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Functional disintegration in paranoid schizophrenia using resting-state fMRI

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Abstract

Functional disintegration has been observed in schizophrenia during task performance. We sought to investigate functional disintegration during rest because an intrinsic functional brain organization, including both "task-negative" (i.e., "default mode") and "task-positive" networks, has been suggested to play an important role in integrating ongoing information processing. Additionally, the brain regions that are involved in the intrinsic organization are believed to be abnormal in schizophrenia. Patients with paranoid schizophrenia ($N=18$) and healthy volunteers ($N=18$) underwent a resting-state fMRI scan. Functional connectivity analysis was used to identify the connectivity between each pair of brain regions within this intrinsic organization, and differences were examined in patients versus healthy volunteers. Compared to healthy volunteers, patients showed significant differences in connectivity within networks and between networks, most notably in the connectivities associated with the bilateral dorsal medial prefrontal cortex, the lateral parietal region, the inferior temporal gyrus of the "task-negative" network and with the right dorsolateral prefrontal cortex and the right dorsal premotor cortex of the "task-positive" network. These results suggested that the interregional functional connectivities in the intrinsic organization are altered in patients with paranoid schizophrenia. These abnormalities could be the source of abnormalities in the coordination of and competition between information processing activities in the resting brain of paranoid patients.

Keywords: Schizophrenia; fMRI; Resting-state; Functional connectivity

1. Introduction

Schizophrenia is a serious mental disorder that is characterized by symptoms such as hallucinations or disorganized thinking, loss of goal-directed behaviors, social withdrawal and cognitive impairments (Schultz and Andreasen, 1999). Additionally, attention deficit and deficits in monitoring one's own and other people's thoughts and intentions (mentalizing) are often observed in patients with schizophrenia (Brune, 2005; Malaspina et al., 2004; Nuechterlein et al., 2004). Recent models of schizophrenia have postulated that the cognitive and

Abbreviations: L, left; R, right; BOLD, blood oxygen level-dependent; CPL, cerebellar posterior lobe; dMPFC, dorsal medial prefrontal cortex; dPM, dorsal premotor cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; Ins, insula; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LP, lateral parietal region; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MT+, middle temporal region; OFG, orbital frontal gyrus; PCC, posterior cingulated cortex; PCu, precuneus; PHG, parahippocampus gyrus; PostCG, postcentral gyrus; SMA/pre-SMA, supplementary motor area/pre-supplementary motor area.

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affective impairments associated with schizophrenia may be related to a failure to integrate the activity of local and distributed neural circuits (Andreasen et al., 1999; Benes, 2000; Bullmore et al., 1997; Friston, 1998; Lewis and Gonzalez-Burgos, 2000; Selemon and Goldman-Rakic, 1999; Stephan et al., 2006). Evidence from functional imaging has supported this hypothesis by observing widely distributed functional disintegration, such as fronto-temporal (Lawrie et al., 2002; Spence et al., 2000; Stephan et al., 2006), fronto-parietal (Kim et al., 2003), dorsolateral prefrontal–hippocampal formation dysconnection (Meyer-Lindenberg et al., 2005) and functional disintegration in cortico-cerebellar–thalamo-cortical circuit (Schlosser et al., 2003a,b), in patients with schizophrenia. However, all these previous findings were observed while the subjects were performing a wide variety of cognitive tasks.

Recently, the ongoing intrinsic activity in the human brain during rest has attracted considerable attention (Raichle and Mintun, 2006). This internally initiated and internally processed activity forms the typical "resting state". This state is considered to be an energetically costly condition characterized by rich cognitive activities, which are temporally interrupted or attenuated by high-demand tasks (Gusnard and Raichle, 2001; Raichle et al., 2001; Raichle and Mintun, 2006). Some researchers even think that the ongoing intrinsic activity within various brain systems may be at least as important as the evoked activity in terms of overall brain function (Raichle and Gusnard, 2005; Raichle and Mintun, 2006). Therefore, we hypothesize that functional disintegration in schizophrenia should not only be demonstrated in the activity evoked by cognitive tasks, but also be reflected in a conscious resting state. It could be helpful in the diagnosis and treatment of schizophrenia to ascertain the types and location of functional disintegration in resting-brain of schizophrenia.

