Published in final edited form as:

Psychiatry Res. 2015 May 30; 232(2): 145–153. doi:10.1016/j.psychres.2015.03.001.

A splitting brain: imbalanced neural networks in schizophrenia

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Abstract

Dysconnectivity between key brain systems has been hypothesized to underlie the pathophysiology of schizophrenia. The present study examined the pattern of functional dysconnectivity across whole-brain neural networks in 121 first-episode, treatment-naïve patients with schizophrenia by using resting-state functional magnetic resonance imaging (rsfMRI). Group independent component analysis (ICA) was first applied to rsfMRI data to extract 90 functional components of the brain. The functional connectivity between these ICA components was then evaluated and compared between the patient and control groups. To examine the functional roles of significantly altered between-component connections in patients, each ICA component was ascribed to one of ten previously well-defined brain networks/areas. Relative to healthy controls (n=103), 29 altered functional connections including 19 connections with increased connectivity and 10 connections with decreased connectivity in patients were found. Increased connectivity was mainly within the default mode network (DMN) and between the DMN and cognitive networks, whereas decreased connectivity was predominantly associated with sensory networks. Given the key roles of DMN in internal mental processes and sensory networks in inputs from the

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Declaration of Interest

None.

external environment, these patterns of altered brain network connectivity could suggest imbalanced neural processing of internal and external information in schizophrenia.

Keywords

schizophrenia; fMRI; resting state; functional connectivity; neural networks

1. Introduction

Bleuler (1911) first described the core symptoms of schizophrenia with the term of ‘psychic splitting’ or a failure of integration of mental function, suggesting that brain dysconnection might underlie the pathophysiological mechanism of schizophrenia (Bleuler, 1911). The literature supporting the dysconnection hypothesis has been summarized by Friston (1998) to explain the relationship between core schizophrenia symptoms, impaired synaptic plasticity and dysconnectivity between brain regions (Friston, 1998).

Indeed, a growing body of studies in schizophrenia has confirmed aberrant functional connectivity, revealed by the technique of resting-state functional magnetic resonance imaging (rsfMRI) (Biswal et al., 1995), in multiple brain regions (Bassett et al., 2008; Collin et al., 2011; Jafri et al., 2008; Liu et al., 2008; Lynall et al., 2010; Skudlarski et al., 2010), particularly in a network named the default mode network (DMN) (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009). Besides the DMN, anomalous functional connectivity has been found in other brain networks and neural circuitries in schizophrenia such as the attention network, executive network (Woodward et al., 2011), thalamocortical circuit (Klingner et al., 2013; Welsh et al., 2010) and DMN-striatum circuit (Hoptman et al., 2010; Salvador et al., 2010). In addition, altered functional connectivity was observed in the auditory cortex and temporal-parietal areas in patients with schizophrenia who reported auditory hallucinations (Gavrilescu et al., 2010; Vercammen et al., 2010). This evidence is compelling to suggest that schizophrenia is characterized by dysconnections within and/or among multiple brain networks.

Although the patterns of functional dysconnectivity in schizophrenia have been extensively explored, most of aforementioned studies occurred while subjects were already being prescribed anti-psychotic medications. It has been repeatedly shown that antipsychotics can significantly affect brain connectivity (Gur et al., 1998; Snitz et al., 2005; Tost et al., 2010), and thus are confounding factors for understanding the pathophysiology of schizophrenia. In addition, schizophrenia undergoes continuous deteriorating courses so the chronicity of the disease adds another layer of complexity (Insel, 2010). Consequently, it is difficult for most of previous studies to disentangle whether the altered functional connectivity reflects the pathophysiological mechanisms of the disease itself or is secondary to the effects of medication or other potential confounders. Therefore, investigating brain dysconnectivity and its implications in functional deficit in first-episode, treatment-naïve patients with schizophrenia is of great importance for elucidating the fundamental neurobiology of schizophrenia.

The goal of the present study is to explore the patterns of aberrant functional connectivity across whole-brain networks and their relationship with clinical manifestations in schizophrenia. We used a relatively large sample of first-episode, treatment-naïve patients with schizophrenia to rule out the confounding factors of chronicity of the illness and treatment effects.

