation in FES patients. In addition, the bilateral thalamus and striatum (peak Talairach coordinates: $(-21, -17, 17)$ and $(15, -2, 14)$, peak $t$: 4.85 and 4.58; cluster size: 10,935 mm$^3$ and 6561 mm$^3$) showed reduced positive correlation to the left DLPFC, and a region (peak Talairach coordinates: $(56, -58, 3)$, peak $t$: $-3.99$; cluster size: 540 mm$^3$) in the posterior temporal lobe (BA 21/37) and a region (peak Talairach coordinates: $(12, 34, -22)$, peak $t$: $-4.79$; cluster size: 1269 mm$^3$) in the right orbital frontal gyrus (OFG, BA11/47) showed stronger positive correlation to the left DLPFC in FES patients. The posterior insula (BA13) (peak Talairach coordinates: $(56, -58, 3)$, peak $t$: $-3.99$; cluster size: 540 mm$^3$) showed enhanced negative correlation with the left DLPFC in FES patients (Fig. 2C and D).

Unlike most previous studies, the present study used correlations in interregional LFFs to investigate the functional connection of the DLPFC during rest. LFFs have been suggested to be physiologically meaningful and interregional correlations found by LFF may reflect endogenously coordinated dynamics.
Alterations in the right and left DLPFC functional connectivity in the FES. The left side of image represents the left side of brain. Color bar indicates the $T$-score. The number beneath each image refers to the $z$ coordinates of Talairach. Threshold was set at $P < 0.002$ (corrected). (A) Regions that showed reduced positive correlation to the right DLPFC. (B) Regions that showed reduced negative correlation to the right DLPFC. (C) Regions that showed difference in positive connectivity to the left DLPFC. (D) Regions that showed difference in negative connectivity to the left DLPFC. Warm color illustrates normal > FES and cool color illustrates normal < FES in (C) and (D). Abbreviations—IPL: inferior parietal lobule; IPS: intraparietal sulcus; Ins: insula; LG: lingular gyrus; MTG: middle temporal gyrus; OFG: orbitral frontal gyrus; PCC: posterior cingulate cortex; SG: supramarginal gyrus; SPL: superior parietal lobule; Str/Tha: striatum and thalamus.

in large-scale neuronal populations [1]. We found that some regions showed abnormally reduced or enhanced functional connectivity to the bilateral DLPFC in FES even during rest. The trend is consistent with our previous study [18] and supports the “dysconnection” opinion. In this case, dysconnection means that improper functional integration not only represents less interaction between neural units, but also implies the possibility of excessive enhanced interaction in schizophrenia [12,30].

In the present study, we found that the bilateral DLPFC showed significantly reduced functional connectivity with the parietal regions. Activities in the prefrontal and parietal lobes have been reported to be interdependent, and these two brain regions are strongly connected anatomically [24]. Frontal–parietal dysconnection in schizophrenia had previously been suggested by the deficit in working memory [17] and by the reduced neural integrity of the white matter tract connecting the two regions [5]. Our result was consistent with these studies. The connectivities of the left DLPFC to the bilateral striatum and thalamus were found to be reduced in FES patients, which was consistent with our previous study [18], supporting the opinion that the dysconnection in prefronto-striato-pallido-thalama-cortical loops may lead to abnormal sensory gating or modulation and induce schizophrenia symptoms, causing a form of “cognitive disorganization” [8].

More interestingly, in the present study, the right DLPFC also showed decreased negative correlations to the PCC. To the best of our knowledge this dysfunctional connectivity has not been noticed in previous studies. PCC is one of the regions having the highest metabolic activity during rest [25] and plays a central role in the “task-negative” network (i.e., the default mode network) [13,25]. The DLPFC is one of those regions constituting the “task-positive” network, which is anti-correlated with the “task-negative” network [10]. The two anti-correlated networks have been suggested as reflecting the intrinsic brain functional organization [10]. In the resting brain of healthy subjects, the right DLPFC has been reported to be negatively correlated with the PCC [11,13], as we observed in the normal group. Although the precise mental processes supported by the intrinsic brain functional organization remain to be elucidated, our finding of the reduced negative correlation between the right DLPFC and the PCC may suggest, for the first time, functional disintegration in the intrinsic brain functional activity.

In addition, we found abnormal enhanced connectivities between the left DLPFC and paralimbic regions (OFG and insula), whose structure and function have been found to be abnormal in schizophrenia [2,7,14]. This finding suggests that further investigation should focus on the dysfunctional integration between the DLPFC and the paralimbic system. Moreover, in the present study, we observed the enhanced functional connectivity between the left DLPFC and the posterior MTG; however, Liang et al. [18] reported that the functional connectivity between the MTG and the prefrontal cortex obtained by computing the correlation using the mean time series of these regions was decreased in schizophrenia. We speculate that this inconsistency may be due to the functional heterogeneity of the temporal sub-regions. This suggests that it will be necessary to investigate the resting-state frontotemporal connectivity in detail in the future.

There are several issues to be addressed in the present study. Although we found significant alterations in the DLPFC functional connection pattern in schizophrenia, it is difficult to distinguish whether the abnormal correlation patterns represent
some sort of “autonomous” pathology that leads to abnormal brain function and subjective experience during scanning, or whether abnormal cognition and experience during scanning, from other neuropsychological causes, lead to the observed intergroup differences in correlation patterns. This needs to be investigated in the future. In addition, in the present study, we used a relatively long sampling rate (TR = 2 s) for multislice acquisitions. Under this sampling rate, cardiac and respiratory fluctuation effects could be aliased into the LFF and could reduce the specificity of the connectivity effect [19]. In future studies, these physiological effects may be estimated and removed by simultaneously recording the respiratory and cardiac cycles during data acquisition.

In summary, the present study not only provides new evidence for the improper functional integration in schizophrenia by investigating the resting-state functional connectivity of DLPFC, but also suggests that this abnormality may relate in part to the disturbed intrinsic brain activity in schizophrenia.

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