Modular-Level Alterations of Single-Subject Gray Matter Networks in Schizophrenia

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Modular-level alterations of single-subject gray matter networks in schizophrenia

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Abstract:

Schizophrenia is often regarded as a psychiatric disorder caused by disrupted
connections in the brain. Evidence suggests that the gray matter of schizophrenia
patients is damaged in a modular pattern. Recently, abnormal topological organization
was observed in the gray matter networks of patients with schizophrenia. However, the
modular-level alteration of gray matter networks in schizophrenia remains unclear. In

this study, single-subject gray matter networks were constructed for a total of 217 subjects (116 patients with schizophrenia and 101 controls). We analyzed the topological characteristics of the brain network and the strengths of connections between and within modules. Compared with the outcomes in the control group, the global efficiency and participation coefficient values of the single-subject gray matter networks in schizophrenic patients were significantly reduced. The nodal participation coefficient of the regions involving the FPN, DMN and SCN were significantly decreased in subjects with schizophrenia. The intermodule connections between the FPN and VIS and between the DMN and SCN, in the FPN were significantly reduced in the patient group. In the FPN, the intramodule nodal connection strength of the left orbital inferior frontal gyrus and right inferior parietal gyrus was significantly decreased in schizophrenia patients. Reduced intermodule nodal connection strength between the FPN and VIS was associated with the severity of schizophrenia symptoms. These findings suggest that abnormal intramodule and intermodule connections in the structural brain network may a biomarker of schizophrenia symptoms.

Key words: Schizophrenia; Structural network; Modularity; Strength; Connection

1. Introduction

Schizophrenia is a devastating and chronically debilitating brain disorder. Clinical symptoms of the disease include auditory hallucinations, confusion, paranoia, gluttony, anhedonia, emotional dullness and apathy. Cognitive impairment affects attention,

memory, emotion, motivation, thought and language processes, social functions and emotional regulation. The various pathogenesis models of schizophrenia are still under debate, but the idea of neurodevelopment and connectivity disorders remains central to these conceptualizations(M. Li et al., 2019; Rapoport, Giedd, & Gogtay, 2012).

Due to advances in neuroimaging technology, graph theory analysis has become a powerful method to examine the complex connectivity of the brain. By means of graph theory analysis, a correlation network of gray matter covariation in patients with schizophrenia was constructed, which is helpful for visually depicting the real structural connection abnormalities between the brain regions of patients with fine classification. He, Chen, and Evans (2007) mapped the brain into a standard space by measuring the cortical thickness of MRI images, constructed the human brain structure network for the first time, and found that the cortical thickness of the subjects in the groups had covariation. Y. Zhang et al. (2012) applied this method in the study of schizophrenia, and proved that there were abnormalities in the gray matter structure of schizophrenia. However, this study built networks at the group level and focused on individual brain regions; therefore, analysis may have ignored the impact of individual differences. To map an individual's brain network, Tijms et al. (2015) constructed single-subject GM networks based on cortical similarity in schizophrenia patients and high-risk subjects, indicating the topological characteristics of brain network changes in high-risk groups that developed schizophrenia. In addition, X. Li et al. (2019) explored the GM network of schizophrenia patients and high-risk groups and found that the brain nodal degree and efficiency were significantly decreased in schizophrenia

patients compared to the controls. Thus, MRI-based single-subject GM networks are a significant method to explore structural abnormalities in the brains of schizophrenic patients.

In general, the modular structure of a healthy brain can be described as an optimized network organization composed of spatially separated modules (Sporns & Betzel, 2016). Recently, Seidlitz et al. (2018) mapped the cortical network based on the interregional similarities of multiple morphometric parameters measured using MRI and found that the resulting morphometric similarity networks of the human brain had a complex topological organization comprising modules and high-degree hubs. In previous research on modularized topology properties, it was found that the connection can more accurately reflect the change in information exchange rules and organizational patterns of each module(Avena-Koenigsberger, Misic, & Sporns, 2017). Numerous studies have found a tendency to modularize areas of the brain that are structurally abnormal in schizophrenia. For instance, Fornito, Yücel, Patti, Wood, and Pantelis (2009) found by a meta-analysis of 37 studies that people with schizophrenia showed widespread loss of GM in the frontal lobe and limbic and subcortical areas. In particular, decreased GM volume in the default mode network (DMN) and visual network (VIS) were also reported in schizophrenia (Chatterjee, Kumar, Rana, Agarwal, & Kumar, 2020; Salgado-Pineda et al., 2011). In addition, the GM networks of schizophrenia patients manifested as a decreased degree of connectivity in the frontal lobe (Tijms et al., 2015) and decreased efficiency in the superior occipital gyrus (X. Li et al., 2019). These results may imply brain structural changes in patients with

schizophrenia and lead to the hypothesis that psychiatric disorders exhibit cross-module and module-specific disorganization patterns in GM brain networks. However, the modular-level alteration of single-subject GM networks in schizophrenia is unclear.