An intrinsic functional brain organization has been identified in the healthy brain during rest (Fox et al., 2005; Fransson, 2005).This intrinsic organization is characterized by the positive correlations within the "task-positive" and "task-negative" network, as well as the negative correlations between the two networks (Fox et al., 2005). Although the specific functions of the intrinsic organization remain unclear, some researchers have speculated as to their function based on prior knowledge about the regions found in the intrinsic organization. The regions in the "task-positive" network, such as the dorsolateral prefrontal cortex (DLPFC), the inferior parietal lobule (IPL) and the middle temporal region (MT+), are generally thought to be related to attention (Fox et al., 2005; Fransson, 2005; Laufs et al., 2003). Thus they may support an extrospectively oriented mode (Fransson, 2005). Similarly the regions in the "task-negative" network, such as the posterior cingulated cortex (PCC), medial prefrontal cortex (MPFC) and lateral parietal region (LP), are linked to cognitive processes that become active during rest, such as self-referential and reflective activity (Fox et al., 2005; Fransson, 2005; Greicius et al., 2003; Gusnard and Raichle, 2001). This indicates that they may support an introspectively oriented mode (Fransson, 2005). The brain recurrently toggles between the extrospectively and introspectively oriented modes, and competitively allocates resources to ready itself, or to be alert, to changes in the external and internal environments (Fransson, 2005; Raichle et al., 2001). The intrinsic organization of correlations within each network and the anti-correlations between the two networks may play an important role in the coordination of and competition between ongoing information processing activities (Fox et al., 2005).

Because the mental processes served by the intrinsic organization are relevant to schizophrenia, we hypothesized that the intrinsic organization may be altered in schizophrenia and that this aberrance may reflect the functional disintegration in schizophrenia during rest.

Functional connectivity analysis, a measure of the temporal synchrony or correlations of the blood oxygen level-dependent (BOLD) contrast fMRI signals between anatomically distinct brain regions (Friston et al., 1993), was used to analyze our data. This method has been used to identify the resting-state functional connectivities in distinct brain systems in healthy subjects (Biswal et al., 1995; Cordes et al., 2001; Greicius et al., 2003; Hampson et al., 2002; Lowe et al., 1998; Jiang et al., 2004), as well as to identify the alterations in the resting-state functional connectivity pattern in neuropsychiatric disorders (Liang et al., 2006; Lowe et al., 2002; Tian et al., 2006; Wang et al., 2006).

The present study aims to determine whether functional connectivities between the regions identified as parts of the intrinsic organization were altered in patients with schizophrenia. First we reconstructed the intrinsic organization in the control group and the patient group, separately, by using the right DLPFC (R. DLPFC) and the PCC/precuneus (PCu) as seed regions and analyzing their resting-state functional connectivities. These two regions have been observed not only to play a vital role in resting-state brain function (Fox et al., 2006; Greicius et al., 2003) but also to show altered functional activities and functional connectivity in schizophrenia (Bunney and Bunney, 2000; Franck et al., 2002; Tendolkar et al., 2004; Weinberger et al., 2001). Then we compared the correlation coefficients of each pair of brain regions in the intrinsic organization

between the normal controls and the patients with schizophrenia. In order to reduce the effect of disease heterogeneity on our results, we performed our analysis on a group of patients with paranoid schizophrenia and a group of matched healthy subjects.

2. Materials and methods

2.1. Subjects

Eighteen patients (8 female, 10 male; mean age 23.7, S.D. 4.9; average years of education 13.4 years, S.D. 2.0) were recruited from the inpatient unit at the Institute of Mental Health, Second Xiangya Hospital of Central South University. These patients met the DSM-IV criteria for schizophrenia with the paranoid subtype. Confirmation of the diagnosis was made by clinical psychiatrists for all patients, using the Structured Clinical Interview for DSM-IV, Patient version (SCID-I/P, First et al., 1995). Patients were free of concurrent psychiatric disorders and had no history of major neurological or physical disorders that could lead to an altered mental state. All patients were recruited during an acute psychotic episode, had a short duration of illness (mean 25 months, S.D. 18) and a mean age of onset of 21.7 (S.D. 5.3). Except for three patients who were on no medications, the patients were receiving atypical antipsychotic medications at the time of scanning (risperidone [$n=8$], clozapine [$n=3$], seroquel [$n=2$], or quetiapine [$n=2$]) and the mean daily dose (in chlorpromazine equivalents) of the medicated patients was 483.3 (S.D. 153.1) mg. At the time of scanning, the schizophrenia symptoms were rated by trained and experienced psychiatrists using the Positive and Negative Symptom Scale (PANSS) (mean total score 81.1, S.D. 20.3). Eighteen healthy subjects were recruited by advertisement as a control group (9 female, 9 male; mean age 24.9, S.D. 3.9; average years of education 13.4 years, S.D. 2.0). Control subjects were free of any known psychiatric condition. None of them had a current or past history of major physical or neurological illness or substance abuse. All patients and control subjects were right-handed. Patients and control subjects were statistically similar in terms of gender composition ($p=0.56$; Pearson Chi-square two-tailed test), age ($p=0.414$; two-tailed t-test) and educational level ($p=0.226$; two-tailed t-test). A subset of these subjects overlapped with a previous study (Liang et al., 2006). 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.

