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Disrupted resting-state functional connectivity in minimally treated chronic schizophrenia

Xijin Wang [a,1], Mingrui Xia [b,1], Yunyao Lai [c], Zhengjia Dai [b], Qingjiu Cao [a], Zhang Cheng [a], Xue Han [a], Lei Yang [a], Yanbo Yuan [a], Yong Zhang [d], Keqing Li [d], Hong Ma [a], Chuan Shi [a], Nan Hong [c], Philip Szeszko [e], Xin Yu [a,*], Yong He [b,**]

[a] Ministry of Health Key Laboratory of Mental Health, Institute of Mental Health, Peking University, Beijing 100191, China
[b] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China
[c] Department of Radiology, Peking University People's Hospital, Peking University, Beijing 100044, China
[d] The Sixth People's Hospital of Hebei Province, Baoding, Hebei Province 071000, China
[e] The Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhassett, NY 11030, USA

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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

* Correspondence to: X. Yu, Institute of Mental Health, Peking University, No. 51 Huayuanbeilu, Haidian District, Beijing 100191, China. Tel.: +86 10 8280 1999; fax: +86 10 6202 6310.
** Correspondence to: Y. He, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, No. 19 Xinjiekouwai Street, Haidian District, Beijing 100875, China. Tel./fax: +86 10 5880 2036.
E-mail addresses: yuxin@bjmu.edu.cn (X. Yu), yong.he@bnu.edu.cn (Y. He).
[1] Xijin Wang and Mingrui Xia contributed equally to this work.

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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.

2.3. Data preprocessing

Data preprocessing and statistical analysis of functional images were conducted using SPM8 (SPM, www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for R-fMRI (DPARSF, www.restfmri.net/forum/DPARSF) (Chao-Gan and Yu-Feng, 2010) toolkits. Briefly, for each individual, the first ten volumes were discarded because of the instability of the initial signal and to allow participants to adapt to the scanning environment. The remaining data were first corrected for within-scan acquisition time differences among slices and then realigned to the first volume to correct for head motion (see Supplementary material for a detailed description regarding consideration of motion in our analysis). The realigned functional data were then normalized to the standard EPI template in Montreal Neurological Institute (MNI) space by using 12-parameter affine transformation and nonlinear deformation, and resampled to 3 mm isotropic voxels. Subsequently, the images were spatially smoothed with a 4 mm full width at half maximum Gaussian kernel. Linear de-trending and temporal band-pass filtering (0.01–0.08 Hz) were further performed to reduce the effects of low-frequency drift and high-frequency physiological noise. In addition, several nuisance signals including six head motion parameters, global mean signal, white matter signal and cerebrospinal fluid signal were regressed out from the data.

2.4. Resting-state functional connectivity strength

We performed whole-brain resting-state functional connectivity analysis on the preprocessed R-fMRI data. Briefly, Pearson's correlation coefficients were first computed between the time series of all pairs of gray matter (GM) voxels, leading to a whole-brain functional connectivity matrix for each individual. This computation was performed within a GM mask obtained by thresholding (probability > 0.2) the GM probability map in SPM8. Individual correlation matrices were transformed into a Z-score matrix using Fisher's r-to-z transformation to improve normality. We further computed regional functional connectivity strength of a voxel as the sum of the connections (Z-values) between a given voxel and all other voxels. Considering the ambiguous interpretation of negative correlations with removal of the global signal (Zalesky et al., 2012), we conservatively restricted our analysis to positive correlations above a threshold of $r = 0.2$. A relatively higher threshold was chosen to eliminate counting the voxels with weak correlations attributable to signal noise. To evaluate the effects of different correlation thresholds, we also analyzed regional functional connectivity strength with different thresholds of $r = 0$, 0.1, 0.3, 0.4, and 0.5, respectively (these results did not change our conclusion, data not shown). Notably, the regional functional connectivity strength metric is similar to the "weighted degree centrality" of a network in terms of graph theory (Rubinov and Sporns, 2010; Zuo et al., 2012). Voxels with higher regional functional connectivity strength values usually indicate their central roles in transferring information flow across brain regions.