In the present study, we investigated the graph properties of single-subject GM networks in schizophrenia patients using a method proposed by (H. Wang, Jin, Zhang, & Wang, 2016) to statistically describe single-subject GM networks using T1-weighted MRI scans. In the first step, the network topological characteristics of the abnormal brain structures were compared with those of the control group to observe the changes in global attributes and nodal participation coefficient (PC) in patients with schizophrenia. Next, we divided the network into five modules to analyze the strength within and between modules. Finally, we explored the relationship between network properties and the severity of schizophrenia.

2. Materials and methods

2.1. Subjects

The MRI data of this study were obtained from the NU Schizophrenia Data Software Tool (NUSDAST) of the public schizophrenia neuroimaging database (<http://schizconnect.org/>). The study included 116 patients with schizophrenia and 101 normal control subjects. MRI data were obtained from all subjects by using a 1.5 T magnetic resonance scanner. T1-weighted scans were acquired with a three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE)

sequence (number of slices = 128; repetition time (TR)=9.7 ms; echo time (TE)=4 ms; slice thickness=1.25 mm; and flip angle = 10°). The detailed demographic and clinical features of the subjects are summarized in Table 1.

2.2. Imaging preprocessing

Structural images were preprocessed using Statistical Parametric Mapping (SPM) software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Individual structural images were first segmented into GM, white matter, cerebrospinal fluid, bone, soft tissue, and air/background using the default tissue probability maps as priors. We visually confirmed all automatic segmentations. Then, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) tools in SPM were used to create a template to determine nonlinear deformations for warping GM and white matter images into Montreal Neurological Institute (MNI) coordinate space. In this process, GM data were resampled to 2 mm³ voxels. The voxel-based GM volume maps were then calculated.

2.3. Extraction of brain networks

Single-subject GM networks were obtained using a method that has been previously described (H. Wang et al., 2016). The large-scale single-subject morphological network for each participant was created based on the regional GM volume maps. A brain morphological network was defined as a set of nodes and edges interconnecting with the nodes; the nodes represented brain regions, and edges

represented interregional similarity in the distribution of the regional GM volume.

To define the network nodes, the GM volume image was parcellated into 90 regions according to the AAL Atlas. The GM volume value of each of the 90 regions was then calculated. The probability density function of these 90 values was estimated using kernel density estimation (KDE) with bandwidths that were chosen automatically. The regional probability density function (PDF) and the Kullback-Leibler divergence-based similarity (KLS) measure between each pair of the 90 regions in their PDFs were then calculated (describing interregional similarity in the distribution of regional GM volume in individual participants). The network edges were defined as KLS with a consecutive sparsity threshold S , ranging from $0.1 < S < 0.4$ (interval=0.01).

2.4. Network properties

GRETNA (J. Wang et al., 2015) software was used to calculate network properties. For each participant, the KLS threshold-based weighted morphological brain network was constructed at each sparsity level (0.05–0.4 with interval of 0.02). The area under the curve (AUC) reflecting measures across the sparsity parameter S was calculated for each network metric, providing a summarizing scalar for the topological characterization of brain networks that avoided the use of an arbitrary single threshold. This approach has been shown to be sensitive for detecting topological alterations of brain networks (Achard & Bullmore, 2007; J. Zhang et al., 2011). Both global and nodal network properties were calculated at each sparsity threshold. Global metrics included local efficiency (Eloc), global efficiency (Eglob), modularity, PC, global

strength and PC after dividing the network into five modules (PC_5). The nodal PC was examined in each ALL region.

We examined modules included in the DMN, VIS, subcortical network (SCN), frontoparietal attention network (FPN), and sensorimotor network (SMN) as defined by Csermely, Xia, Wang, and He (2013). Brain regions were divided as shown in supplementary material Table S1. We calculated the AUC at each sparsity level (0.05–0.4 with interval of 0.02) of the strength of all ROI-ROI connections within and between each module.

