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Disrupted resting-state functional connectivity in minimally treated chronic schizophrenia

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ABSTRACT

Objective: The pathophysiology of chronic schizophrenia may reflect long term brain changes related to the disorder. The effect of chronicity on intrinsic functional connectivity patterns in schizophrenia without the potentially confounding effect of antipsychotic medications, however, remains largely unknown.
Method: We collected resting-state fMRI data in 21 minimally treated chronic schizophrenia patients and 20 healthy controls. We computed regional functional connectivity strength for each voxel in the brain, and further divided regional functional connectivity strength into short-range regional functional connectivity strength and long-range regional functional connectivity strength. General linear models were used to detect between-group differences in these regional functional connectivity strength metrics and to further systematically investigate the relationship between these differences and clinical/behavioral variables in the patients.
Results: Compared to healthy controls, the minimally treated chronic schizophrenia patients showed an overall reduced regional functional connectivity strength especially in bilateral sensorimotor cortex, right lateral prefrontal cortex, left insula and right lingual gyrus, and these regional functional connectivity strength decreases mainly resulted from disruption of short-range regional functional connectivity strength. The minimally treated chronic schizophrenia patients also showed reduced long-range regional functional connectivity strength in the bilateral posterior cingulate cortex/precuneus, and increased long-range regional functional connectivity strength in the right lateral prefrontal cortex and lingual gyrus. Notably, disrupted short-range regional functional connectivity strength mainly correlated with duration of illness and negative symptoms, whereas disrupted long-range regional functional connectivity strength correlated with neurocognitive performance. All of the results were corrected using Monte-Carlo simulation.
Conclusions: This exploratory study demonstrates a disruption of intrinsic functional connectivity without long-term exposure to antipsychotic medications in chronic schizophrenia. Furthermore, this disruption was connection–distance dependent, thus raising the possibility for differential neural pathways in neurocognitive impairment and psychiatric symptoms in schizophrenia.

1. Introduction

Schizophrenia is a severe mental disorder characterized by disturbances in thought and emotion as well as neurocognitive deficits (Heinrichs and Zakzanis, 1998). Although the pathophysiological mechanism(s) of this disease are still unknown, many studies have suggested that the symptoms of schizophrenia could result from the failure of functional integration among brain regions (Friston, 1999). Functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that patients with schizophrenia demonstrate abnormal functional connectivity

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between temporal and frontal regions (Friston et al., 1996; Lawrie et al., 2002; Meyer-Lindenberg et al., 2005), and that these abnormalities were related to both symptoms (e.g., auditory hallucinations) and cognitive performance (e.g., working memory) (Lawrie et al., 2002; Meyer-Lindenberg et al., 2005). All of these studies thus converge with the hypothesis that schizophrenia is a typical disconnection syndrome (Volkow et al., 1988; Friston and Frith, 1995; McGuire and Frith, 1996; Friston, 1999).

Through comprehensive and integrated analysis, researchers (Davis et al., 2005; Pettersson-Yeo et al., 2010) have determined that medication is an important factor with significant potential to confound results of functional brain imaging studies. A critical, unanswered question in the field, however, is whether untreated, chronic patients with schizophrenia demonstrate abnormal intrinsic functional connectivity patterns as measured by resting-state fMRI (R-fMRI). Here, we used R-fMRI to investigate whole-brain resting-state functional connectivity patterns in minimally treated chronic schizophrenia patients. Such a dataset can allow us to minimize medication effects as a potential confound on the brain's functional connectivity and focus on the natural progression of illness effects.

In this study, we constructed whole-brain functional connectivity networks by measuring temporal correlations of every pair of brain voxels and further analyzed the underlying topological properties using graph-theory. Specifically, we investigated regional functional connectivity strength, which captures functional integration strength between a given voxel and the rest of the brain. Additionally, the anatomical distance effect on the functional connectivity strength was further studied by dividing the connections into short- and long-range connections according to their anatomical distance (Achard et al., 2006; He et al., 2007). Finally, we examine the relationship between functional connectivity strength and cognitive and psychiatric measures in patients. Based on the above-mentioned studies, we hypothesized that minimally treated chronic schizophrenic relative to controls would show abnormal regional functional connectivity patterns mainly in the prefrontal cortex and DMN regions, and that the regional disconnectivity would correlate with clinical symptoms and cognitive functioning in patients.

