Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging

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Sponsorship: This work was partially supported by the Natural Science Foundation of China, Grant Nos 30425004 and 60121302, the National Key Basic Research and Development Program (973), Grant No. 2004CB318107.

Received 5 November 2005; accepted 15 November 2005

Using resting-state functional magnetic resonance imaging, we examined the functional connectivity throughout the entire brain in schizophrenia. The abnormalities in functional connectivity were identified by comparing the correlation coefficients of each pair of 116 brain regions between 15 patients and 15 controls. Then, the global distribution of the abnormal functional connectivities was examined. Experimental results indicated, in general, a decreased functional connectivity in schizophrenia during rest, and such abnormalities were widely distributed throughout the entire brain rather than restricted to a few specific brain regions. The results provide a quantitative support for the hypothesis that schizophrenia may arise from the disrupted functional integration of widespread brain areas. *NeuroReport* 17:209–213 © 2006 Lippincott Williams & Wilkins.

Keywords: functional connectivity, functional magnetic resonance imaging, resting state, schizophrenia

Introduction

Although the causes and mechanisms of schizophrenia are still unclear to date, the disconnection hypothesis for this disorder has become popular, which assumes that schizophrenia could arise from dysfunctional integration of a distributed network of brain regions [1]. Recently, more and more convergent evidence from functional magnetic resonance imaging (fMRI) and diffusion tensor imaging on schizophrenia has supported the disconnection hypothesis, indicating improper functional integration within the brain [2–5].

Functional connectivity, which refers to temporal synchrony or correlation between two or more spatially separate regions, has been used to investigate the dysfunctional integration of brain regions in schizophrenia and various other brain diseases. The disconnectivities between many cortical and subcortical regions in schizophrenia, such as the frontal lobe, the temporal lobe, the parietal lobe, the basal ganglia, the thalamus and the cerebellum, have been reported using functional connectivity with fMRI (e.g. [2–4]). Some diffusion tensor imaging studies have reported abnormalities in white matter of various brain regions and provided anatomical evidence for functional disintegration in schizophrenia [5]. These studies involved nearly all major brain areas as well as the connections related to them. This implied that schizophrenia might arise from the improper functional integration of widely distributed brain areas [6].

Few of the previous functional connectivity studies, however, provided a direct investigation of the hypothesis of widespread dysfunctional integration throughout the entire brain as they used the conventional 'seed voxels' method. This conventional method only focuses on the functional connectivities associated with one or a few preselected seed regions of interest (ROIs) while ignoring other potentially interesting patterns of connectivity. Furthermore, seed ROIs usually were selected according to anatomical (e.g. specific gyrus or sulci) or functional information (e.g. activated voxels or clusters in some specific tasks). Such methods are, however, easily biased by the actual strategy of choosing the seed ROIs [7]. To avoid such limitations, we examined the functional connectivity of the entire brain of patients with schizophrenia by dividing the entire brain into 116 regions automatically and performing correlation analysis on each pair of these regions.

In addition, to our knowledge, most of the previous fMRI studies are based on tasks and no functional connectivity analysis with resting-state fMRI has been carried out on schizophrenia to date. Xiong *et al.* [8] suggested that a rest-based interregional connectivity analysis might detect a more complete and more accurate connectivity map than

does a task-driven analysis. Low-frequency (<1 Hz) fluctuations from resting-state fMRI data are considered to be physiologically meaningful and related to neural spontaneous activity [9]. A number of resting-state functional connectivity studies have been performed on normal participants [9–13] as well as various diseases [14–16]. In this study, we used resting-state fMRI to investigate the functional connectivity in schizophrenia.

In the present study, we hypothesize that schizophrenia may arise from widespread improper functional integration, even in the resting state. To test this hypothesis, we used functional connectivity analysis with fMRI to investigate whether a dysfunctional integration involving a widely distributed network of brain regions exists in schizophrenic patients during rest.