2. Subjects and Methods

2.1. Subjects

136 adult (aged from 18 to 50 years old) patients with schizophrenia from the Mental Health Center in West China Hospital were enrolled in the present study from August 2005 to March 2011. All patients were at their first episode of psychosis and were treatment naïve at recruitment and neuroleptic-naïve or minimally treated with antipsychotics less than 3 days before the fMRI scanning. They were interviewed and assessed using the Structured Clinical Interview for the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) (SCID-I/P) (First MB, 1997) by one of two qualified psychiatrists (W.D. and M.L.), and fulfilled diagnostic criteria for schizophrenia or schizophreniform disorder in the DSM-IV. 45 patients diagnosed with schizophreniform disorder when they first participated this study were followed up for at least 6 months to confirm the diagnosis of schizophrenia. All patients underwent the evaluations of psychopathology using the positive and negative syndrome scale (PANSS) (Kay SR, 1987). 113 adult (aged from 18 to 50 years old) healthy controls were recruited from the local area by poster advertisement. All controls were screened for the lifetime absence of psychiatric illnesses by using the SCID non-patient version (SCID-I/NP) (First MB, 1996). In addition, control subjects were interviewed to ascertain that there was no psychiatric illness in their first-degree relatives. Subjects with evidence of organic brain disorders, alcohol or drug abuse (including sedative, cannabis, stimulant, opioid, cocaine, hallucinogen, phencyclidine but not nicotine), or any other severe physical illness such as brain tumor or epilepsy were excluded from the study.

All participants were ethnic Han Chinese. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of West China Hospital, Sichuan University. After a complete description of the study, written informed consent was obtained from all healthy controls, patients and patients' guardians.

2.2. MRI data acquisition

All participants were scanned on a Signa 3.0-T scanner (General Electric, Medical Systems, Milwaukee, WI, USA) at the Department of Radiology at West China Hospital. The subject was instructed to lie inside the scanner, remained relaxed with eyes closed when T2*-weighted fMRI images were acquired with a gradient-echo echo-planar imaging (EPI) sequence: repetition time/echo time = 2000/30 milliseconds; flip angle = 90°; slice thickness = 5 mm (no slice gap), 30 axial slices; 64×64 matrix size; field of view = 240×240 mm²; voxel size = 3.75×3.75×5 mm³. The rsfMRI run contained 200 image volumes. Data from 15 patients and 10 controls were discarded due to excessive head motion (translational movement > 1.5 mm and/or rotation > 1.5°). As a result, data from 121 patients and 103 controls were used for further analysis.

2.3. Image Analysis

2.3.1. Image processing—rsfMRI image processing was carried out using Statistical Parametric Mapping (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (DPARSF)(Yan and Zang, 2010). The first 10 time points were removed to allow the fMRI signal to reach steady state. Raw rsfMRI images were first slice time corrected and realigned, and were subsequently unwarped to correct for susceptibility-by-movement interaction. Motion correction results showed that there was no significant difference between the patient and control groups in all six motion parameters (Van Dijk et al., 2012). Next, each image volume was spatially normalized to the Montreal Neurological Institute (MNI) EPI template, and smoothed with a Gaussian kernel (full-width half maximum = 4mm). Finally, all images were linearly detrended and band-pass filtered (0.01–0.08 Hz) to eliminate high-frequency physiological noise (Biswal et al., 1995). Nuisance covariates including six motion parameters, cerebrospinal fluid (CSF) and white matter signals were regressed out (Fox et al., 2005; Fox et al., 2009).

Group independent component analysis (ICA) was performed using the GIFT toolbox(<http://www.nitrc.org/projects/gift/>) to parcellate the whole brain into elementary components. To generate a fine-grained parcellation of the brain, a relatively high model order was selected (component number = 90). The Infomax ICA algorithm was used to perform spatial ICA in ICASSO (<http://www.cis.hut.fi/projects/ica/icasso>). Subject-specific spatial maps and time courses were estimated using the GICA1 back reconstruction method based on PCA compression and projection (Calhoun et al., 2001; Erhardt et al., 2011). This projection method can well preserve the functional connectivity of individual subjects (Erhardt et al., 2011). Independent components were scaled to z-scores. The spatial maps of individual components were defined by the group ICA results in the healthy control group, and the time series of each component in both controls and patients was extracted by averaging the time series of all voxels with z scores > 2 (equivalent to $p < 0.05$) in the corresponding component map obtained from healthy controls (Figure 1).