The intramodule strength is calculated as the average strength of all nodes in the module by the equation

$$Str_{module_tra}(M) = \frac{1}{N} \sum_{i \neq j \in M} S_{i,j}$$

where N is the number of nodes in module M , and $S_{i,j}$ is the strength between node i and node j . The intramodule strength of the node is computed as the average value of the sum of the connection strengths between this node and other nodes in the same module.

The intermodule strength measures the connection strength of nodes between different modules in the weighted network. It can be computed in the equation

$$Str_{module_ter}(M_a, M_b) = \frac{1}{N_a + N_b} \sum_{i \in M_a, j \in M_b} S_{i,j}$$

where N_a is the number of nodes in module M_a , N_b is the total number of nodes in module M_b , i and j are the nodes in module M_a and M_b , respectively, and $S_{i,j}$ is the strength between node i and node j . The intermodule strength of the nodes is defined as the average value of the sum of the connections between this node and all nodes that

belong to another module.

2.5. Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 20 (<http://www.spss.com/>). Between-group differences in network characteristics were analyzed using an independent sample T test. We adopted the false discovery rate (FDR) to correct for multiple comparisons when comparing nodal properties across groups. Region pairs with between-group differences in nodal characteristics were identified using the GRETNA toolbox. We chose nodes that exhibited between-group differences in intramodule or intermodule strength and then created a difference matrix among those nodes. The differential connection was then graphically illustrated using the BrainNet Viewer toolbox (Csermely et al., 2013). Spearman's correlations were performed to evaluate relationships between significantly different edges and positive or negative scores on the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS scores, respectively) in schizophrenia patients.

3. Results

3.1. Alterations of global brain network properties

The topology of brain networks was altered in patients with schizophrenia. The graphs from schizophrenia patients were characterized by decreased Eglob ($t = -2.25$, $p = 0.03$), PC ($t = -2.29$, $p = 0.03$), strength ($t = -2.28$, $p = 0.03$) and PC_5 ($t = -2.95$, $p <$

0.01). There were no significant differences between groups in Eloc ($t = 0.93$, $p=0.35$) or modularity ($t = 0.03$, $p = 0.97$, Figure 1).

3.2 Alterations in the nodal PC

Brain regions exhibiting significant between-group differences in nodal PC were identified (FDR corrected $p<0.05$). Compared with control subjects, the schizophrenia patients exhibited decreased nodal PC in the precentral gyrus, the orbital part of the superior frontal gyrus, the orbital part of the middle frontal gyrus, the opercular part of the inferior frontal gyrus (IFG), the triangular part of the IFG, the olfactory cortex and the left caudate nucleus (Figure 2, Table 2).

3.3. Intermodule connectivity

We examined the differences in intermodule strength among the five modules and found that compared to normal control subjects, the intermodule strength of schizophrenia patients was significantly reduced for FPN-VIS ($t = -3.64$, $p < 0.01$) and SCN-DMN ($t = -2.38$, $p = 0.02$) connections. Schizophrenia patients showed significant weakening of the FPN-VIS comprising 31 brain regions and 93 anatomic connections and in the SCN-DMN comprising 41 brain regions and 33 anatomic connections (Figure 3).

Brain regions exhibiting significant between-group differences in intermodule nodal strength were identified (FDR corrected $p < 0.05$). Compared with that of normal control subjects, the patients with schizophrenia exhibited decreased FPN-VIS

intermodule nodal strength in the orbital part of the middle frontal gyrus, the opercular part of the IFG, the triangular part of the IFG, the right orbital part of the IFG, the left supplementary motor area, the right calcarine fissure and surrounding cortex, the lingual gyrus, the right superior occipital gyrus, the left middle occipital gyrus and the left inferior occipital gyrus (Figure 4A, Table 3). The schizophrenia patients exhibited decreased SCN-DMN intermodule nodal strength in the left gyrus rectus, right median cingulate, paracingulate gyri, right lenticular nucleus, and putamen (Figure 4B, Table 4).

3.4. Intramodule connectivity

We found that the intramodule strength of the FPN ($t = -2.09$, $p = 0.04$) was significantly reduced in schizophrenia patients. We identified significantly reduced networks composing 17 brain regions and 41 anatomic connections in the schizophrenia group (corrected for multiple comparisons using FDR) (Figure 5). In the FPN, the nodal intrastrength of the left orbital part of the IFG ($t = -3.85$, $p < 0.01$), right inferior parietal gyrus, and supramarginal and angular gyri ($t = -4.22$, $p < 0.01$) were significantly decreased in schizophrenia patients (Figure 6).