Participants and methods

Study population

Patients with schizophrenia were recruited from the Institute of Mental Health, Second Xiangya Hospital, China. The study involved 15 patients with schizophrenia diagnosed using Diagnostic and Statistical Manual-IV criteria and 15 healthy, paid volunteers who were recruited by advertisements. All of the patients were on atypical antipsychotic medications at the time of scanning and the mean duration of the illness was 25.8 ± 18.3 months. At the time of scanning, the symptoms of these patients were assessed with the Positive and Negative Symptom Scale (total PANSS score=78.47 ± 19.58) and Clinical Global Impression scale (CGI score=4.53 ± 1.06). The two groups showed no statistically significant difference on the basis of age (22.9 ± 1.6 years for patients, 23.3 ± 2.9 years for volunteers, $P=0.59$) and were matched in sex (seven males and eight females in both groups). In addition, no significant difference was observed on the basis of education level ($n=3.73 \pm 0.46$ for patients, $n=4.07 \pm 0.59$ for volunteers, $P=0.1$, where n is defined below), which was rated as follows: elementary school, $n=1$; middle school, $n=2$; high school, $n=3$; 1–4 years college, $n=4$; more than 4 years in college, $n=5$. The two groups had similar head motion during fMRI scanning and showed no significant difference (see details in Data preprocessing). All participants were right handed and had no history of neurological or systemic illness, head injury, and drug or alcohol abuse. All participants 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.

Scan acquisition

Imaging was performed on a 1.5-T GE scanner. Echo planar imaging blood oxygen level-dependent images of the whole brain were acquired in 20 axial slices (TR/TE=2000/40 ms, matrix=64×64, 5 mm thickness, and 1 mm gap). The fMRI scanning was carried out in darkness, and the participants were instructed explicitly to keep their eyes closed and move as little as possible. For each participant, the fMRI scanning lasted for 6 min and 180 volumes were obtained.

Data preprocessing

Image preprocessing was conducted using statistical parametric mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). The first 10 volumes of each functional time series were discarded. The remaining fMRI 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 0.7 mm maximum displacement in x, y or z and less than 0.7° of angular motion about each axis. As correlation analysis is sensitive to gross head motion effects, we examined the difference between the two groups in total head motion, which was calculated by the following formula:

$$\text{Headmotion} = \sum_{i=2}^{170} \sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2 + (z_i - z_{i-1})^2},$$

where x_i, y_i and z_i are translations at the ith time point in x, y and z direction, respectively. The two groups showed no significant difference ($P=0.9$) in the total head motion using a two-sample t test. For further reducing the head motion effects, six motion parameters (in addition the linear drift) were removed from the data through linear regression after the fMRI images were normalized to the standard echo planar imaging template and smoothed with a Gaussian kernel of $4 \times 4 \times 4\,\text{mm}^3$ full-width at half maximum. To reduce low-frequency drift and high-frequency noise, the fMRI data were temporally band-pass filtered (0.01–0.08 Hz) [13].

Anatomical parcellation

The fMRI volumes registered with the Montreal Neurological Institute template were further divided into 116 regions according to the anatomically labeled template previously validated and reported by Tzourio-Mazoyer *et al.* [17]. This anatomically labeled template divides the cerebra into 90 regions (45 in each hemisphere) and the cerebella into 26 regions (nine in each cerebellar hemisphere and eight in the vermis) (see Table 1).

Functional connectivity analysis

The mean time series of each of 116 regions was obtained by simply averaging the fMRI time series over all voxels in this region. Correlation coefficients were then computed between each pair of these regions. For further statistical analysis, the correlation coefficients were transformed to z values using Fisher r-to-z transformation to improve normality. The functional connectivities considered as significantly different in schizophrenic patients compared with normal controls met the following criteria: (1) there were significantly different z values between the two groups at the threshold of $P<0.01$ [$t(28)>2.763$, uncorrected] by using a two-sample two-tailed t test; (2) z values of those connectivities were significantly different ($P<0.05$) from zero at least in one group by using a one-sample two-tailed t test.