2.3.2. Functional connectivity evaluated by correlation analysis—The time courses of ICA components were used in functional connectivity analysis. For each subject, the correlation coefficient (r value) between the time courses of each pair of components was calculated. All r values were then transformed to z scores using Fisher's z transformation as a quantitative measure of functional connectivity strength. These steps yielded a connectivity matrix for each subject. Each element of this matrix represented the strength of functional connectivity between two components (Liang et al., 2011). To estimate the reliability of between-component connectivity in both control and patient groups, all subjects within each group were randomly divided into two subgroups, respectively. Functional connectivity strength of each individual connection was averaged across each subgroup. Reproducibility of between-component connectivity strength was assessed by the correlation of the mean connectivity strength of all connections between two subgroups in either the control or patient group. This procedure was repeated 100 times and the correlation coefficient averaged across 100 repetitions for both control and patient groups was respectively calculated.

2.3.3. Functional connectivity difference between controls and patients—

Difference in individual functional connections (i.e. individual elements in the connectivity matrix) between controls and patients was statistically evaluated using two-sample t-tests. Statistical significance level was thresholded at $P < 0.05$, corrected for multiple comparisons using the false discover rate (FDR) criterion.

2.3.4. Ascribe each component to a functional brain network—In order to explain the functional significance of the aberrant between-component connectivity in patients with schizophrenia identified in the previous step, all components were ascribed to one of well-known resting-state neural networks (RSNs) reported in the literature (Beckmann, 2005) including the Default Mode Network (DMN), Left Dorsal Attention Network (ATN_L), Right Dorsal Attention Network (ATN_R), Executive control and Salience Network (ESN), Somatomotor Network (SMN), Primary Visual Network (PVN), Extrastriate Visual Network (EVN), Auditory Network (AUN) and two important functional areas including Thalamostriatal System (TSS) and Cerebellum (Robinson et al., 2009).

The spatial templates of all eight networks and two functional areas were generated based on a low-dimensionality group ICA results (ICA number = 30, $z = 2$) in the control group. This procedure was routinely used (Jafri et al., 2008). Anatomical locations of all networks were in excellent agreement with the literature (Beckmann, 2005). A template-matching algorithm based on the goodness of fit was used to ascribe each of 86 components to a functional network (Greicius et al., 2007). For each component, the goodness-of-fit score for each network was calculated as the number of voxels (z score > 2) inside the network template divided by the number of voxels (z score > 2) outside the network template ((Greicius et al., 2007), the goodness-of-fit was calculated as the number of voxels inside network template minus the number of voxels outside the network). The component was ascribed to the network with the highest goodness-of-fit score.

2.4. Relationship between aberrant functional connectivity and the clinical characteristics

For each aberrant functional connection identified from the previous processing, the correlation between strength of abnormal functional connectivity and PANSS scores (positive symptoms, negative symptoms, disorganization symptoms, excitement, emotional distress) (van der Gaag et al., 2006), and untreated illness duration were assessed by Pearson correlation analysis. Considered that hallucination and delusion were common symptoms in schizophrenia, the scores of these two symptoms were also included in the analysis. SPSS15.0 statistical software was used and the statistical significance threshold was set at $p < 0.05$.

3. Results

3.1. Demographics and clinical assessment

The demographics of all subjects are listed in Table 1 including a total of 121 patients: 62 females and 59 males. Difference in demographics was examined by using Chi-square tests or independent two sample t-tests. There was no significant difference in sex ($p = 0.859$), while the education years were significantly longer ($p = 0.042$) in healthy controls, who

were also slightly older ($p = 0.001$) than subjects with schizophrenia. Summary of PANSS scores is also listed in Table 1, suggesting that these individuals were at the acute stage of psychosis at the time of recruitment.

