Schizophrenia Research 210 (2019) 115–121

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Functional fractionation of default mode network in first episode schizophrenia

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ARTICLE INFO

Article history:
Received 11 January 2019
Received in revised form 15 May 2019
Accepted 26 May 2019
Available online 8 July 2019

Keywords:
Schizophrenia
Default network
Functional fractionation
Graph
Resting state
Functional MRI

ABSTRACT

A disruption in the connectivity between brain regions may underlie the core pathology in schizophrenia. One of the most consistent observations in human functional imaging is a network of brain regions referred to as the default network (DMN) that contains core subsystem, the dorsomedial prefrontal cortex (dMPFC) subsystem and the medial temporal lobe (MTL) subsystem, with differential contributions. The goal of this study was to examine abnormalities of different DMN subsystems in first episode schizophrenia and associations between these abnormalities and individual psychopathology. We recruited 203 patients and 131 healthy controls. A seed-based resting-state functional connectivity (RSFC) analysis on the 2D surface was conducted. Individual DMN functional connectivity matrices were then obtained by calculating spatial correlations between pairs of RSFC maps, characterizing the functional fractionation of the DMN. Patients showed patterns similar to controls but markedly reduced strength of DMN fractionation, with the degree centrality of the MTL subsystem significantly reduced, including the posterior inferior parietal lobule (pIPL), parahippocampal cortex (PHC) and lateral temporal cortex (LTC). Patients also exhibited hypo-connectivity within the MTL subsystem and between the MTL and dMPFC subsystems. Clinical symptoms were negatively correlated with degree centrality of LTC, pIPL and PHC in patients. Hyper-fractionation of different DMN components implied that communication and coordination throughout the dissociated components of the DMN are functionally over-segregated in schizophrenia. The associations between the hyper-fractionation with clinical symptoms suggest a role of the high fractionation in the DMN in the abnormal neuropathology observed in schizophrenia.

1. Introduction

Schizophrenia is characterized by a lack of integration between thought, emotion, and behavior (Bleuler, 2010). A disruption in the connectivity between brain processes may underlie this schism. The efforts to understand altered brain connectivity in schizophrenia have been aided by recent work identifying core networks in the brains of healthy individuals. One of the most consistent observations in human functional imaging is that there is a network of brain regions referred to as the "default mode network" (DMN), a system of brain regions that are active at rest or during passive viewing of stimuli, but which deactivate during performance of a wide range of cognitive tasks (Buckner et al., 2008; Gusnard and Raichle, 2001; Raichle et al., 2001). The DMN includes the anterior cingulate, inferior parietal, posterior cingulate, medial-prefrontal and lateral temporal neocortices, as well as the precuneus (Broyd et al., 2009; Buckner et al., 2008; Fox et al., 2005;

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https://doi.org/10.1016/j.schres.2019.05.038
0920-9964/

Fransson, 2005; Fransson and Marrelec, 2008; Mannell et al., 2010; Whitfield-Gabrieli et al., 2009).

A dysfunctional DMN in schizophrenia has been observed in many previous studies, including increased and reduced DMN activity as well as a mixed pattern. Some studies have reported a failure of deactivation of the DMN during performance of the Sternberg working memory task in both chronic schizophrenia (Kim et al., 2009) and early psychosis (Fryer et al., 2013), and also using an n-back working memory task (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). Somewhat consistent with this finding, Salvador et al. (Salvador et al., 2010) found that a medial prefrontal region of the DMN showed hyper-connectivity among individuals with schizophrenia in an overall brain connectivity analysis. In contrast, Harrison et al. (Harrison et al., 2007) found that patients with schizophrenia showed greater deactivation than controls in the anterior and posterior midline nodes of the DMN during a task requiring response suppression. A number of other studies have found either reduced connectivity in the DMN in schizophrenia (Bluhm et al., 2007; Bluhm et al., 2009; Camchong et al., 2011; Rotarska-Jagiela et al., 2010) or a mixed pattern of increased and decreased connections within the DMN (Garrity et al., 2007; Mannell et al., 2010). Two recent studies have found evidence of structural abnormalities associated with dysfunctional regions in the DMN. Camchong et al. (Camchong et al., 2011) identified functional connectivity abnormality in the anterior node of the DMN, plus reduced fractional anisotropy (FA) on diffusion tensor imaging (DTI) in the white matter subjacent to this area. Pomarol-Clotet et al. (Pomarol-Clotet et al., 2010) found that grey matter volume reductions in a group of patients with chronic schizophrenia predominated in the medial frontal cortex, where they overlapped substantially with the area where failure of deactivation was found during performance of the n-back task. Overall, the nature of these abnormalities of the DMN has been variable across studies.