2.2. Image acquisition

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°, FOV = 24 cm) with an in-plane resolution of 256 × 256 and slice thickness of 1.8 mm. 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 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 × 3.75 mm in-plane resolution. For each participant, the fMRI scanning lasted for 6 min. At the same locations as the functional images, a T1-weighted sequence (TR/TE = 2045/9.6 ms, flip angle = 90°) was acquired for anatomical information.

2.3. Data preprocessing

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 remaining 170 images were corrected for the acquisition delay between slices and for head motion. All participants in this study had less than 1 mm maximum displacement in x, y or z and less than 1° of angular rotation 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 (Jiang et al., 1995; Lowe et al., 1998). No significant difference in the peak displacements caused by head motion was found between the normal subjects and the paranoid patients using a two-sample t-test (mean 0.29 mm, S.D. 0.17 for normal controls; mean 0.31 mm, S.D. 0.13 for schizophrenia, $p=0.66$). 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 echo planar imaging template, resampled to $3 \times 3 \times 3$ mm^3 and smoothed with a Gaussian kernel of $4 \times 4 \times 4$ mm^3 full-width at half maximum. Then the fMRI data were band-pass filtered (0.01–0.08 Hz) using AFNI (http://afni.nimh.nih.gov/) (Lowe et al., 1998; Greicius et al., 2003; Fox et al., 2005). A mask was then created by taking the intersections of the normalized T1 anatomical

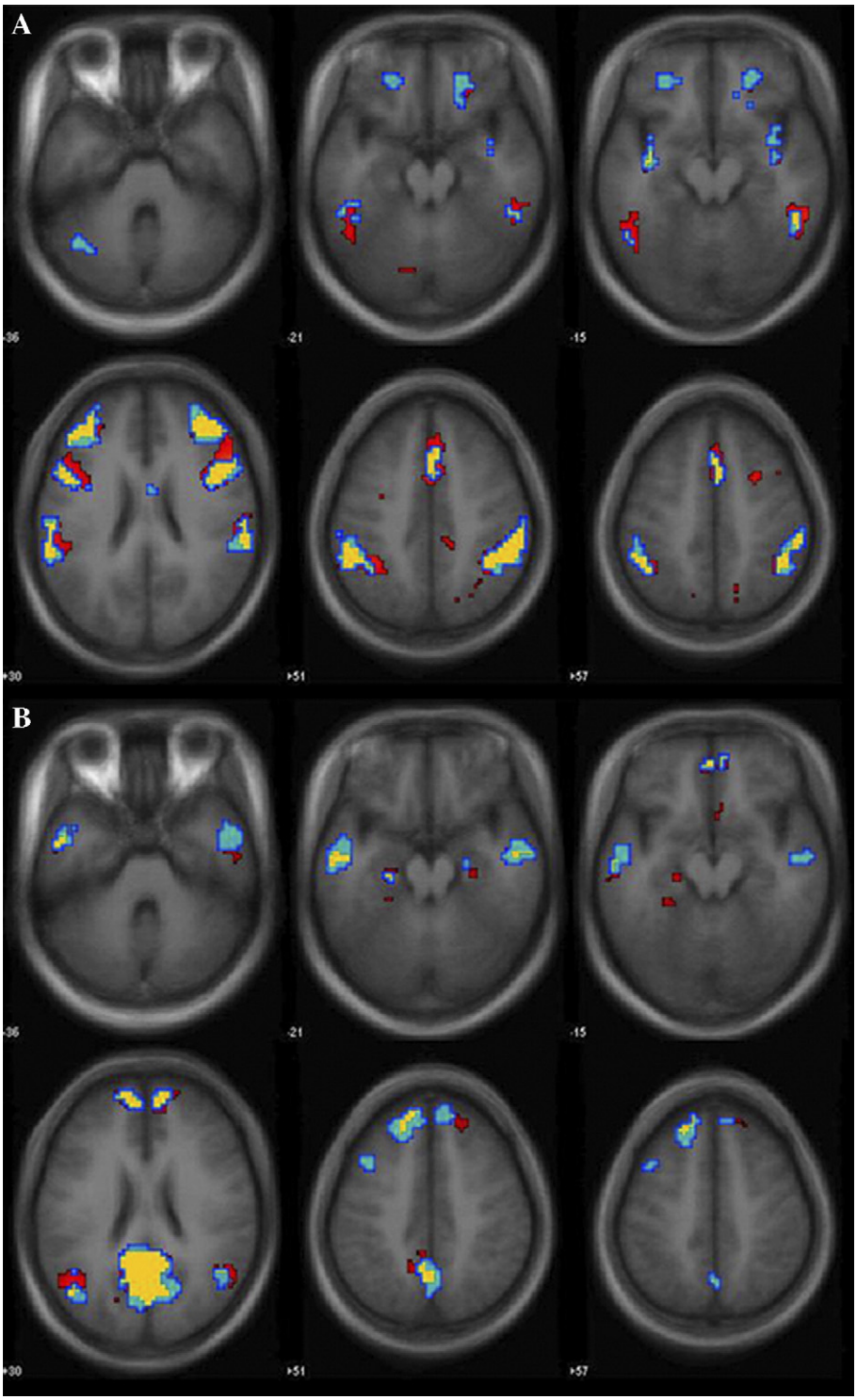

Fig. 1. Regions constituting the task-positive network (A) and task-negative network (B). Red, blue and yellow respectively represent the regions within the control group, within the schizophrenia group and the overlapped regions between groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