3.2. Aberrant individual functional connections in patients with schizophrenia

Figure 1 shows the spatial maps of 90 components generated by group ICA. Among the spatial maps of all 90 components, four components (C14, C20, C33 and C59) were located at CSF areas and were identified as artifactual components. A low number of artifactual components identified was due to the majority of physiologic noise had been eliminated by regressing out the signals from the white matter and ventricles in data preprocessing. These artifactual components were eliminated, with the remaining 86 components entering further between-group comparison analysis. To estimate the reliability of between-component connectivity, the correlation of the corresponding connectivity between two halves of randomly divided subgroups was calculated. Mean correlation coefficients (averaged from 100 repetitions) were 0.98 ($p < 10^{-10}$) for both control and patient groups, demonstrating excellent reliability of between-component connectivity (Figure 2).

Difference in between-component functional connections was revealed by comparing 86×86 connectivity matrices between the control and patient groups with two-sample t-tests. We identified 29 abnormal individual functional connections with 19 connections demonstrating increased connectivity and 10 connections demonstrating decreased connectivity ($p < 0.05$, FDR corrected) as shown Table 2a / 2b and Figures 3a / 3b.

3.3. Aberrant connectivity between brain networks in patients with schizophrenia

The maps of all eight networks and two functional areas were shown in Figure 4. After ascribing each of 86 components to a functional network, altered individual between-component connections can be interpreted in terms of abnormal connectivity between well-characterized RSNs. The results showed (Figure 5, Table 2a and Table 2b) hyperconnectivity within DMN, between DMN and ATN_L, ATN_R, ESN and TSS, as well as between ATN_R and ESN, while hypoconnectivity was observed between EVN and AUN, ESN and DMN, between PVN and DMN, and between AUN and SMN. In addition, as indicated by the line weight in Figure 5, the strength of abnormal functional connectivity between brain networks was evaluated by the number of aberrant individual connections between components respectively belonging to networks.

3.4. Correlation between abnormal functional connectivity and clinical assessments

In patients group, one connection between the SMN and AUN was found negatively correlated with negative symptoms (between C23 and C73, $r = -0.193$, $p = 0.036$). Excitement symptoms were positively correlated to one connection between the ESN and DMN (between C31 and C77, $r = 0.204$, $p = 0.027$) and negatively related to one connection between the SMN and AUN (between C23 and C73, $r = -0.248$, $p = 0.007$). Disorganization symptoms were found positively correlated to one connection between the DMN and DMN (between C13 and C77, $r = 0.198$, $p = 0.032$). Delusion was found positively correlated to one connection between the DMN and ESN (between C31 and C90, $r = 0.186$, $p = 0.044$). Hallucination was found negatively correlated to one connection between the DMN and

EVN (between C35 and C65, $r = -0.203$, $p = 0.028$). And the untreated illness duration was negatively correlated to two connections between the EVN and ESN (between C7 and C35, $r = -0.180$, $p = 0.048$; between C7 and C75, $r = -0.230$, $p = 0.011$). However, none of these significant correlations survived Bonferroni multiple-comparison correction.

4. Discussion

In the present study, the spatial pattern of resting-state functional connectivity across the whole brain networks was evaluated in a large sample of subjects with first-episode treatment-naïve schizophrenia. We found hyperconnectivity mainly existed within DMN and between DMN and networks associated with attention and executive functions, while hypoconnectivity was associated with sensory networks including auditory, visual and somatomotor networks in schizophrenia. Importantly, aberrant functional connections were correlated with clinical symptoms.

Aberrant functional connectivity between RSNs identified in the present study is in general consistent with previous studies in chronic patients. For instance, hyperconnectivity has been shown to exhibit within DMN (Holt et al., 2011; Salvador et al., 2010; Whitfield-Gabrieli et al., 2009), between DMN and ESN (Jafri et al., 2008), between DMN and TSS (Klingner et al., 2014; Salvador et al., 2010), and hypoconnectivity has been reported between DMN and visual network (Kang et al., 2011; Sehatpour et al., 2010), between AUN and SMN (Jafri et al., 2008; Skudlarski et al., 2010; Vercammen et al., 2010) in chronic patients with schizophrenia. Nevertheless, we found that several aberrant functional connections revealed here were not previously reported, including increased connectivity between DMN and DAN, between DAN and ESN, as well as weaker connectivity between EVN and AUN/ ESN, indicating that these altered functional connections might be characteristic to first-episode, drug naïve patients. It is also possible that these new findings might result from higher statistical power due to the large sample size we used.