Importantly, inconsistencies among previous reports of aberrant functional connectivity may have attributed to regional differences in the network organization of the DMN. However, patterns of aberrant regional connections within the DMN could vary across patients, depending on individual psychopathology, medication, or compensatory mechanisms. Specifically, the DMN comprises multiple interacting subsystems, a midline core and two distinct subsystems, with differential contributions (Andrews-Hanna, 2012; Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014a; Buckner et al., 2008), that are altered even in the early stages of psychosis (Alonso-Solis et al., 2012). The core components of this network are two midline cortical regions, the medial prefrontal cortex (MPFC) and the precuneus/posterior cingulate cortex (PCC), which are active when people make self-relevant, affective decisions (Andrews-Hanna et al., 2010). The two subsystems, including the dorsal MPFC (dMPFC) subsystem and the medial temporal lobe (MTL) subsystem, contribute to distinct component processes that are differentially linked to participants considering their present mental state and memory-based scene construction, respectively (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014a). In these cases, analyses of pattern differences within and between DMN subsystems may complement regional analyses to characterize group differences in default network connectivity.

Given the above considerations, the goal of the current study was to examine the abnormalities of different DMN subsystems to provide further evidence of aberrant DMN in first episode schizophrenia. We also investigated associations between these abnormalities and individual psychopathology in patients with schizophrenia.

2. Materials and methods

2.1. Participants

The study included 203 patients with first episode schizophrenia (95 males, 108 females, mean age 24.7 ± 5.6 years, ranging from 15.5 to 43.8 years) and 131 normal controls (73 males, 58 females, mean age 27.8 ± 6.0 years, ranging from 16.3 to 40.0 years). The patients had 10.6 years of education on average, while the controls had 13.2 years of education ($P < 0.001$). The study was conducted at three clinical sites all equipped with a 3 Tesla scanner and following the same recruitment criteria. Dataset 1: Ninety-five patients with first episode schizophrenia (mean age 24.7 ± 6.1 years) and forty-nine normal controls (mean age 25.3 ± 5.4 years) were recruited at Chongqing Three Gorges Central Hospital, Chongqing, China. Dataset 2: Seventy-five patients with first episode schizophrenia (mean age 24.4 ± 4.7 years) and thirty-nine normal controls (mean age 31.9 ± 6.5 years) were recruited at Zhumadian Psychiatry Hospital, Henan Province, China. Dataset 3: Thirty-five patients with first episode schizophrenia (mean age 25.7 ± 5.9 years) and forty-two normal controls (mean age 27.1 ± 4.1 years) were recruited at Beijing Huilongguan Hospital.

The inclusion criteria for patients included: (1) DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia; (2) First outpatient treatment or first hospitalization of <2 weeks; (3) At least 6 years of education; (4) Right-handed, confirmed by the short version of the Edinburgh Handedness Scale; (5) Aged 15 years and above. The exclusion criteria for patients and controls included: (1) A history of head trauma; (2) Concurrent or previous substance dependence, besides smoking, or alcoholism; (3) Gross brain organic disease confirmed on T2 MRI; (4) Symptoms of significant involuntary movement; (5) Learning disability or mental retardation. Demographic data are presented in Table 1 (details of the three sites shown in Table S1). Healthy volunteers had no family history of psychotic illnesses, according to the Family History Research Diagnostic Criteria. All participants gave written informed consent approved by the Ethics Committee of Beijing Huilongguan Hospital, Beijing, China, which was considered the lead site of the study.

2.2. Clinical procedures

Regardless of whether they would be treated on an inpatient or outpatient basis, patients were started on antipsychotic medication treatment without delay. If patients met all the above inclusion and none of the exclusion criteria, and if the treating physician considered them stable enough to participate in a research MRI scan, they were asked whether they would consider participating in this study. After providing written informed consent, a case report form was completed, including demographic information and clinical symptoms. A MRI scan was then scheduled. All patients underwent MRI within 2 weeks of the initiation of the antipsychotic medication treatment.