images of all subjects after the normalized images were stripped using the software MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html). Only the voxels within the mask were further processed. In addition, to visualize the statistical results, a mean anatomical image was obtained by averaging the normalized high-resolution 3D T1-weighted images across all subjects.

2.4. Reconstruction of the intrinsic organization

We reconstructed the intrinsic organization in the present study by selecting the right DLPFC (R.DLPFC), a region in the "task-positive" network, and the PCC/PCu, a region in the "task-negative" network, as two seed regions and analyzing their functional connectivity pattern during rest.

2.4.1. Definition of seed regions

The two seed regions were generated using the free software WFU_PickAtlas (http://www.ansir.wfubmc.edu) (Maldjian et al., 2003), which has been used in previous studies (Schon et al., 2005; Williams et al., 2004). In the present study, R.DLPFC refers to BA46 in the right middle frontal gyrus, and PCC/PCu refers to BA31 in the bilateral posterior cingulate cortices and the adjacent precuneus. The generated seed regions were respectively intersected with the mask to create the final seed regions. For each seed region, the BOLD time series of the voxels within the seed region were averaged to generate the reference time series for this seed region.

2.4.2. Resting-state correlation maps of seed regions

For each subject and each seed region (R.DLPFC and PCC/PCu), a correlation map was produced by computing the correlation coefficients between the reference time series and the time series from all other brain voxels. Correlation coefficients were converted to z values using Fisher's r-to-z transform to improve the normality. Then, individual z-values were entered into a random effect one-sample t-test in a voxel-wise manner to determine the brain regions that showed significant positive or negative correlation with the seed region within each group. The False Discovery Rate (FDR, Genovese et al., 2002) procedure was used to find a threshold that would restrict the expected proportion of type I errors to $q=0.05$. And a minimum cluster size of 20 voxels was used in order to obtain the connection maps within groups for each seed region.

2.4.3. Reconstruction of the intrinsic organization

First, we constructed the intrinsic organization (i.e., the "task-positive" network and the "task-negative" network) in the control group and separately in the patient group. Within each group, by intersecting the regions significantly positively correlated with the R.DLPFC with those significantly negatively correlated with the PCC/PCu, we obtained the regions belonging to the "task-positive" network for each group. Similarly, by intersecting the regions significantly negatively correlated with the R.DLPFC with those significantly positively correlated with the PCC/PCu, we obtained the regions belonging to the "task-negative" network for

Table 1
The regions in the intrinsic organization

Index	Region	BA	Cluster size	MNI coordinates of peak voxels			Mean T
"Task-positive" network							
1	R.DLPFC	9/46/10	1054	45	42	15	11.89
2	L.DLPFC	9/46/10	637	−48	39	12	8.42
3	R.IFG	44/45	239	54	12	18	8.72
4	L.IFG	44/45	137	−51	9	27	6.77
5	R.OFG	11	79	24	39	−18	4.48
6	L.OFG	11	42	−24	39	−21	4.16
7	R.Ins	13/47	358	42	3	3	6.45
8	L.Ins	13/47	273	−36	18	3	6.14
9	R.IPL/PostCG	40/2	589	60	−33	51	8.56
10	L.IPL/PostCG	40/2	551	−60	−30	39	8.05
11	R.MT+	37/20	152	51	−42	−15	4.99
12	L.MT+	37/19	193	−54	−57	−12	5.65
13	SMA/pre-SMA	32/6	241	6	9	51	8.29
14	R.dPM	6	38	27	3	57	2.96
15	L.CPL	–	29	−27	−66	−33	2.3
"Task-negative" network							
16	PCC/PCu	31/7	1610	6	−54	30	21.02
17	R.dMPFC	9/10/8	462	3	51	21	7.05
18	L.dMPFC	10/9/8/32	616	−3	54	6	8.66
19	R.LP	39	134	48	−57	30	6.45
20	L.LP	39	203	−42	−69	33	9.59
21	R.ITG	21/20	249	63	−3	−24	5.76
22	L.ITG	21/20	203	−60	−6	−24	6.97
23	R.PHG	–	25	27	−12	−30	2.32
24	L.PHG	–	26	−24	−21	−21	4.28
25	L MFG	6/8	28	−39	12	51	2.32

Abbreviations: L: left; R: right; CPL: cerebellar posterior lobe; dMPFC: dorsal medial prefrontal cortex; dPM: dorsal premotor cortex; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; Ins: insula; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; LP: lateral parietal region; MFG: middle frontal gyrus; MNI: Montreal Neurological Institute; MT+: middle temporal region; OFG: orbital frontal gyrus; PCC: posterior cingulated cortex; PCu: precuneus; PHG: parahippocampus gyrus; PostCG: postcentral gyrus; SMA/pre-SMA: supplementary motor area/pre-supplementary motor area.

each group. In this manner we obtained an intrinsic organization for both the control group and the patient group. Then, we merged the regions identified as belonging to the intrinsic networks in the control group and those in the patient group in order to obtain the final intrinsic network to be compared. These steps were all done using the ImCalc toolbox in SPM2.