In order to investigate the global distribution of abnormal functional connectivities in schizophrenia and simplify the reporting of results, all the 116 regions were classified into nine brain area categories according to their anatomical location and functional similarity. These brain area categories were the prefrontal lobe, the rest of the frontal lobe, the parietal lobe, the occipital lobe, the temporal lobe including the medial temporal structures, the insula, the corpus striatum, the thalamus and the cerebellum

Table 1 Anatomical parcellation of the whole brain and the classification of the subregions

Prefrontal lobe (PreF)	**Occipital lobe (Occ)**	**Parietal lobe (Par)**
Superior frontal gyrus, dorsolateral	Calcarine fissure	Postcentral gyrus
Superior frontal gyrus, orbital	Cuneus	Superior parietal lobule
Superior frontal gyrus, medial	Lingual gyrus	Inferior parietal lobule
Superior frontal gyrus, medial orbital	Superior occipital gyrus	Supramarginal gyrus
Middle frontal gyrus	Middle occipital gyrus	Angular gyrus
Middle frontal gyrus, orbital	Inferior occipital gyrus	Precuneus
Inferior frontal gyrus, opercular	**Temporal lobe & medial temporal system (Tem)**	Paracentral lobule
Inferior frontal gyrus, triangular		Posterior cingulate gyrus
Inferior frontal gyrus, orbital	Superior temporal gyrus	**Corpus striatum (CS)**
Olfactory cortex	Temporal pole: superior	Caudate nucleus
Gyrus rectus	Middle temporal gyrus	Putamen
Anterior cingulated	Temporal pole: middle	Pallidum
Other parts of frontal lobe (OthF)	Inferior temporal gyrus	**Thalamus (Tha)**
Precentral gyrus	Heschl gyrus	**Cerebellum (Cer)**
Supplementary motor area	Fusiform gyrus	Cerebellum hemisphere (9 regions in each hemisphere)
Median cingulated	Hippocampus	Vermis (8 regions)
Rolandic operculum	Parahippocampal gyrus	
Insula (Ins)	Amygdala	

Cerebra include 90 subregions (45 in each hemisphere) and cerebella include 26 subregions (9 in each cerebellar hemisphere and 8 in the vermis). See details in reference Tzourio-Mazoyer *et al.* (2002) [17].

(see Table 1). Thus, each connection can be classified as within or between these nine brain area categories. In order to conveniently visualize the results, these nine brain area categories are arranged in a circle and the functional connections between them are represented as lines linking two areas in a schematic diagram (see Fig. 1). To further analyze the distribution of abnormal functional connectivities in each of the nine brain area categories, we also counted the numbers of the decreased/increased connectivities related to each of the nine brain area categories [i.e. at least one of the two ends (subregions) of the connectivity links belongs to this brain area category]. As the nine brain area categories include different numbers of subregions, the number of the abnormal connectivities related to each of the nine brain areas was normalized by dividing the number of all possible connectivities related to this area. We used the normalized numbers to measure the extent of disconnectivity related to each of the nine brain areas.

Results

In total, 177 connectivities were significantly different between the schizophrenic patients and the controls. Of the 177 connectivities, the patients showed significantly decreased z values in 158 connectivities and increased z values in 19 other connectivities compared with the controls. As we are more interested in the global distribution of these abnormal functional connectivities rather than in each specific connection, we have only provided a schematic diagram (Fig. 1a and b) without details of each significantly different connectivity. Figure 1a shows that the decreased functional connectivities in schizophrenia are distributed widely throughout the entire brain and are not confined to one or a few specific brain areas. Figure 1c shows the normalized numbers of the decreased functional connectivities related to each of the nine brain areas. We found that the decreased functional connectivities were involved with all the nine brain areas, although four areas, the insula, the temporal lobe, the corpus striatum and the prefrontal lobe, exhibited larger normalized numbers relative to other areas.