The clinical assessment rating (Positive and Negative Syndrome Scale, PANSS) (He and Zhang, 2000; Kay et al., 1987) was conducted by one

Table 1
Demographics of participants.

	FES (n = 203)	CON (n = 131)	$\chi 2/t$	P
Demographic information				
Gender(M/F)	95/108	73/58	2.4	0.12
Age (year)	24.75 ± 5.58	27.82 ± 6.02	4.77	3.00×10^{-06}
Education (year)	10.61 ± 3.17	13.24 ± 3.64	6.96	1.82×10^{-11}
Illness duration (year)	0.96 ± 1.06			
Onset age (year)	23.83 ± 5.63			
Duration of onset to therapy (year)	0.70 ± 1.01			
Symptoms				
PANSS positive	21.47 ± 6.51			
PANSS negative	17.56 ± 7.01			
PANSS general psychopathology	37.94 ± 8.40			
PANSS total	76.96 ± 17.03			

Note: FES = first episode schizophrenia; CON = control.

attending psychiatrist from each site, who were trained to be reliable and had achieved intraclass correlation coefficient (ICC) values of 0.80 or above before the trial. Medication dosages (chlorpromazine equivalents, CPZ) were calculated individually for each patient (Woods, 2003).

2.3. MRI protocol

The MRI dataset 1 was acquired on a Siemens 3T Trio MRI scanner, and consisted of 95 patients and 49 normal controls. Parameters for structural MRI were acquired covering the whole brain with a sagittal 3D-magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence: echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, repetition time (TR) = 2300 ms, flip angle (FA) = 9°, field of view (FOV) = 240 × 256 mm^2, matrix size = 256 × 240, thickness/gap = 1/0 mm. The resting-state functional images were obtained with the following parameters: TR = 2000 ms, TE = 30 ms, FA = 90°, in-plane resolution = 64 × 64, FOV = 200 × 200 mm^2, 32 axial slices, thickness/gap = 4/0 mm and 210 volumes (7 min).

The MRI dataset 2 was acquired on a GE 3 T MRI scanner, and consisted of 75 patients and 39 normal controls. T1-weighted images were acquired covering the whole brain with a sagittal 3D-MPRAGE sequence: TE = 2.49 ms, TI =1100 ms, TR =6.77 ms, FA = 7°, FOV = 256 × 256 mm^2, matrix size = 256 × 256, thickness/gap = 1/0 mm. The resting-state functional images were obtained with the following parameters: TR = 2000 ms, TE = 30 ms, FA = 90°, in-plane resolution = 64 × 64, FOV = 220 × 220 mm^2, 33 axial slices, thickness/gap = 4/0 mm and 210 volumes (7 min).

The MRI dataset 3 was acquired on a Siemens 3T Prisma MRI scanner, and consisted of 35 patients and 42 normal controls. Parameters for structural MRI were acquired covering the whole brain with a sagittal 3D-MPRAGE sequence: TE = 2.98 ms, TI = 1100 ms, TR = 2530 ms, FA = 7°, FOV = 256 × 224 mm^2, matrix size = 256 × 224, thickness/gap = 1/0 mm. The resting-state functional images were obtained with the following parameters: TR = 2000 ms, TE = 30 ms, FA = 90°, in-plane resolution = 64 × 64, FOV = 224 × 224 mm^2, 33 axial slices, thickness/gap = 3.5/0.7 mm and 240 volumes (8 min).

For the resting-state scan, all participants were instructed to close their eyes and remain awake. Head motion was minimized by foam pads in all three scanners.

Besides the MPRAGE and the resting fMRI scans, these participants also underwent DTI, and the MPRAGE and DTI data from site 1 and site 2 have been published (as subcortical structure data) as part of the ENIGMA consortium (van Erp et al., 2018; Kelly et al., 2018). None of the resting-state fMRI data have been published earlier.