3.5. Correlation of network alterations with schizophrenia symptom severity

To investigate the relationship between the severity of schizophrenia symptoms and both inter- and intramodular connection alterations, we investigated their correlation with the SANS and SAPS scores. In schizophrenia, a significant correlation

of the SAPS score with connection strength was observed between the left orbital part of the middle frontal gyrus and the left lingual gyrus ($r = -0.19$, $p = 0.04$), the right opercular part of the IFG and the right calcarine fissure ($r = -0.20$, $p = 0.03$), the right opercular part of the IFG and the left lingual gyrus ($r = -0.28$, $p < 0.01$), the right opercular part of the IFG and the right lingual gyrus ($r = -0.28$, $p < 0.01$), the right opercular part of the IFG and the left inferior occipital gyrus ($r = -0.20$, $p = 0.03$), the left triangular part of the IFG and the left lingual gyrus ($r = -0.21$, $p = 0.03$), the left triangular part of the IFG and the right lingual gyrus ($r = -0.22$, $p = 0.02$) (Figure 7), and the right triangular part of the IFG and the left lingual gyrus ($r = -0.19$, $p = 0.04$) (Figure 7). We did not detect significant correlations between SANS scores and network parameters.

4. Discussion

The present study investigated single-subject GM networks showing alterations in schizophrenia. Our results indicate that schizophrenia patients demonstrated impaired large-scale integration, reflected in decreased Eglob, strength and PC values compared to the values of controls. The nodal PC of the regions involving the FPN, DMN and SCN were significantly decreased in schizophrenia. In addition, we examined differences in connectivity within and between known brain networks in patients with schizophrenia and the control group to test whether schizophrenia patients demonstrated disruptions in the coordinated activity of brain regions. Our results suggest that individuals with schizophrenia have impaired brain connectivity and that

these impairments are prominent in the FPN. In addition, the intermodule strength of the DMN-SCN and FPN-VIS was significantly reduced in schizophrenia patients. We also found that among regions with nodal alterations, eight edges between the FPN and VIS were significantly correlated with SAPS scores, thus indicating schizophrenia symptom severity.

4.1 Decreased capacity for brain network integration in schizophrenia patients

The human brain can efficiently generate and integrate information on a global and local scale, maintaining a perfect balance between local necessities (fault tolerance) and large-scale interactions. Our findings of decreased Eglob and strength in schizophrenia patients indicated their diminished capacity for efficient information processing compared to that of controls, resulting in a limited structural capacity to transmit information across brain regions; this finding is in agreement with that of a previous analysis of GM networks at the group level (Y. Zhang et al., 2012). The results of the study further support the notion that the interruption of brain connections forms the basis of how schizophrenia exerts its clinical impact.

The PC quantifies the diversity of brain region connections across modules (Guimera & Amaral, 2005), which refers to the optimal integration of modules in brain networks. Regions with a high PC have strong connections to many modules, whereas regions with a low PC have strong connections to a few modules (Baum et al., 2017). We found a significant decrease in PC in schizophrenia, further confirming that the level of brain integration in schizophrenia is lower than normal, which is consistent

with previous research findings (Yan et al., 2015).

4.2 Decline in nodal participation coefficient values

At a regional level, our findings included decreased nodal PC in the FPN involving the orbital part of the middle frontal gyrus, the opercular part of the IFG, and the triangular part of the IFG and in DMN regions including the precentral gyrus and the orbital part of the superior frontal gyrus. Past studies have shown that the GM volume in the frontal gyrus (Frascarelli et al., 2015; Kikinis et al., 2010) and precentral gyrus (Quinn et al., 2018) shrinks in schizophrenia patients. In addition, Mahdi Zarei demonstrated abnormal connections in the precentral gyrus in schizophrenia patients by analyzing its functional connectivity with the rest of the brain regions (Zarei, 2018). A reduced PC of the frontal gyrus and precentral gyrus in schizophrenia indicates greater isolation from other regions and may lead to control, attention and mood disorders in schizophrenia patients. In addition, we also found that the PC of the right olfactory cortex in DMN regions as well as the left olfactory cortex and left caudate nucleus in SCN regions decreased. Since the pioneering psychophysical studies of olfactory recognition memory in patients with schizophrenia by Campbell and Gregson (Campbell & Gregson, 2007), a host of investigators have reported that schizophrenia patients exhibit olfactory dysfunction (Moberg et al., 1999; Turetsky, Hahn, Borgmann-Winter, & Moberg, 2009). It has been suggested that the anatomical connectivity of the olfactory cortex may allow it to perform complex operations such as learning, memory retrieval, and other associative functions (Haberly, 1998). Therefore,