In the present study, the most prominent connectivity change was found within the DMN. Abnormally enhanced DMN connectivity was detected in chronic schizophrenic patients (Holt et al., 2011; Salvador et al., 2010; Whitfield-Gabrieli et al., 2009) and in their relatives without psychotic symptoms (van Buuren et al., 2012; Whitfield-Gabrieli et al., 2009). Consistent with these studies, our results suggest that the abnormality in DMN already displayed at the early stages of psychosis and might be a fundamental pathophysiological feature of schizophrenia. Normally, the DMN is characterized by elevated coherent spontaneous activities at rest, and deactivated activities when subjects perform cognition-related tasks (Raichle et al., 2001). A large number of studies suggested that DMN is involved in introspection activities including endogenously generated thought, self-projection, theory of mind, social cognition and mind wandering (Buckner et al., 2008; Gusnard et al., 2001; Raichle et al., 2001) as well as supports a broad low-level focus of attention to monitor the external environment for unexpected events as a “sentinel” of the brain (Hahn et al., 2007; Mason et al., 2007). Hyperconnectivity within the DMN observed in the present study and others may suggest a potential alteration of these functions in schizophrenia such as excessive immersion in their own inner world or lack of ability to rule out messy information from outer world. In addition, increased connectivity was also

detected between DMN and networks associated with attention and executive functions (e.g. ATN_L, ATN_R and ESN). As suggested in previous studies, neurocognitive deficits especially in attention, executive and memory functions are important clinical features of schizophrenia (Aleman et al., 1999; Ma et al., 2007; Wang et al., 2007). One proposed neural mechanism underlying these neurocognitive deficits is that schizophrenic patients fail to deactivate the DMN during cognitive tasks (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). Excessively tight connectivity between DMN and ATN as well as ESN observed in the present study could be related to this process and contribute to the neurocognitive deficits in schizophrenia.

Another striking finding of the present study is decreased functional connectivity between sensory networks including visual, auditory and somatomotor networks, as well as between sensory networks and higher-level cognitive networks including DMN and ESN in individuals with schizophrenia. These results indicated that the integration of sensory information and the cooperation between sensory and cognitive networks could be compromised in schizophrenia. And Furthermore, deficits in perceptual organization have been demonstrated in schizophrenia and suggested to be one manifestation of a wider disturbance in the integration of contextually related information across space and time (Silverstein and Keane, 2011; Uhlhaas and Silverstein, 2005). Researchers indicated that perceptual organization deficits in schizophrenia were related to impaired functional interactions between occipital, temporal, parietal and frontal regions (Silverstein and Keane, 2011). These results collectively suggested that schizophrenia is associated with connectivity deficits across distributed sensory networks and higher-order cognitive regions. The integration of sensory processing and cognitive processing can involve two processes: the bottom-up process and the top-down process. Both impaired top-down control of visual search and bottom-up deficits during visual attention have been detected in schizophrenia (Butler et al., 2008; Neuhaus et al., 2011). In addition, auditory hallucination has been considered as a failure of top-down control of bottom-up perceptual processes (Hugdahl, 2009). Collectively, weaker functional connectivity between sensory and cognitive networks in schizophrenia may imply a distorted representation of the external world and impaired coordination between perception and cognitive functions in individuals with schizophrenia.

In addition to aberrant functional connectivity between cortical networks, abnormal connectivity was also detected in a cortico-subcortical circuit between thalamus (belonging to TSS) and the prefrontal cortex (belonging to the DMN) in individuals with schizophrenia. Evidence has showed that thalamus plays a pivotal role in information communication and integration between the thalamostriatal system and prefrontal cortex (Haber and McFarland, 2001). Altered thalamic-prefrontal connectivity has been reported in individuals with schizophrenia in both neuroimaging (Klingner et al., 2014; Pakkenberg et al., 2009; Salvador et al., 2010; Welsh et al., 2010) and neuropathological studies (Hirschfeld et al., 2000), which suggested that thalamo-prefrontal cortical circuitry is an important pathophysiologic feature of schizophrenia. Hyperconnectivity between thalamus and prefrontal cortex could lead to excessive information transferring to the prefrontal cortex without enough thalamic control on motor/sensory information processing (Klingner et al., 2014).