2.4. Data preprocessing

For each participant, image preprocessing was carried out using the Connectome Computation System (CCS: http://lfcd.psych.ac.cn/ccs.html) (Xu et al., 2015), which provides a common platform for brain connectome analysis by integrating the functionality of afni, fsl, and FreeSurfer, thereby extending the utility of FCP scripts (FCON_1000: http://www.nitrc.org/frs/downloadlink.php/2628), and by integrating the brain surface information reconstructed by FreeSurfer (version 6.0). The preprocessing comprised both anatomical and functional processing steps. The anatomical processing steps consisted of: 1) Removal of MR image noise using a spatially adaptive non-local means filter (Xing et al., 2011; Zuo and Xing, 2011); 2) Brain surface reconstruction via the *recon-all* command in FreeSurfer (Dale et al., 1999; Fischl, 2012; Fischl et al., 2002; Fischl et al., 1999; Segonne et al., 2004); 3) Spatial normalization from an individual functional space to the MNI152 standard brain space; and 4) Boundary-based registration between individual structural and functional images. The functional preprocessing steps included: 5) Rejection of the first 10 EPI volumes from the beginning of each scan to allow for signal equilibration; 6) Slice timing correction; 7) 3D motion correction; 8) 4D global mean-based intensity normalization; 9) Denoising of head motion with ICA-AROMA (Pruim et al., 2015a; Pruim et al., 2015b) as well as denoising of individual white matter (WM) and cerebrospinal fluid (CSF) mean signals derived from the WM/CSF masks output using the segmentation routine of FreeSurfer; 10) Band-pass temporal filtering (0.01–0.1 Hz); and 11) Removal of linear and quadratic trends. Of note, surface-based brain registration (steps 3 and 4) was estimated for subsequent assessments on the basis of the functional fractionation of the default network. The inclusion criteria were a maximum absolute head motion displacement/rotation of <3 mm/° in x/y/z and a mean frame displacement <0.2 (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012); three controls (2.3% of all controls) and 17 patients (8.4% of all patients) were excluded.

2.5. Data analysis

We examined resting-state functional connectivity (RSFC) associated with the 11 seed regions (spheres with a 6-mm radius) in the default network (MNI152 standard space) derived from a previous study of Andrew-Hanna et al. (Andrews-Hanna et al., 2010). All seeds were transformed into surface-based space, including the aMPFC, the PCC, the dMPFC, the temporal parietal junction (TPJ), the lateral temporal cortex (LTC), the temporal pole (TempP), the ventral MPFC (vMPFC), the posterior inferior parietal lobule (pIPL), the retrosplenial cortex (Rsp), the parahippocampal cortex (PHC), and the hippocampal formation (HF+) (Fig. 1 and Table S2). Then the seed regions were further masked with the group-level mask including all voxels showing non-zero temporal variances to produce the final seed regions of interest (ROIs). For each of the 11 predefined seeds (see Andrews-Hanna et al., 2010: upper-middle illustration in Fig. 1), we performed a whole-brain seed-based RSFC analysis for each participant in the left and right hemisphere, vertex by vertex. Individual DMN functional connectivity matrices or graphs were then obtained by calculating spatial correlations between each pair of the 11 RSFC maps, characterizing the functional fractionation of the DMN. The degree centrality of each of the 11 nodes (i.e., DMN seeds) and the strength of connection among them were used for the subsequent group analysis. Group differences for the above network measures were examined using two-sample *t*-tests with Bonferroni corrections for multiple comparisons, using *P*-values thresholded at 0.0045 (i.e., 0.05/11 seeds) for degree centrality and at 0.0009 for strength (0.05/55 connections between 11 seeds) and controlling for the effect of age, sex, education, site, and head motion.

2.6. Correlation analysis

To examine whether the network measures were correlated with symptom severity in the patient sample, we conducted a partial correlation analysis by controlling for the effect of medication dosage, age, sex, education, site, and head motion, all of which were demeaned prior to the application of the general linear model.

3. Results

3.1. Behavioral data

The demographic and clinical characteristics of the participants are shown in Table 1. Age (24.8 ± 5.6 vs. 27.8 ± 6.0) and education (10.6 ± 3.2 vs. 13.2 ± 3.6) significantly differed among the groups, and were used as covariates in all analyses. Age of onset for patients was 23.8 ± 5.6 (mean ± s.d.) years. Duration of untreated psychosis (DUP) was 0.7 ± 1.0 (mean ± s.d.) years, which is defined as the duration from the onset of psychosis to the first antipsychotic medication administration.