2.4.4. Validation of the intrinsic organization

In order to validate the intrinsic organization (correlations within networks and anti-correlations between networks), the functional connectivity analysis was conducted between each pair of these regions within the control group and separately within the patient group. The mean time series of these regions in the intrinsic organization was obtained by averaging the fMRI time series over all voxels in the region. Pearson's correlation coefficients then were computed between each pair of these regions. The correlation coefficients were converted to z values using Fisher's r-to-z transform. Then, individual z-values were entered into a random effect one-sample t-test to determine the significant positive and negative connectivity within each group. If the regions belonging to the same network (i.e., the "task-positive" network or the "task-negative" network) were significantly positively correlated with each other ($q<0.05$, FDR), and the regions belonging to different networks were significantly negatively correlated with each other ($q<0.05$, FDR), then the intrinsic organization was validated.

2.5. Identification of the differences of functional connectivity in the intrinsic organization between groups

The functional connectivities between the two groups were considered to be significantly different if they satisfied the following two conditions: (1) the z-values of this connectivity were significantly different from zero in at least one group by a one-sample t-test ($q<0.05$, FDR); (2) the two groups showed significantly different z-values for this connectivity at the threshold of $p<0.05$ (uncorrected) by a two-sample t-test.

3. Results

3.1. Identification of the intrinsic organization

We observed that most regions constituted the intrinsic organization in the control group overlapped