In the present study, we also found that altered functional connectivity in schizophrenia was associated with the severity of clinical symptoms. For instance, excitement and delusion were positively correlated to increased functional connectivity between DMN and ESN, and disorganization was associated with increased functional connectivity within DMN. Conversely, the severity of negative symptoms (e.g. apathy and anhedonia) as well as hallucination increased with decreased functional connectivity between sensory and motor networks as well as between sensory and DMN. These results suggest that aberrant connectivity between DMN and other networks or within DMN might to some extent contribute to these symptoms in schizophrenia. In addition, the duration of untreated psychosis negatively associated with weaker connectivity between EVN and ESN implied functional connectivity would change with disease duration.

There are several limitations of the present study that need to be further addressed in future studies. First, the mean age of healthy controls (28.97 years) was about 3.5 years older than patients (25.48 years). There exists the possibility that functional connectivity changes observed in the present study may result from the difference in brain development (Kelly et al., 2009). However, almost identical results were generated in subset of patients (n=120) and healthy controls (n=93) with no significant difference in age ($p=0.06$). Second, sample selected bias might exist in the present study. Patients with hostility and violence were not included in the present study because these patients could not cooperate during fMRI scanning.

The present study revealed the pattern of functional dysconnectivity between brain networks in a first-episode, treatment-naïve adults with schizophrenia. We observed hyperconnectivity within the DMN and between the DMN and other cognitive networks, as well as hypoconnectivity between sensory networks and cognitive networks. These results can be important for understanding the neural mechanism underlying the primary clinical features of the disease including impaired sensory functions, cognitive deficits, hallucination, delusion, disorganized symptoms, social functioning and avolition.

Acknowledgements

This work was partly supported by National Nature Science Foundation of China (81130024, 30530300 and 30125014, TL), the Ph.D. Programs Foundation of Ministry of Education of China (20110181110014, TL), National Key Technology R & D Program of the Ministry of Science and Technology of China during the 12th Five-Year Plan (2012BAI01B00, TL), NARSAD Independent Investigator Award (TL), the National Basic Research Program of China (973 Program 2007CB512301, TL), and the Wellcome Trust (International Collaborative award to TL and DAC), the Chinese National Nature and Science Foundation (Grant No.81071089) and by Doctoral Fund of Ministry of Education of China (Grant No.20110181120033). The work was also supported by the National Institutes of Health Grant Numbers R01MH098003 (PI: Nanyin Zhang, PhD) from the National Institute of Mental Health and R01NS085200 (PI: Nanyin Zhang, PhD) from the National Institute of Neurological Disorders and Stroke.

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Highlights

1. A large sample of first-episode drug-naïve schizophrenic patients was acquired.
2. Increased connectivity within default-mode network was observed in schizophrenia.
3. Hypoconnectivity was predominantly associated with sensory networks in patients.

Figure 1. Spatial maps of 90 ICA Components

Each slice shows a separate component. The z coordinate is labeled at the top left corner of each slice.

Figure 2. Between-component connectivity in both groups

Left: Mean matrices of between-component connectivity (in z scores) for the control and patient groups.

Right: The correlation of the corresponding between-component functional connectivity strength (in z scores) between two randomly divided subgroups in one trial for the control and patient groups. Mean correlation coefficient averaged from 100 repetitions was 0.98 for both the control group and patient group.

Figure 3. Altered functional connectivity between elementary functional clusters in patients
a) 19 functional connections with hyperconnectivity; b) 10 functional connections with hypoconnectivity.

Figure 4. Ten Resting-state functional networks

A: Auditory Network (AUN) including superior temporal gyrus, temporal pole, Heschl gyrus, part of middle temporal gyrus; B: Somatomotor Network (SMN) including precentral gyrus, postcentral gyrus, rolandic operculum, paracentral lobule, supplementary motor area; C: Primary Visual Network (PVN) including lingual gyrus, calcarine, cuneus; D: Extrastriate Visual Network (EVN) including occipital gyrus, inferior occipital gyrus; E: Left Dorsal Attention Network (DAN_L) including left inferior parietal lobule, part of left superior parietal lobule; F: Right Dorsal Attention Network (DAN_R) including right parietal lobule, part of right superior parietal lobule; G: Executive control and Salience Network (ESN) including part of anterior cingulate cortex, dorsolateral prefrontal cortex, insular, middle frontal gyrus, inferior frontal gyrus-triangular part/orbital part/opercular part, Inferior parietal, part of angular gyrus; H: Default mode Network (DMN) including

precuneus, posterior cingulate, anterior cingulate, medial prefrontal cortex, dorsomedial prefrontal cortex, part of superior parietal gyrus, angular, part of middle temporal; I: Thalamostriatal System (TSS) including thalamus, caudate, putamen; J: Cerebellum.