3.2. DMN subsystems in healthy controls

Consistent with prior reports (Andrews-Hanna et al., 2010; Buckner et al., 2008), the PCC exhibited the highest betweenness centrality

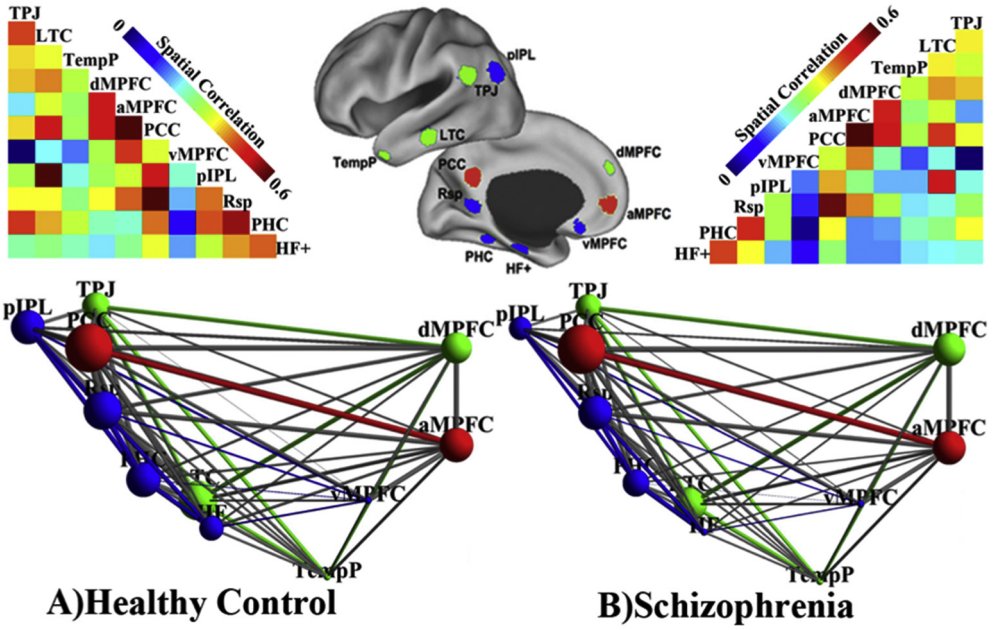

Fig. 1. Correlation strengths among regions within the default network are shown using network centrality measures in the two groups. The size of the circle represents the centrality of a given node. The thickness of the lines reflects the strength of the correlation between regions. The anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex (PCC) are the core hubs of the network and both are significantly connected to every other node.

(Fig. 1A). No region of the default network was completely dissociated from the remaining regions (see Fig. 1A). The core network and the two DMN subsystems (green and blue seeds, respectively) showed strong within- and between-network connectivity.

3.3. DMN subsystems in patients with schizophrenia

As shown in Fig. 1B, patients with schizophrenia in the present study showed similar patterns to controls, but with markedly reduced connectivity strength of the DMN. Specifically, the core regions and the remaining nine regions from the two subsystems showed lower betweenness centrality in patients than in controls.

3.4. Aberrant connectivity within and between default network subsystems in schizophrenia

As shown in Fig. 2, compared with healthy controls, the degree centrality of the MTL subsystem (including the pIPL and PHC) and the dMPFC subsystem (including the LTC) was significantly reduced in the schizophrenia group. Patients exhibited hypo-connectivity (i.e., increased functional fractionation) within the MTL subsystem