To further explore the effects of anatomical distance on connectivity analysis, we divided the regional functional connectivity strength into two categories, short-range regional functional connectivity strength and long-range regional functional connectivity strength. The short-range regional functional connectivity strength of a voxel referred to the sum of those connections (Z-values) between the voxel and other GM voxels with anatomical distances less than 75 mm to the given voxel, whereas the long-range regional functional connectivity strength of a voxel referred to the sum of its connections (Z-values) with distances greater than 75 mm (Achard et al., 2006; He et al., 2007). In this study, the anatomical distance between two GM voxels was defined as the Euclidean distance (approximately corresponding to anatomical distances) between their MNI coordinates.

2.5. Statistical analysis

Age, years of education and the scores of every cognitive domain were compared by two-sample t-tests. Sex composition of the two groups was compared using a Pearson Chi-square test (two-tailed). To explore differences in regional functional connectivity strength, short-range regional functional connectivity strength and long-range regional functional connectivity strength between minimally treated chronic schizophrenic patients and healthy controls, general linear models were performed in a voxel-wise fashion. Age, gender and their interactions were treated as covariates. Considering that head motion between groups was significantly different ($p = 0.0095$ for maximum displacement; $p = 0.14$ for maximum rotation) and the influences of head motion on functional connectivity were reported recently (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), we also included the individual maximum displacement of head-motion profiles as a covariate. The between-group statistical threshold was set at $p < 0.01$ and cluster size of >459 mm^3, which corresponded to a corrected $p < 0.05$. This correction was determined by Monte Carlo simulations (Ledberg et al., 1998) using the REST AlphaSim utility program (www.restfmri.net) (Song et al., 2011). To investigate the relationship between functional connectivity and behavioral/clinical relationships, we used the partial correlation for those mean connectivity metrics (regional functional connectivity strength, short-range regional functional connectivity strength and long-range regional functional connectivity strength) in the clusters demonstrating between-group differences and behavioral/clinical variables (PANSS scores and MCCB T scores) in the minimally treated chronic schizophrenic group. We controlled for age, gender, the age-by-gender interaction and head-motion in these analyses.

3. Results

3.1. Demographic and clinical data

There were no significant differences in gender distribution ($p = 0.39$), age ($p = 0.84$), educational level ($p = 0.95$) and BMI ($p = 0.44$) between the minimally treated chronic schizophrenic and healthy control groups. As expected, however, patients scored significantly lower than controls on all the neuropsychological domains (all $ps < 0.0001$). The demographic characteristics and clinical information for both groups are provided in Table 1.

3.2. Functional connectivity strength mapping

The first row of Fig. 1 illustrates the regional functional connectivity strength maps in minimally treated chronic schizophrenia and healthy controls groups. In healthy subjects, functional brain hubs with high regional functional connectivity strength values were found primarily in the DMN including the medial frontal and parietal cortices [e.g., the medial prefrontal cortex (mPFC) and posterior cingulate cortex/precuneus (PCC/PCu)] and lateral temporal and parietal cortices (e.g., superior temporal gyrus and inferior parietal lobe). Moreover, functional brain hubs were also observed in the lateral prefrontal cortex (lPFC), dorsal anterior cingulate cortex (dACC), insula, and sensorimotor and visual cortices. The spatial pattern of regional functional connectivity strength in the minimally treated chronic schizophrenia group was highly similar to that of the healthy control group (Row 1 of Fig. 1). However, statistical analysis revealed that, compared to the healthy controls, the minimally treated chronic schizophrenia patients showed decreased regional functional connectivity strength in the bilateral postcentral gyrus (PoCG), right lPFC, right lingual gyrus, left middle temporal gyrus, and left insula (Row 1 of Fig. 1).

After considering the effects of anatomical distance, we observed differentially influenced spatial patterns of short-range regional functional connectivity strength and long-range regional functional connectivity

strength. (i) *Short-range regional functional connectivity strength*. In healthy subjects (Row 2 of Fig. 1), we observed short-range hubs mainly in the mPFC, dACC, insula, sensorimotor and visual cortices. Again, the short-range regional functional connectivity strength maps in the minimally treated chronic schizophrenia group exhibited a similar pattern as those in the healthy controls group. Further group comparisons revealed significantly reduced short-range regional functional connectivity strength values in the minimally treated chronic schizophrenic group in the bilateral PoCG, supplemental motor area, lPFC, insula and lingual gyrus (Row 2 of Fig. 1). (ii) *Long-range regional functional connectivity strength*. In healthy subjects (Row 3 of Fig. 1), we observed long-range hubs mainly in the PCC/PCu, mPFC, lPFC, insula and lateral temporal and parietal cortices. The spatial patterns of long-range regional functional connectivity strength in the minimally treated chronic schizophrenia group were similar to those in the healthy controls group. Compared to the healthy controls, the minimally treated chronic schizophrenia patients showed decreased long-range regional functional connectivity strength in the bilateral PCC/PCu and increased long-range regional functional connectivity strength in the right lPFC and lingual gyrus (Row 3 of Fig. +1).