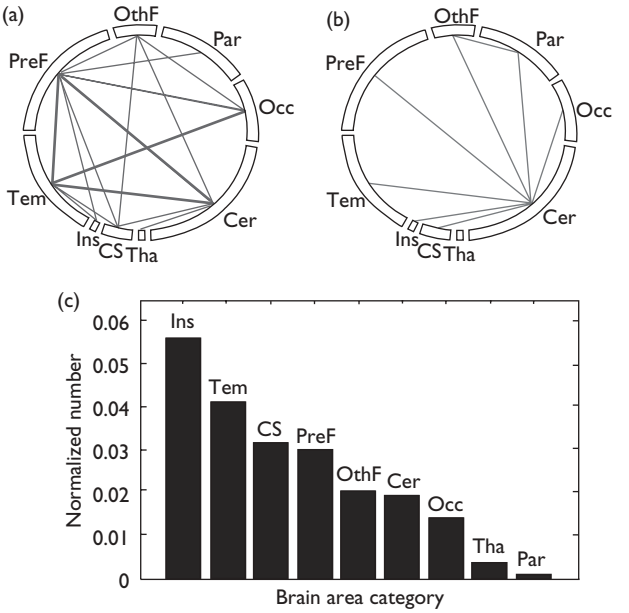

Fig. 1 Schematic diagram showing the global distribution of the decreased (a) and increased (b) functional connectivities in schizophrenia and the normalized numbers of the decreased functional connectivities related to each of the nine brain area categories (c). In (a) and (b), nine brain area categories are arranged in a circle that is divided into nine sections, and the abnormal functional connections between two brain area categories are represented as lines linking the two corresponding sections (the abnormal connections within areas are not shown in order to simplify visualization of the results). The number of subregions included in every brain area is indicated by the size of the corresponding section and the number of decreased/increased functional connections between two brain areas is indicated by the thickness of the corresponding line. PreF, prefrontal lobe; OthF, other parts of frontal lobe excluding prefrontal lobe; Par, parietal lobe; Occ, occipital lobe; Tem, temporal lobe including medial temporal structures; Ins, insula; CS, corpus striatum; Tha, thalamus; Cer, cerebellum.

From Fig. 1b, interestingly, we see that the increased functional connectivities in schizophrenia are mainly related to the cerebellum.

Discussion

Different from most other functional connectivity studies on schizophrenia with fMRI, we investigated the abnormal functional connections in schizophrenia from the following two aspects: (1) We examined the functional connectivity during the resting state and (2) we focused on the global distribution of abnormal functional connectivities throughout the entire brain rather than the connectivities only associated with a few ROIs.

To our knowledge, there have been no resting-state fMRI studies on schizophrenia to date although a number of studies have used resting-state fMRI to investigate the functional connectivity pattern in healthy humans [9–13] and in patients with other brain diseases [14–16]. The blood oxygen level-dependent signal of fMRI has been confirmed to reflect neural activity [18] and the low-frequency fluctuations in the resting state have been attributed to neural spontaneous activity [9] though this has not been conclusively proven. In addition, because no stimulation paradigm is required and the performance is easier, especially for patients, resting-state fMRI has practical advantages for clinical applications.

In our study, schizophrenic patients mainly showed decreased functional connectivities (158 out of a total of 177 abnormal functional connectivities) during the resting state compared with controls. This result supports the hypothesis of disconnection in schizophrenia.