abnormalities in this region may cause impairment of olfactory function and complex manipulation in schizophrenia patients. A reduced GM volume in the left caudate nucleus (Li et al., 2018) has been found in schizophrenia patients. Notably, the caudate nucleus plays an important role in higher order motion control and in learning and memory, especially in feedback processing (Packard & Knowlton, 2002). Our results further demonstrate that a reduced PC in the caudate nucleus may lead to behavioral disorders in schizophrenia.

4.3 Decline in intermodule connections

We found reduced intermodule strength between regions in the VIS and FPN. Existing research findings show that schizophrenia has been linked to abnormalities in early developmental stages of visual processing (Barnett et al., 2008; Butler & Javitt, 2005). In an experiment in which schizophrenia patients were tested for visual changes known to activate the FPN, cortical responses to visual changes were reduced when schizophrenia patients were reacting to stimulus changes, and connections in the FPN region were reduced (Roiser et al., 2013). As mentioned above, our results more directly demonstrate reduced connectivity of structural networks between the VIS and FPN in patients with schizophrenia, which may lead to attentional disturbances in the processing of visual change information in schizophrenic patients.

We found that nodal strength was significantly decreased in the IFG (including the opercular part, triangular part, and orbital part), left supplementary motor area, occipital gyrus, right calcarine fissure and lingual gyrus in schizophrenia patients

between the FPN and VIS. Past studies have found that patients with severe mood disorders have GM changes in the bilateral IFG (Stegmayer et al., 2014b) and supplementary motor area (Stegmayer et al., 2014a). The supplementary motor area is a region that is primarily involved in autonomic movement and plays an important role in motor function (Sutherling & Levesque, 1996). Abnormalities in the IFG and left supplementary motor area may result in motor and executive impairment in schizophrenia patients. In addition, the occipital region and calcarine fissure are parts of the main processing center of visual stimuli. The lingual gyrus is involved in logical analysis and visual memory processing. Abnormal occipital gyrus (Chatterjee et al., 2020; R. Yu et al., 2013), lingual gyrus (T. Yu et al., 2018) and calcarine fissure (Berge et al., 2014) findings have been reported in patients with schizophrenia. The intermodule strength of the occipital gyrus, lingual gyrus and calcarine fissure in schizophrenia patients was significantly reduced, which is in line with the escalated visual and imaginary problems observed in patients with schizophrenia due to the difficulty in appropriately processing information (such as auditory, visual, and olfactory).

In addition, we found reduced intermodule strength between regions in the SCN and DMN, and nodal strength was significantly decreased in the left gyrus rectus, right putamen and right median cingulate and paracingulate gyri in schizophrenia patients. The DMN has been identified as being involved in processes such as attention to internal emotional states (Raichle & Snyder, 2007), self-referential processing (Gusnard, Akbudak, Shulman, & Raichle, 2001), or task-independent thought

(McGuire, Paulesu, Frackowiak, & Frith, 1996). The structural changes of the SCN in patients with schizophrenia are related to affective disorder and threat delusion (Stegmayer et al., 2014b). The reduction in the strength between the two modules may result in abnormalities in emotion processing and regulation.

Together, the decrease in strength between networks in schizophrenia patients indicates that the ability of these regions to process and transmit information is decreased, which may lead to attention disorders and emotional instability. The significant dysconnectivity between the VIS and FPN, and between the DMN and SCN was associated with increased illness duration and greater severity of psychopathology of schizophrenia.