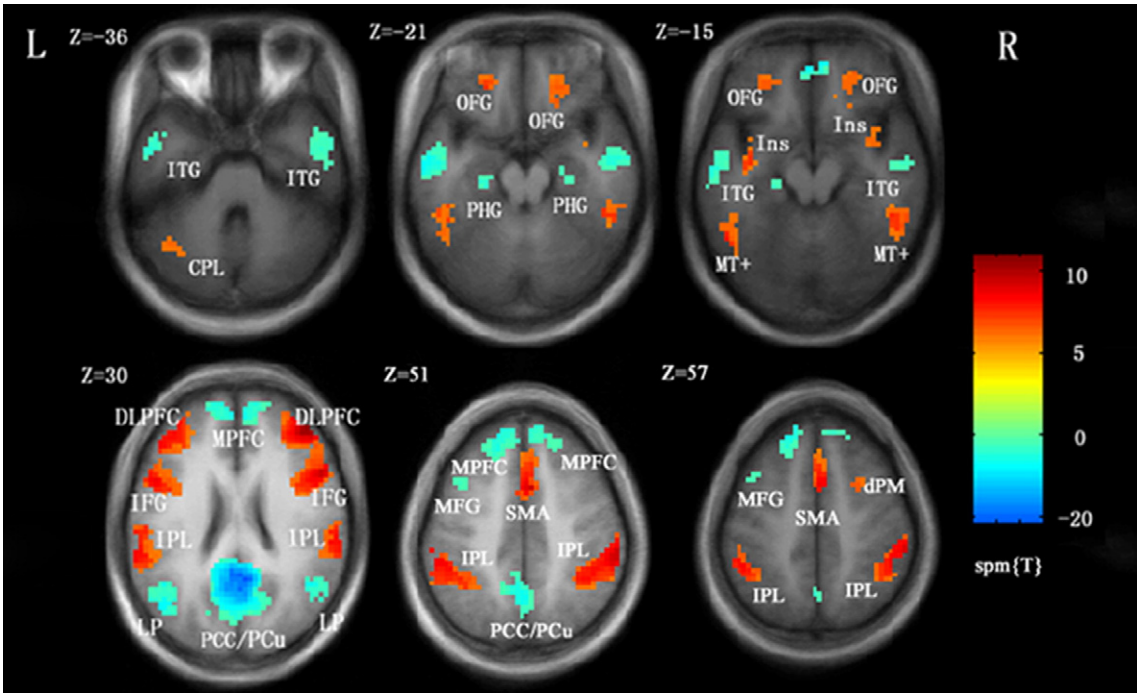

Fig. 2. The regions constituting the intrinsic organization. The left side of image represents the left side of brain. Warm colors illustrate brain regions in the "task-positive" network. Cool colors illustrate brain regions in the "task-negative" network. Color bar indicates T-score. The statistical threshold was $q<0.05$ (FDR corrected) and cluster size ≥ 20 voxels. For abbreviations, please see Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with those in the schizophrenia group (Fig. 1A, and B), although there were several regions which predominantly appeared in the control group (such as the right dorsal premotor cortex, dPM) or in the schizophrenia group (such as the bilateral orbital frontal gyrus, OFG). In order to provide more complete information on the intrinsic organization, we merged the regions of the intrinsic networks in the normal group with those in the patients group and finally obtained a complete view of the regions that constitute the intrinsic organization as follows: The "task-positive" network consisted of 15 regions, including the bilateral DLPFC, inferior frontal gyrus (IFG), OFG, insula, IPL, MT+, supplementary motor area (SMA)/pre-SMA, right dPM and left cerebellar posterior lobe (CPL). The "task-negative" network consisted of 10 regions, including the PCC/PCu, bilateral dorsal MPFC (dMPFC), LP, inferior temporal gyrus (ITG), parahippocampus gyrus (PHG) and left middle frontal gyrus (MFG) (Table 1 and Fig. 2). These were consistent with the previous studies that had identified these networks (Fox et al., 2005; Fransson, 2005). By computing the correlation coefficients between regions using the control group, we found that the regions within each network were positively correlated. (There were 70 significant positive connectivities out of a total of 105 possible connectivities within the "task-positive" network and 31 significant positive connectivities out of a total of 45 possible connectivities within the "task-negative" network at the $q=0.05$ threshold of FDR correction.) In addition, the

Table 2
The differences between groups in connectivities of regions constituting the intrinsic organization

Connections		Normal: z	Patients: z	Patients — normal	p value
Region 1	Region 2	(Mean/S.D.)	(Mean/S.D.)		
Within the "task-positive" network					
R.OFG	R.DLPFC	0.27/0.24	0.42/0.16	+	0.037
L.OFG	R.DLPFC	0.11/0.19	0.27/0.25	+	0.049
L.Ins	L.IFG	0.66/0.21	0.47/0.27	−	0.026
SMA	R.OFG	0.11/0.21	0.25/0.20	+	0.037
L.CPL	R.IPL	0.24/0.21	0.11/0.14	−	0.046
Within the "task-negative" network					
R.PHG	PCC/PCu	0.13/0.22	0.30/0.22	+	0.025
R.ITG	R.dMPFC	0.35/0.23	0.56/0.21	+	0.008*
L.MFG	R.dMPFC	0.09/0.19	0.26/0.28	+	0.042
R.ITG	L.dMPFC	0.26/0.26	0.53/0.24	+	0.003**
L.MFG	L.dMPFC	0.14/0.24	0.42/0.35	+	0.009*
R.ITG	L.LP	0.29/0.29	0.54/0.33	+	0.023
L.MFG	L.ITG	0.20/0.21	0.41/0.34	+	0.029
Differences between networks					
R.dPM	PCC/PCu	−0.35/0.271	−0.06/0.26	−	0.002**
R.Ins	R.dMPFC	−0.32/0.27	−0.54/0.24	+	0.017
L.Ins	R.dMPFC	−0.32/0.23	−0.50/0.21	+	0.017
R.OFG	L.dMPFC	−0.10/0.278	−0.27/0.20	+	0.048
L.OFG	L.dMPFC	−0.01/0.21	−0.21/0.27	+	0.018
R.Ins	L.dMPFC	−0.29/0.28	−0.52/0.24	+	0.017
L.Ins	L.dMPFC	−0.28/0.28	−0.53/0.23	+	0.008*
L.OFG	R.LP	−0.02/0.27	−0.18/0.13	+	0.032
R.dPM	R.LP	−0.22/0.25	−0.01/0.22	−	0.012
L.OFG	L.LP	−0.07/0.28	−0.22/0.11	+	0.043
L.Ins	L.LP	−0.21/0.28	−0.40/0.26	+	0.035
R.dPM	L.LP	−0.28/0.21	−0.010/0.24	−	0.02
R.DLPFC	R.ITG	−0.34/0.24	−0.49/0.17	+	0.044
L.CPL	R.ITG	0.04/0.32	−0.17/0.21	+	0.027
R.OFG	L.ITG	−0.12/0.25	−0.29/0.22	+	0.035
L.Ins	L.ITG	−0.19/0.21	−0.34/0.21	+	0.041
R.DLPFC	L.MFG	−0.05/0.29	−0.22/0.18	+	0.046

* $p<0.01$, ** $p<0.005$.
"+" means that the absolute correlation coefficient value (z value) between regions in the patient group is larger than that in the control group; "−" means that the absolute correlation coefficient value (z value) in the patient group is smaller than that in the control group. For abbreviations, please see Table 1.

regions in the "task-positive" network were negatively correlated with the regions in the "task-negative" network in the control group. (There were 90 significant negative connectivities out of a total of 150 possible connectivities at the $q=0.05$ threshold of FDR correction.) Similarly, the pattern of correlations within each network and anti-correlations between networks could also be found in our patients group. (There were 71 and 35 significant positive connectivities within the "task-positive" network and the "task-negative" network, respectively, and 102 significant negative connectivities between the two networks at the $q=0.05$ threshold of FDR correction.)