3.3. Relationship between regional functional connectivity strength and clinical/behavioral variables in the minimally treated chronic schizophrenia patients

3.3.1. Correlations between regional functional connectivity strength and psychiatric symptoms

The regional functional connectivity strength of right PoCG was negatively correlated with the total PANSS scores ($r = -0.51$, $p = 0.043$) and the negative PANSS scores ($r = -0.52$, $p = 0.038$). Short-range regional functional connectivity strength of right lPFC were negatively correlated with the total PANSS scores ($r = -0.64$, $p = 0.007$), the negative PANSS scores ($r = -0.63$, $p = 0.009$) and the general psychopathology symptoms of PANSS ($r = -0.64$, $p = 0.008$). Additionally, we also observed negative correlations between short-range regional functional connectivity strength of right PoCG and the PANSS ($r = -0.51$, $p = 0.042$). There was no significant correlation found between long-range regional functional connectivity strength and symptoms.

3.3.2. Correlations between regional functional connectivity strength and duration of illness

The duration of illness correlated negatively with the regional functional connectivity strength in right lingual gyrus ($r = -0.52$, $p = 0.034$) and short-range regional functional connectivity strength in right cuneus ($r = -0.49$, $p = 0.047$).

3.3.3. Correlations between regional functional connectivity strength and cognition

A significant positive correlation was found between regional functional connectivity strength of the left lateral temporal cortex and verbal learning ($r = 0.74$, $p = 0.002$), and a negative correlation was found between regional functional connectivity strength of right lPFC and speed of processing ($r = -0.72$, $p = 0.004$). Long-range regional functional connectivity strength positively correlated with verbal learning in visual cortex ($r = 0.57$, $p = 0.034$), whereas it negatively correlated with speed of processing in PCu ($r = -0.61$, $p = 0.021$) and the reasoning and problem solving in right lPFC ($r = -0.59$, $p = 0.025$). There were no significant correlations between short-range regional functional connectivity strength and cognitive variables.

4. Discussion

In this exploratory study we investigated whole-brain resting-state functional connectivity patterns in minimally treated chronic schizophrenia patients. We found that, although both minimally treated chronic schizophrenia and healthy controls groups showed similar patterns of regional functional connectivity strength, short-range regional functional connectivity strength and long-range regional functional connectivity strength, statistical analysis revealed significant connectivity abnormalities in minimally treated chronic schizophrenia group and these abnormalities were distance-dependent. Specifically, in minimally treated chronic schizophrenia patients, we observed significantly decreased short-range regional functional connectivity strength in the bilateral PoCG, supplemental motor area, lPFC, insula and lingual gyrus, and decreased long-range regional functional connectivity strength in the bilateral PCC/PCu. Additionally, we also observed increased long-range regional functional connectivity strength in the right lPFC and lingual gyrus in minimally treated chronic schizophrenia patients. Intriguingly, disrupted short-range regional functional connectivity strength significantly correlated negatively with duration of illness and negative symptoms, whereas disrupted long-range regional functional connectivity strength significantly correlated with neurocognitive performance in minimally treated chronic schizophrenia patients. Our findings suggest that abnormal short-range regional functional connectivity strength and long-range regional functional connectivity strength might represent different alterations of neural circuitries in minimally treated chronic schizophrenia patients.

4.1. Disrupted regional functional connectivity strength in schizophrenia

Compared to healthy controls group the minimally treated chronic schizophrenia patients showed significantly decreased regional functional connectivity strength of PoCG, right lPFC, right lingual gyrus, left middle temporal gyrus, and left insula. Many studies indicated that disrupted functional connectivity in lPFC plays an important role in various neural circuits in schizophrenia (Bunney and Bunney, 2000). The correlations analysis finding negative correlations between lower regional functional connectivity strength in right lPFC and speed of processing in the minimally treated chronic schizophrenia group supports prior work that many higher cognitive functions (e.g., disturbances in cognitive control and working memory) (MacDonald et al., 2005; Tan et al., 2006) have been robustly associated with impaired functional specialization within lPFC in schizophrenia.