4.4 Decline in intramodule connections in the FPN

We found a significant reduction in the intramodule strength of the FPN in schizophrenia patients. The FPN is involved in a wide range of advanced cognitive tasks and adaptive task control (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2007; Fair et al., 2009). In schizophrenia, fMRI studies have shown that nodes in this network respond abnormally to different tasks, such as attention, executive control and working memory (Backes et al., 2011; K. Wang et al., 2005; Weiss et al., 2009). In a study using functional connectivity MRI (fcMRI) to observe the connectivity of the FPN in schizophrenia, it was found that schizophrenia is associated with both within- and between-network dysconnectivity in the FPN (Tu, Lee, Chen, Li, & Su, 2013). Our results validate this conclusion at the structured network

level. A past study has shown that parietal GM loss may contribute to the onset of schizophrenia, while orbitofrontal GM loss is associated with illness duration (Burke, Androutsos, Jogia, Byrne, & Frangou, 2008). We found that nodal strength was significantly decreased in the left orbital IFG and in the right inferior parietal supramarginal and angular gyri in schizophrenia patients within the FPN. We believe that impaired connectivity in these two regions of schizophrenia is associated with increased morbidity and duration in schizophrenia patients. Our results support the hypothesis that FPN dysfunction is the basis of generalized cognitive impairment in schizophrenia (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004).

4.5 Correlation between edge strength and SAPS scores

Among regions with nodal alterations, eight edges involving the IFG, occipital gyrus, lingual gyrus and calcarine fissure were significantly negatively correlated with SAPS scores reflecting schizophrenia symptom severity, suggesting that the reduced intermodule strength between the FPN and VIS led to increased positive symptom severity in schizophrenia, including hallucinations, delusions, erratic behavior, and positive thinking disorders. Past studies have found that leftward laterality of bilateral FPN connectivity was negatively correlated with positive symptoms in schizophrenia (Son et al., 2017). Our results further prove that the connection between the FPN and VIS plays an important role in the exploration of the pathogenesis and the development of disease diagnoses of schizophrenia.

5. Conclusions

In conclusion, we analyzed single-subject GM networks in patients with schizophrenia and found that schizophrenia patients demonstrated impaired large-scale integration, reflected in decreased Eglob, strength, PC_5, and PC. The nodal PC of the regions involving the FPN, DMN and SCN were significantly decreased in schizophrenia. Schizophrenia patients also demonstrated a significant reduction in intramodule strength of the FPN and intermodule strength between the FPN and VIS, and between the SCN and DMN. In addition, our results indicate that the strength between the FPN and VIS was significantly correlated with positive symptom scores. This complex disconnection pattern may provide a potential approach to explain the cognitive and emotional symptoms of schizophrenia. Our findings provide important insight into the pathophysiological mechanisms of specific mental disorders from a modular perspective.

Ethical Approval

Not applicable.

Consent to Participate

We use data from the NU Schizophrenia Data Software Tool (NUSDAST) of the public schizophrenia neuroimaging database. All participants gave informed consent.

Consent to Publish

This manuscript has not been previously published and is not currently in press, under review, or being considered for publication by another journal. All authors have read and approved the manuscript being submitted, and agree to its publish to this

journal.

Authors Contributions

Bin Wang, Jie Xiang and Yunxiao Ma conceived the idea, performed the data analysis, and wrote the draft. All authors discussed the results, and contributed to the final manuscript.

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Competing Interests

There are no conflicts of interest reported by any of the authors.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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Table 1 Subject characteristics and cognitive scores

	NC	SC	P value
Number of subjects	101	116	-
Mean age (SD)	31.75(13.76)	33.92(12.88)	0.23 ^a
Gender (F/M)	55/46	78/38	0.05 ^b
SAPS	-	22.83±15.50	-
SANS	-	31.26±16.48	-

583 Abbreviations: SD, standard deviation; SAPS, positive symptoms score; SANS,

584 negative symptoms score

585 ^a p value was obtained by two-tailed two-sample t test.586 ^b p value was obtained by two-tailed Pearson χ^2 test.

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Table 2 Patients with schizophrenia exhibited decreased nodal participation

coefficients			
brain region	NC (/100)	SC (/100)	p value (FDR)
left precentral gyrus	79.56±0.16	79.45±0.16	0.010
right precentral gyrus	79.63±0.11	79.56±0.11	0.012
left superior frontal gyrus, orbital part	79.47±0.21	79.35±0.19	0.014
right superior frontal gyrus, orbital part	79.53±0.18	79.43±0.16	0.011
left middle frontal gyrus, orbital part	79.53±0.09	79.46±0.06	0.001
right middle frontal gyrus, orbital part	79.54±0.09	79.46±0.08	0.001
left inferior frontal gyrus, opercular part	79.5±0.10	79.42±0.07	0.001
right inferior frontal gyrus, opercular part	79.57±0.07	79.51±0.06	0.001
left inferior frontal gyrus, triangular part	79.59±0.06	79.56±0.06	0.017
right inferior frontal gyrus, triangular part	79.61±0.06	79.58±0.05	0.023
left olfactory cortex	79.64±0.07	79.6±0.07	0.023
right olfactory cortex	79.73±0.05	79.7±0.05	0.010
left caudate nucleus	79.61±0.11	79.56±0.10	0.024