3.2. Differences between groups in functional connectivity in the intrinsic organization

By comparing the functional connectivities between groups, we found 29 significantly abnormal connectivities in the patients group. The abnormality in the intrinsic organization demonstrated altered positive correlations (correlations) within the "task-positive" network, increased correlations within the "task-negative" network and, primarily, increased negative correlations (anti-correlations) (farther from zero) in the patients group between networks ($p<0.05$, uncorrected). The abnormal correlations/anti-correlations were mainly associated with the bilateral dMPFC, LP and ITG of the "task-negative" network and with the right DLPFC of the "task-positive" network. In addition, some decreased anti-correlations were also found. These were all related to the right dPM (Table 2).

4. Discussion

Unlike previous studies on the resting brain function in schizophrenia (Liang et al., 2006; Liu et al., 2006), the present study focused on the intrinsic organization of brain function. By reconstructing the intrinsic organization, we found that abnormal correlations/anti-correlations between regions were widely distributed either within networks or between networks in patients with paranoid schizophrenia. This abnormality in the intrinsic organization suggested a source for the abnormalities in coordination of and competition between information processing activities in resting brain of paranoid patients.

We observed that the connectivities within networks primarily increased in the patients with paranoid schizophrenia, implying a concomitant increase in synchrony within either network. Neuronal synchrony or correlation has been thoroughly investigated and has been suggested as serving to facilitate the coordination and organization of information processing in the brain across several spatial and temporal ranges (Buzsaki and Draguhn, 2004; Fox et al., 2005). Therefore the increased synchrony may reflect an abnormality in the coordination of information processing, as observed in encephalographic studies in schizophrenia (Sritharan et al., 2005; Lee et al., 2003a; Spencer et al., 2004). In addition, the abnormal, increased synchrony may be explained as resulting from cortical hyperexcitability or abnormally increased connectivity (excessive or erroneous synaptic connectivity) in particular neural circuits (Lee et al., 2003b; Spencer et al., 2004). Within the "task-positive" network, the increased functional connectivities, associated with the R.DLPFC, SMA and bilateral OFG, may be related to the excessive alertness or sensitivity of paranoid schizophrenia to the external environment. Within the "task-negative" network, the increased connectivities mainly involved those associated with the bilateral dMPFC, ITG, left LP and PCC/PCu. These regions are similar to the set of regions that are associated with mentalizing, such as the posterior superior temporal sulci/temporo-parietal junction (similar to our LP), the temporal lobe (closer to our ITG), the MPFC and the PCC (Frith and Frith, 2003, 2006; Gallagher and Frith, 2003). The term "mentalizing" refers to the process by which we can make inferences about our own and another's mental state (Frith et al., 1991). The process is thought to be automatic and not requiring a deliberate decision to attend (Kampe et al., 2003). Some researchers have suggested that a patient with paranoid delusions has no problem ascribing intentions to other people, but forms wrong intentions (over-mentalizing) (Frith, 2004; Brune, 2005). It is possible, therefore, that paranoid patients use a different neuronal strategy, excessive connectivities or excessive cooperation; which lead to the over-mentalizing process.

The predominance of increased anti-correlations between networks that we found in patients with paranoid schizophrenia would seem to imply that the competition between networks was abnormally enhanced. The anti-correlation between regions is rarely investigated but has been speculated to be as important as correlation in brain organization (Fox et al., 2005). Unlike the correlations within each intrinsic network, which may integrate the neuronal activities that subserve similar goals or representations, the anti-correlations between the two intrinsic networks may differentiate the neuronal processes that subserve opposite goals or competing representations (Fox et al., 2005). In the present study, the abnormal connectivities mainly involved those associated with the bilateral dMPFC, LP and ITG of the "task-negative" network and the R.DLPFC, bilateral insula and OFG of

the "task-positive" network. As mentioned above, these "task-negative" regions may be involved in introspectively oriented mental activities (Fransson, 2005), especially mentalizing. These regions in the "task-positive" network may be involved in extrospectively oriented mental activities, such as attention to changes in the extrapersonal space (DLPFC) or in the 'inner milieu' (insula) (Fransson, 2005) and motivated attention (OFG) (Liddle et al., 2006). The two types of mental activities compete in the resting-brain of healthy subjects but are balanced. Specifically, the introspectively oriented mental activities decrease while the extrospectively oriented mental activities increase, and vice versa (Fox et al., 2005). So the increase in anti-correlations between the two networks in paranoid patients may suggest that the mental activities served by the two networks compete excessively. This may contribute to some of the symptoms of schizophrenia, such as over-mentalizing and attention deficit.