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Figure 5. Altered functional connectivity between networks in schizophrenia

Red: Increased functional connectivity in schizophrenia; Blue: Decreased functional connectivity in schizophrenia. A: Auditory Network; B: Somatomotor Network; C: Primary Visual Network; D: Extrastriate Visual Network; E: Left Dorsal Attention Network; F: Right Dorsal Attention Network; G: Executive control and Salience Network; H: Default mode Network; I: System; J: Cerebellum

Table 1

Demographic and clinical characteristics of two groups

Subjects with schizophrenia (N=121)		Healthy controls (N=103)			
	Mean	SD	Mean	SD	
Age (years)	25.48	7.46	28.97	8.35	T (2-tailed)
Education (years)	12.38	3.38	13.36	3.78	df
Illness Duration (months)	9.96	19.04			P
PANSS_ scores					
Total	91.74	16.94			
Positive	28.03	5.71			
Negative	20.95	9.14			
Disorganization	34.30	7.21			
Excitement	21.96	5.35			
Emotional distress	23.28	6.11			
Delusion	5.29	1.15			
Hallucination	3.71	1.91			
	N	%	N	%	
Sex					χ^2
Male	59	48.76	49	47.57	df
Female	62	51.24	54	52.43	P

Table 2

Statistical significance: $P < 0.05$, FDR correction for multiple comparisons.

a. Functional connections with hyperconnectivity in schizophrenia.

Between Networks	Between Components [MNI (x y z)]	P Value
DMN - DMN	C13: Middle frontal gyrus, orbital part_R (39 57 -3)	C22: Superior frontal gyrus, dorsolateral_L (-21 42 51)
		Superior frontal gyrus, dorsolateral_R (21 42 51)
	C13: Middle frontal gyrus, orbital part_R (39 57 -3)	C55: Posterior cingulate gyrus (0 -42 21)
	C13: Middle frontal gyrus, orbital part_R (39 57 -3)	C77: Superior frontal gyrus, medial (0 57 6)
	C13: Middle frontal gyrus, orbital part_R (39 57 -3)	C90: Precuneus (0 -63 36)
	C78: Precuneus (-6 -75 36)	C79: Superior frontal gyrus, medial orbital_L (-33 57 -6)
		Superior frontal gyrus, medial orbital_R (33 60 -9)
	C79: Superior frontal gyrus, medial orbital_L (-33 57 -6)	C90: Precuneus (0 -63 36)
	Superior frontal gyrus, medial orbital_R (33 60 -9)	
DMN - DAN_L	C39: Inferior frontal gyrus, orbital part_L (-42 48 -12)	C6: Posterior cingulate gyrus (-3 -60 15)
	Inferior frontal gyrus, orbital part_R (42 48 -12)	
	C39: Inferior frontal gyrus, orbital part_L (-42 48 -12)	C22: Superior frontal gyrus, dorsolateral_L (-21 42 51)
	Inferior frontal gyrus, orbital part_R (42 48 -12)	Superior frontal gyrus, dorsolateral_R (21 42 51)
	C39: Inferior frontal gyrus, orbital part_L (-42 48 -12)	C55: Posterior cingulate gyrus (0 -42 21)
	Inferior frontal gyrus, orbital part_R (42 48 -12)	
	C39: Inferior frontal gyrus, orbital part_L (-42 48 -12)	C78: Precuneus (-6 -75 36)
	Inferior frontal gyrus, orbital part_R (42 48 -12)	
	C39: Inferior frontal gyrus, orbital part_L (-42 48 -12)	C90: Precuneus (0 -63 36)
	Inferior frontal gyrus, orbital part_R (42 48 -12)	
DMN-DAN_R	C88: Angular_R (42 -66 51) Angular_L (-39 -66 51)	C11: Superior frontal gyrus, medial orbital (0 45 -9)
	C88: Angular_R (42 -66 51) Angular_L (-39 -66 51)	C77: Superior frontal gyrus, medial (0 57 6)
DMN-TSS	C12: Thalamus (3 -21 3)	C2: Middle frontal gyrus_L (-39 36 39)
		Middle frontal gyrus_R (48 18 45)

a. Functional connections with hyperconnectivity in schizophrenia.