Table 3 Patients with schizophrenia exhibited decreased intermodule nodal strength for FPN-VIS

brain region (FPN-VIS)	NC	SC	p value (FDR)
left middle frontal gyrus, orbital part	0.37±0.04	0.21±0.03	0.006
right middle frontal gyrus, orbital part	0.43±0.05	0.26±0.03	0.015
left inferior frontal gyrus, opercular part	0.26±0.04	0.14±0.02	0.016
right inferior frontal gyrus, opercular part	0.71±0.07	0.47±0.05	0.016
left inferior frontal gyrus, triangular part	1.06±0.08	0.75±0.07	0.015
right inferior frontal gyrus, triangular part	1.43±0.09	1.06±0.07	0.006
right inferior frontal gyrus, orbital part	1.95±0.07	1.68±0.07	0.020
left supplementary motor area	1.83±0.09	1.43±0.08	0.006
right calcarine fissure and surrounding cortex	0.86±0.06	0.66±0.05	0.024
left lingual gyrus	1.66±0.05	1.39±0.05	0.003
right lingual gyrus	1.8±0.06	1.5±0.05	0.003
right superior occipital gyrus	1.87±0.05	1.67±0.05	0.015
left middle occipital gyrus	1.56±0.04	1.37±0.04	0.006
left inferior occipital gyrus	1.7±0.04	1.56±0.04	0.025

Table 4 Patients with schizophrenia exhibited decreased intermodule nodal strength for the SCN-DMN

brain regions (SCN-DMN)	NC	SC	p value (FDR)
left gyrus rectus	0.89±0.06	0.63±0.05	0.018
right median cingulate and paracingulate gyri	1.22±0.07	0.93±0.06	0.037
right lenticular nucleus, putamen	0.93±0.05	0.66±0.06	0.018

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608 **Figure 1 Group differences in the global topological properties between the**
609 **schizophrenia patients and controls. Abbreviations: PC, participation coefficient.**

610 **The asterisks indicate the difference between the groups; * represents $p < 0.05$**
611 **and ** represents $p < 0.01$.**

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Figure 3 Group differences in the intermodule strength between the schizophrenia patients and controls. (A) The group differences in intermodule strength between FPN and VIS. (B) Nodal strength decreased in schizophrenia patients between the FPN and VIS, red nodes in FPN and blue nodes in VIS. (C) Schizophrenia with significantly decreased connectivity is presented in blue. (D) The group differences in connection strength between the SCN and DMN. (D) Nodal strength decreased in schizophrenia patients between the SCN and DMN, orange nodes in the DMN and magenta nodes in the SCN.

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Figure 4 Intermodule nodal strength exhibiting significant alterations in

schizophrenia versus control participants. The left figure shows schizophrenia

patients who exhibited decreased FPN-VIS intermodule nodal strength, and the

right figure shows SCN-DMN patients. Abbreviations: ORBmid: middle frontal

gyrus (orbital part); IFGoperc: inferior frontal gyrus (opercular part) ;

IFGtriang: inferior frontal gyrus (triangular part); ORBinf: inferior frontal

gyrus (orbital part); SMA: supplementary motor area ; CAL: calcarine fissure ;

LING: lingual gyrus; SOG: superior occipital gyrus; MOG: middle occipital

gyrus; IOG: inferior occipital gyrus; REC: gyrus rectus; MCG median cingulate

and paracingulate gyri; PUT: lenticular nucleus, putamen.

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650 **Figure 5 (A) Group differences in the intramodule strength between the**
651 **schizophrenia patients and controls. (B) Regions and connectivity with significant**
652 **decreases within the FPN in schizophrenia patients.**

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Figure 6 Intramodule nodal strength exhibiting significant alterations in

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schizophrenia versus control participants. Abbreviations: ORBinf: orbital part of

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middle frontal gyrus; IPL: inferior parietal, but supramarginal and angular gyri.

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Figure 7 Scatterplots of the relationship between the edge strength measurements and SAPS scores.

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