In addition, we found that all of the decreased anti-correlations in the present study were related to the R.dPM. The premotor cortex has traditionally been implicated in the planning and execution of voluntary movements; however, its role in cognitive operations has been reported more recently (Boussaoud, 2001; Picard and Strick, 2001; Schubotz and von Cramon, 2003). Functional imaging studies have suggested that the dorsal portion of the PM is related to attention-related activations, such as spatial attention/memory and prospective attention to sensory events (Boussaoud, 2001; Schubotz and von Cramon, 2003). These decreased anti-correlations between the R. dPM and several important regions in the "task-negative" network (the PCC and bilateral LP) suggest that the R.dPM may play an important role in modulating the competitive effect between the two intrinsic networks, especially since other regions associated with attention in the "task-positive" network showed increased anti-correlation with the "task-negative" regions, as we discussed above.

In contrast to our previous study (Liang et al., 2006), which found decreased functional connectivity in the resting brain of schizophrenia, in the present study we found that the aberrance of the intrinsic organization in paranoid patients mainly appeared as abnormally increased correlations/anti-correlations between regions either within a network or between networks. We speculate this apparent discrepancy may have resulted from the complexity of schizophrenia rather than from sample heterogeneity because there was an overlap in the sample between the two studies (the subjects in the present study included 11 patients and 13 control subjects used in the previous study). First, improper functional integration in schizophrenia not only indicates less interaction between neural units, but also implies the possibility of excessive enhanced interaction (Friston, 1998; Stephan et al., 2006). Overconnectivity (overintegration) and disconnectivity (disintegration) between and within interconnected systems may result in different profiles of schizophrenic symptoms (Peled, 1999). Secondly, the exact regions investigated in the two studies were different. These differences in the regions may indicate different avenues along which to further investigate various profiles of schizophrenia. In the present study, we reconstructed the intrinsic organization by using the R.DLPFC and the PCC/PCu as seed regions and analyzing their functional connections. In our previous study, we divided the whole brain into 116 regions according to anatomical information using an anatomically labeled template (Tzourio-Mazoyer et al., 2002). We noticed that the regions of the intrinsic organization in the present study often belong to a part of one or several template regions, such as the dMPFC. It is possible that the increased functional connectivity in the intrinsic organization that we found in this study coexists along with decreased connectivity outside the intrinsic organization. This needs to be investigated in future studies.

Several methodological issues in the present study need to be addressed. First, having noticed that the regions that constituted the intrinsic organization were somewhat different in our schizophrenic patients from those in our control group, we reconstructed the intrinsic organization by merging the regions that constituted the intrinsic organization in the control group with those in the patient group. The "merge" method is sensitive for identifying the connectivity that predominately appear in one group, and thus can provide more complete information. In addition to using the merge method, we also compared the intrinsic organization between the groups based only on the regions that constituted the intrinsic organization in the control group. As expected, we found that these altered functional connectivities were a subset of the findings obtained using the merge method (for details see Tables S1 and S2 in Supplementary Materials). Secondly, we only recruited patients with paranoid schizophrenia, which limits the ability to generalize our findings. It will be necessary to investigate whether the intrinsic organization is altered in patients with other subtypes. In addition, in the present study, we used a relatively low sampling rate (TR = 2s) for multislice acquisitions. Under this sampling rate, cardiac and respiratory fluctuation effects could be aliased into the low frequency ranges at which resting-state connectivity is detected and could reduce the specificity of the connectivity effects (Lowe et al.,

1998). In future studies, these physiological effects may be estimated and removed by simultaneously recording the respiratory and cardiac cycles during data acquisition.

In conclusion, this investigation of the resting brain function provides a novel access into the pathophysiology of schizophrenia. The aberrant functional connectivity in the intrinsic organization suggests an explanation for the abnormality in coordination and competition of information processing in the resting-brain of paranoid patients. This provides new evidence for the hypothesis that schizophrenia is a disease of improper functional integration. However, it is unknown if the abnormality in the intrinsic organization that we found in paranoid schizophrenia also exists in other subtypes of schizophrenia. Future research may provide a further understanding of the functional implications of the intrinsic organization and the relationship between the intrinsic organization and the phenomenology of schizophrenia.

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Contributors

All authors were involved in the design and implementation of the study and the writing of the manuscript. Authors Yuan Zhou, Meng Liang and Tianzi Jiang devised the concept. Authors Yuan Zhou and Meng Liang carried out the analysis. Author Tianzi Jiang supervised the study. Authors Zhening Liu, Yihui Hao and Haihong Liu collected the imaging data and clinical information.

Conflict of interests

None

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2007.05.029.

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