Between Networks	Between Components [MNI (x y z)]		P Value
	C12: Thalamus (3 -21 3)	C82: Superior frontal gyrus, medial orbital_L (-3 42 -12)	0.0019
DMN-ESN	C31: Middle frontal gyrus_L (-36 48 15)	C55: Posterior cingulate gyrus (0 -42 21)	0.0003
	Middle frontal gyrus_R (36 48 15)		
	C31: Middle frontal gyrus_L (-36 48 15)	C77: Superior frontal gyrus, medial (0 57 6)	0.0004
	Middle frontal gyrus_R (36 48 15)		
	C31: Middle frontal gyrus_L (-36 48 15)	C90: Precuneus (0 -63 36)	0.0007
	Middle frontal gyrus_R (36 48 15)		
DAN_R-ESN	C10: Middle frontal gyrus_R (45 45 21)	C47: Superior frontal gyrus_R (27 54 36)	0.0014
	Middle frontal gyrus_L (-45 39 21)		

b. Functional connections with hypoconnectivity in schizophrenia.

Between Networks	Between Components [MNI (x y z)]		P Value
EVN - AUN	C49: Superior occipital gyrus_R (21 -96 21)	C1: Superior temporal gyrus_L (-48 -24 9)	0.0016
	Superior occipital gyrus_L (-18 -99 18)	Superior temporal gyrus_R (57 -18 9)	
	C49: Superior occipital gyrus_R (21 -96 21)	C86: Superior temporal gyrus_R (63 0 -3)	0.0023
	Superior occipital gyrus_L (-18 -99 18)	Middle temporal gyrus_L (-63 -7 -3)	
EVN - ESN	C7: Inferior frontal gyrus, orbital part_L (-51 18 -3)	C35: Calcarine (3 -99 6)	0.0018
	Middle temporal gyrus_L (-60 -51 -3)		
	C7: Inferior frontal gyrus, orbital part_L (-51 18 -3)	C74: Fusiform gyrus_L (-21 -75 -12)	0.0019
	Middle temporal gyrus_L (-60 -51 -3)	Fusiform gyrus_R (24 -72 -12)	
	C7: Inferior frontal gyrus, orbital part_L (-51 18 -3)	C75: Inferior occipital gyrus_L (-27 -96 -12)	0.0020
	Middle temporal gyrus_L (-60 -51 -3)	Inferior occipital gyrus_R (27 -99 -6)	
EVN - DMN	C35: Calcarine (3 -99 6)	C45: Precuneus (0 -54 48)	0.0011
	C35: Calcarine (3 -99 6)	C65: Middle temporal gyrus_R (60 -24 -15)	0.0007
PVN - DMN		Middle temporal gyrus_L (-60 -27 -9)	
	C61: Cuneus (0 -87 33)	C54: Middle temporal gyrus_R (63 -45 6)	0.0008
		C65: Middle temporal gyrus_R (60 -24 -15)	0.0020
	C61: Cuneus (0 -87 33)	Middle temporal gyrus_L (-60 -27 -9)	
AUN - SMN	C23: Postcentral gyrus_R (24 -42 72)	C73: Superior temporal gyrus_L (-63 -27 18)	0.0003
	Postcentral gyrus_L (-24 -42 72)	Superior temporal gyrus_R (63 -27 18)	

Abbreviations:

C: Component, L: Left, R: Right

AUN: Auditory Network, TSS: Thalamostriatal System, DAN_L: Left Dorsal Attention Network, DAN_R: Right Dorsal Attention Network, DMN: Default mode Network, ESN: Executive control and Salience Network, EVN: Extrastriate Visual Network, PVN: Primary Visual Network, SMN: Somatomotor Network