By investigating the global distribution of these decreased functional connectivities throughout the entire brain, we found that these existed in all the nine brain areas and were widely spread among most brain areas including the cortical and subcortical structures rather than being restricted to a few specific regions (Fig. 1a and c). Many functional connectivity studies on schizophrenia exist, but most of them have used the method of 'seed voxels' that can only explore the functional connectivity associated with one or a few preselected ROIs and thus cannot provide a direct investigation of widely distributed disconnection in schizophrenia. Summing up previous functional connectivity studies on schizophrenia, abnormal functional connectivities among a number of brain regions have been reported. For example, Lawrie *et al.* [2] found reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations during a sentence completion task. Honey *et al.* [4] found disrupted integration between the medial superior frontal gyrus and both the anterior cingulate and the cerebellum in schizophrenic patients using a continuous performance task. Boksman *et al.* [3] reported a widespread unfocussed interaction between the right anterior cingulate and other parts of the brain in schizophrenic patients, while normal controls showed a localized interaction between the right anterior cingulate and the left temporal lobe using a word fluency paradigm. In addition, some diffusion tensor imaging studies have focused on the anatomical disconnection of schizophrenia and reported reduced fractional anisotropy of the whole-brain white matter, the frontotemporal lobe, the corpus callosum, the anterior cingulum and various other brain regions [5]. Our results in the current study were compatible with these previous results and suggested that schizophrenia might arise from the widespread disconnectivity throughout the entire brain.

Relative to other areas, four regions including the insula, the temporal lobe (including the medial temporal structures), the prefrontal lobe and the corpus striatum exhibited a larger number of decreased functional connectivities after normalization in patients (Fig. 1c). Many studies have focused on dysfunctional prefrontal, temporal lobe and corpus striatum and the connectivities related to them and have suggested that these were very important in the pathophysiology of schizophrenia [6,19–21]. Although there were fewer studies relating to the involvement of the insula in schizophrenia, several of these have indicated an abnormal volume and function of the insula in schizophrenia [22–24]. Our results showed decreased functional connectivities between the insula and these three regions, the prefrontal lobe, the temporal lobe and the corpus striatum, during rest and indicated that dysfunctional integration between the insula and other areas might also play an important role in the pathophysiology of schizophrenia.

Our current results also showed a few increased functional connectivities in schizophrenic patients, most of which were related to the cerebellum (Fig. 1b). This is an interesting finding and further investigations should be focused on the connections between the cerebellum and other regions.

It should be noted that, like most other functional connectivity studies using resting-state fMRI, we can reduce, but cannot completely eliminate, the effects of physiologic noises such as heart rhythm by band-pass filtering of 0.01–0.08 Hz, because we used a relatively low sampling rate (TR=2 s) for multislice acquisitions and thus the cardiac effect would be aliased into the low-frequency fluctuations. In future studies, simultaneous cardiac rate recording could provide a way to remove the cardiac effects. In addition, the patients in this study were medicated and the effects of medication should be considered in interpreting the differences between the patients and normal controls. A recent review [25] suggested that treatment with antipsychotic medication seemed to normalize brain function and to make the brain function of patients with schizophrenia more similar to that of healthy individuals. Therefore, the results of our study were likely primarily because of this disease rather than the medication, although we cannot eliminate completely the medication effects. Of course, future studies with first episode schizophrenic patients are required to eliminate the medication effects and confirm the findings of this study. In future, we will also evaluate these findings with different subtypes of this disorder.

Conclusion

We investigated the functional connectivities throughout the entire brain in schizophrenia with resting-state fMRI. Using the method in the present study, we directly investigated the global distribution of abnormal functional connectivities throughout the entire brain rather than only exploring those associated with a few preselected ROIs. We found that during rest the patients mainly showed decreased functional connectivities, which were distributed widely throughout the entire brain rather than being restricted to a few specific brain regions. In addition, a paucity of increased functional connectivities was found in schizophrenic patients during rest. The present study supports the hypothesis that schizophrenia may arise from the disrupted functional integration of widespread brain areas. The

current results, however, need to be considered with caution and confirmed by additional studies because of the medication effects and the complexity of syndromes in schizophrenia.

Acknowledgements

The authors thank Xiaobo Li, Yufeng Zang, Chaozhe Zhu and Jun Li for their helpful comments on this work. The authors also thank Drs Edmund and Rhoda Perozzi of Beijing University of Technology for extensive editing assistance.

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