Prior work indicated that top down interactions in post/precentral regions may contribute to symptoms such as hallucinations (Whitford et al., 2012). In minimally treated chronic schizophrenia patients, we found decreased regional functional connectivity strength in the PoCG and a negative correlation with the total PANSS score and negative symptoms. Further seed-based functional connectivity analysis revealed that the decreased functional connectivity of PoCG were mainly located in the bilateral sensorimotor cortices (Fig. S2g, h). A previous R-fMRI study from Hoptman et al. (2012) demonstrated that the functional coupling of the bilateral sensorimotor cortices was negatively correlated with the total PANSS score, which was compatible with our findings. Such results indicate that the deficits in the PoCG might contribute to psychiatric symptomatology. Moreover, a prior study suggested that most sensory processing is active instead of passive (Schroeder et al., 2010) and thus, it is conceivable that disruptions in this kind of "active sensing" may lead to symptoms.

Many R-fMRI studies have reported lower functional connectivity involving the left middle temporal gyrus in schizophrenia (Jeong et al., 2009; Skudlarski et al., 2010; Liu et al., 2011) that were consistent with our results. The middle temporal gyrus belongs to Brodmann area 21, which is specialized for semantic processing (Martin et al., 1996; Visser et al., 2012). An earlier electrophysiological study indicated that responses in the middle temporal gyrus were linked to verbal memory scores (Elger et al., 1997). Similarly, we found that verbal learning and memory correlated positively with lower regional functional connectivity strength in the left middle temporal gyrus. Our data thus suggest that disrupted regional functional connectivity