2. Method

2.1. Participants

We screened 152 patients with chronic schizophrenia who had never been hospitalized in four counties of Hebei Province and Chaoyang District of Beijing from March, 2011 to April, 2012. Twenty five of the 152 patients met the following criteria: (i) DSM-IV diagnosis of schizophrenia according to the SCIDI/P, and no other Axis I diagnosis in their lifetime; (ii) had a long duration of illness (over 6 years) and a lifetime exposure to antipsychotic medications of no more than 3 months; (iii) had never received electroconvulsive shock treatment; (iv) 18 to 45 years old; (v) Chinese Han origin; (vi) right-handed; (vii) no history of major neurological or physical disorders; (viii) no drug abuse; (ix) no pregnancy for women; (x) no metal in the body; (xi) cooperative for travel; (xii) completing at least one neurocognitive test; and (xiii) normal brain structure. Two and four subjects were further excluded due to abnormal brain structure and excessive head motion, respectively. Therefore, data from the remaining 21 patients participated in the analysis. The mean body mass index (BMI) of patients was 23.3 (S.D. 2.9). The duration of illness in the patients (according to patients' family members) ranged from 6 to 29 years (mean 15.2 years, S.D. 7.1) and the mean age of onset was 20.4 years (S.D. 7.3). Twelve patients were antipsychotic naïve, seven patients had received informal low-dose antipsychotic treatment (at first onset, two patients had taken clozapine for 25–50 mg per day for less than two months; one had taken chlorpromazine for 300 mg per day less than three months; one had taken risperidone for an unknown dosage for one month; one had taken 4–6 mg perphenazine occasionally no more than three months; one had taken penfluridol for 80 mg per week no more than two months; one was taking paliperidone for 12 mg per day for one month and was injected with 25 mg Risperdal Consta only once before MRI data acquisition). Two patients took 2.5–5 mg diazepam occasionally for insomnia.

Twenty matched healthy controls were recruited from one county in Hebei Province by advertisement. The inclusion criteria were the same as the patients except that they were not diagnosed as having any Axis I disorder according to SCID-I/P.

The psychiatric symptoms were rated using the Positive and Negative Symptom Scale (PANSS). All patients and control subjects were assessed using the MATRICS Consensus Cognitive Battery (MCCB). Each cognitive domain score was calculated from several sub-test scores by the Chinese norm formula converting raw scores to T scores (Table 1).

All participants (and legal guardian of patients) provided written informed consent approved by the Medical Research Ethics Committee of Peking University Institute of Mental Health. The consent process was supervised by the patient's legal guardians.

2.2. Image acquisition

MRI data acquisition was performed on a GE HDx 3.0 T scanner in the department of radiology of Peking University People's Hospital. Patients had not taken any medicine 24 h before the scan and were lying quietly in the scanner with their eyes closed and remained awake. Foam pads and earplugs were used to minimize head motion and scanner noise, respectively. The functional images were obtained using an echo-planar imaging sequence with the following parameters to minimize the potential motion artifacts: thickness/gap = 5 mm/1.2 mm, repetition time = 2000 ms, echo time = 40 ms, flip angle = 90°, field of view = 240 × 240 mm^2, matrix = 64 × 64, NEX = 1, 22 slices. The scan lasted for 8 min.

Table 1
Demographic and clinical characteristics for minimally treated chronic schizophrenia patients and healthy controls.

	MTCS (N = 21)	HC (N = 20)	P
Age (years)	35.5 ± 7.1	35.0 ± 7.9	0.84[f]
Gender (female/male)	12/9	14/6	0.39[g]
Education (years)	7.5 ± 3.9	7.5 ± 3.1	0.95[f]
BMI	23.3 ± 2.9	22.5 ± 4.1	0.44[f]
Illness duration (years)	15.2 ± 7.1	NA	NA
Age of onset (years)	20.4 ± 7.3	NA	NA
PANSS scores[a]			
Total	77.4 ± 17.4	NA	NA
Negative symptoms	21.2 ± 6.5	NA	NA
Positive symptoms	21.5 ± 4.4	NA	NA
General psychopathology symptoms	35.3 ± 9.2	NA	NA
MCCB T scores			
Speed of processing	32.1 ± 8.2[c]	52.4 ± 7.0[c]	<0.0001[f]
Verbal learning	38.2 ± 8.9[c]	58.8 ± 12.2	<0.0001[f]
Visual learning	34.9 ± 13.3[b]	57.6 ± 12.9	<0.0001[f]
Reasoning and problem solving	35.3 ± 11.2[c]	50.6 ± 10.6	<0.0001[f]
Social cognition	35.1 ± 11.2[d]	51.6 ± 9.3	<0.0001[f]
Attention/vigilance	37.6 ± 10.4[e]	53.8 ± 8.6	<0.0001[f]
Working memory	38.2 ± 11.1[b]	51.9 ± 10.2	<0.0001[f]

MTCS, minimally treated chronic schizophrenia; HC, healthy controls; PANSS, Positive and Negative Symptom Scale; MCCB, MATRICS Consensus Cognitive Battery; NA, not available.
[a] 20 subjects participated in test.
[b] 19 subjects participated in test.
[c] 18 subjects participated in test.
[d] 15 subjects participated in test.
[e] 12 subjects participated in test.
[f] Obtained by two-sample t test.
[g] Obtained by Pearson Chi-square two-tailed test.

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