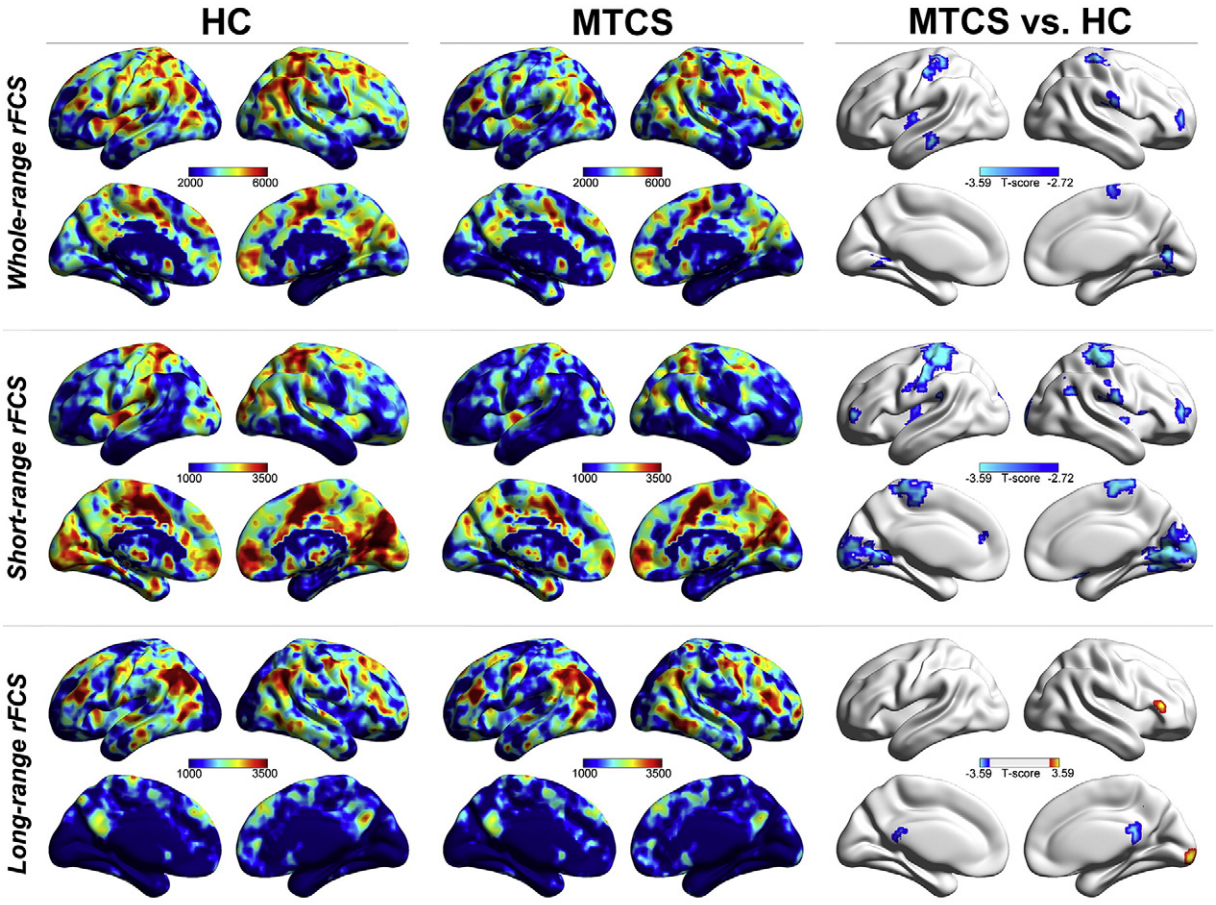

Fig. 1. Regional functional connectivity strength maps. The first column and second column show the mean regional functional connectivity strength maps in healthy controls and minimally treated chronic schizophrenia. The last column illustrates the difference of regional functional connectivity strength between the two groups, represented as a T score. HC, healthy control; MTCS, minimally treated chronic schizophrenia; rFCS, regional functional connectivity strength. These surfaces mapping were visualized using BrainNet Viewer (http://www.nitrc.org/projects/bnv/, Xia et al., 2013).

strength in the middle temporal gyrus contributes to cognitive impairment in schizophrenia.

We found a reduction of regional functional connectivity strength in the insula among minimally treated chronic schizophrenia patients. A recent meta-analysis showed that insula and cingulate deficits are shared and that left lateralized deficits may occur in patients with schizophrenia (Cheung et al., 2010). Other studies of other psychotic conditions, however, suggested that insula deficits may not be specific to schizophrenia (Palaniyappan and Liddle, 2012). The insula is a core component of the salience network. Attenuated coactivation of the regions comprising the salience network has been observed in schizophrenia (Henseler et al., 2009). Direct evidence comes from a functional connectivity analysis showing impairment in the interaction between the salience network and the DMN in schizophrenia, and failure to deactivate the DMN (White et al., 2010).

The right visual hemisphere may be biased toward processing of low spatial frequencies (Sergent and Bindra, 1981). The right hemisphere also appears to be specialized for spatial orientation (Umilta et al., 1974), line bisection (Bowers and Heilman, 1980) and mental rotation (Robertson et al., 1987). Disrupted functional connectivity involving the lingual gyrus likely results in visual–spatial disorders. Many studies indicated there are visual–spatial working memory deficits in schizophrenia (Glahn et al., 2003; Girard et al., 2010). In the present study, regional functional connectivity strength in the right lingual gyrus was significantly lower in minimally treated chronic schizophrenia patients and correlated negatively with duration of illness. It is possible that disturbances involving the lingual gyrus become more severe over time. Of note Collin et al. (2011) also found impaired functional connectivity between the cerebellum and lingual gyrus. It should also be acknowledged, however, that other investigators (Butler et al., 2005, 2008) have reported deficits in low level function that may be relevant to lingual gyrus abnormalities.

4.2. The significance of disrupted short- and long-range regional functional connectivity strengths for schizophrenia

In healthy populations the primary sensory and motor cortical regions are observed to have abundant (predominantly) short distance connectivity and are recognized as short-range connection hubs (Liang et al., 2013). In contrast, heteromodal cortical areas have abundant long-distance connections, and that the core components of the DMN as well as paralimbic regions have both abundant short- and abundant long-distance connectivity (Sepulcre et al., 2010). Our results further demonstrate that regional functional connectivity strength and short-range regional functional connectivity strength were mainly lower in primary sensory, visual cortical and prefrontal areas (predominantly short-distance connections) in patients, and may implicate a functional deficit basis of schizophrenia.

The balance between long range projections and local area interactions is important for efficient cortical processing (Mesulam, 1990, 1998). Greater long-range regional functional connectivity strength indicates a shorter path length such that the efficiency of information management and processing is more efficient (Bullmore and Sporns, 2009; van den Heuvel et al., 2009). In our study, we found long-range regional functional connectivity strength of some regions (predominantly short-distance connections) were greater, including right lPFC

and lingual gyrus, so that information might be transmitted to other brain regions for processing, but this may not be absolutely necessary under normal circumstances. In other words, the abnormal increase of long-range regional functional connectivity strength, which, in theory may have the ability to improve information processing could be counterproductive because information is being sent to the wrong brain regions. It should be emphasized, however, that long-range regional functional connectivity strength of the PCu, an important hub of DMN (predominantly both long- and short-distance connections), was lower, so efficiency of information processing decreased greatly. It should be noted that a previous study reported patients with schizophrenia may suffer from "cognitive dysmetria" due to dysfunctional prefrontal–thalamic–cerebellar circuitry (Andreasen et al., 1996). Along these lines Schlosser et al. indicated that the relationship between pathology in brain networks and associated functional connectivity is complex and may include aspects of increased and decreased strength of connectivity consistent with the notion of "cognitive dysmetria" in schizophrenia (Schlosser et al., 2003).

Investigation of structure–function relations indicated that lower short-range regional functional connectivity strength correlated negatively with negative symptom severity and disrupted long-range regional functional connectivity strength correlated with neurocognitive impairment. Our study thus suggests that lower short-range regional functional connectivity strength might reflect an evolution of the pathophysiology of schizophrenia, similar to Ronan et al. (2012), while the disrupted long-range regional functional connectivity strength might be a kind of "compensatory" or "adaptive" response to illness. This notion was verified in studies of autism spectrum disorders (Kana et al., 2011) and mild cognitive impairment (Bajo et al., 2010). This compensatory processing may have prevented further decline on neurocognitive tasks. Fornito et al. (2012) speculated that both increases and decreases in connectivity, could point to either a diffuse dysregulation of neural dynamics or possible compensatory changes in response to primary deficits. Divided functional connectivity into long- and short-distance by anatomical distance could help us to determine this kind of "compensatory" or "adaptive" process more clearly.

In the present study, verbal learning and memory correlated positively with mean long-range regional functional connectivity strength in the visual cortex in patients. Thus, it may be that the higher long-range regional functional connectivity strength in the visual cortex could play a compensatory role in patients. Tan et al. reported that activation of the ventral prefrontal cortex compensates for the loss of specialized cognitive function in dorsal prefrontal cortex (Tan et al., 2006). It should be acknowledged, however, that greater long-range regional functional connectivity strength in the right inferior frontal gyrus was negatively associated with worse speed of processing. It is conceivable that speed of processing may be more dependent on local connections and that the relationship between motor processing and long-range connectivity could lead to information conduction disturbances and/or disrupt information processing through other brain connectivity patterns. Thus, brain regions related to lower short-range regional functional connectivity strength and higher long-range regional functional connectivity strength may not strictly correspond with each other in the current study, and thus, the observed correlation with speed of processing could conceivably be moderated, in part, by other brain regions. This possibility needs additional data and replication to substantiate these claims.

There were several limitations to our study that should be acknowledged. First, our patients were minimally treated, and thus, we do not know if similar results would be obtained following a longer course of treatment. Second, the structural basis of functional connectivity changes needs to be further investigated consistent with Skudlarski et al. (2010) who reported a complex interplay between structural and functional disconnectivity in schizophrenia. Third, we did our best to improve our scanning parameters, however from our clinical observations, patients could not lie still on the scanner table longer than 8 min and hence this time limits our selection of slice thickness and other relevant parameters. In further studies, rapid scan sequences, involving multi-band techniques, might be equipped to optimize scan parameters and improve image quality. Fourth, because of the small sample size, the results of the correlational analyses were not corrected for Type-I error. Fifth, in this study, we analyzed the resting-state functional connectivity strength using a cross-sectional design in chronic schizophrenia patients. It should be acknowledged that such a design limited our ability to discriminate what is a consequence of chronicity, or progression and what is a stable pattern in schizophrenia. Future studies based on follow up exams could help to clarify this issue (Kasparek et al., 2013).

5. Conclusions

In this study, our results showed that functional connectivity disruption was connection–distance dependent, thus raising the possibility for differential neural pathways in neurocognitive impairment and psychiatric symptoms in chronically ill schizophrenia patients with minimal psychotropic treatment.

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Contributors

XY, YH and NH conceived the study, and participated in its design and coordination. XW, ZC, LY, XH, YY, YZ, KL, HM and CS contributed to the participants' enrollment and assessment. YL and NH conducted the MRI scans. MX, ZD and YH performed the data analysis. XW and MX drafted the manuscript. QC and PS reviewed the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

All authors reported no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.03.033.

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