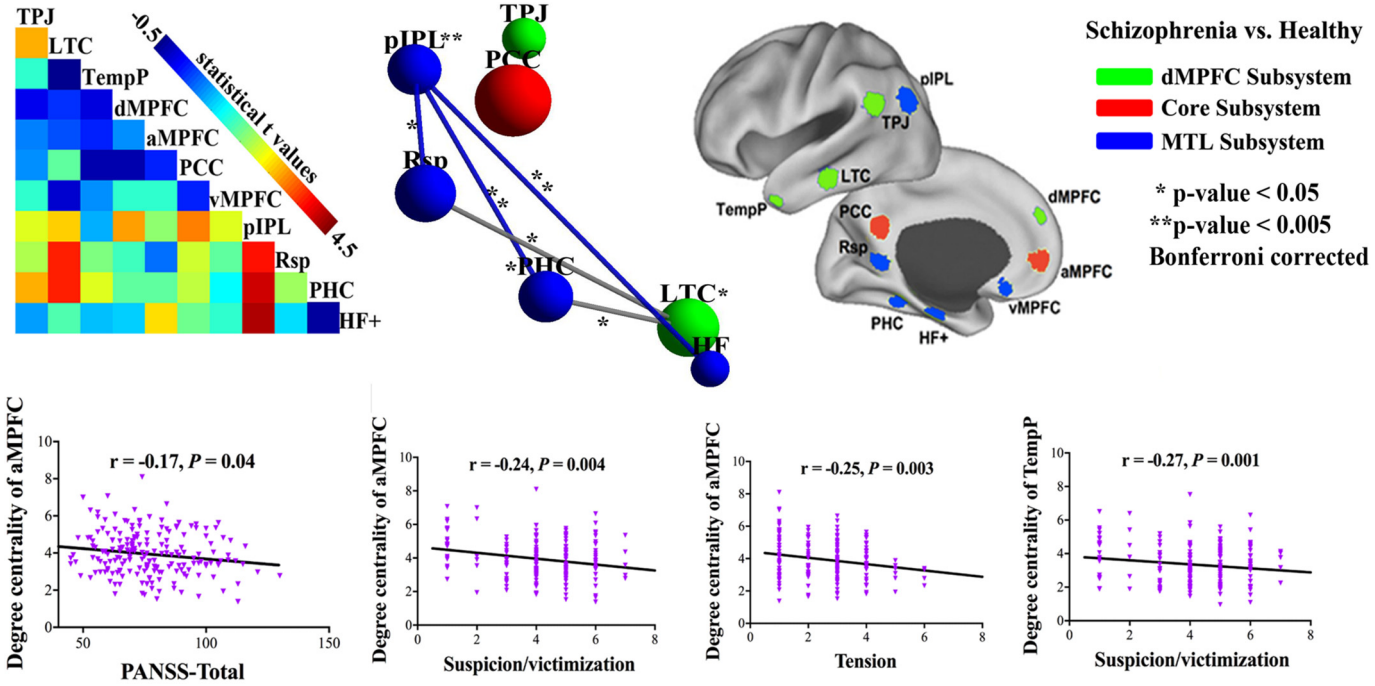

Fig. 2. Group differences in nodal centrality and edge strength, and its relationship with clinical symptoms in schizophrenia.

(pIPL-Rsp, pIPL-PHC, and pIPL-HF connections). Interestingly, the DMN functional fractionation between the MTL and dMPFC subsystems (LTC-Rsp and LTC-PHC connections) was significantly reduced in patients, suggesting a functional disconnection between the MTL and dMPFC subsystems of the DMN.

3.5. Relationship between aberrant connectivity and behavior

In patients with schizophrenia, PANSS total symptoms were negatively correlated with the degree centrality of the aMPFC ($r = -0.17$, $P = 0.04$, Fig. 2). Moreover, suspicion/victimization symptoms were negatively correlated with the degree centrality of the aMPFC ($r = -0.24$, $P = 0.004$, Fig. 2), and a negative correlation between tension symptoms and the degree centrality of the aMPFC ($r = -0.25$, $P = 0.003$) and the TempP ($r = -0.27$, $P = 0.001$) was detected.

4. Discussion

In the current study, we examined the functional fractionation of the default network in patients with first episode schizophrenia using resting-state fMRI. Overall, the pattern of altered connectivity we observed in schizophrenia shows reduced degree centrality and hyper-fractionation within the MTL and dMPFC subsystems, and also hyper-fractionation between the MTL and dMPFC subsystems. The present study shows reduced DMN connectivity, which is consistent with the disconnection hypothesis in schizophrenia (Camchong et al., 2011; Friston, 1999; Friston and Frith, 1995). Interestingly, patients with more severe suspicion/victimization and tension symptoms showed lower degree centrality of the aMPFC and TempP, suggesting a role of the high fractionation in DMN in the abnormal neuropathology observed in schizophrenia.

We detected reduced degree centrality and hyper-fractionation within the MTL subsystem in patients with schizophrenia. The present study supports the notion that schizophrenia arises from the disrupted functional integration of widespread brain areas (Liang et al., 2006). Recent neuroimaging evidence suggests that the MTL subsystem contributes to autobiographical memory and future thought by enabling individuals to retrieve prior information and bind this information into a mental scene, while the dMPFC subsystem contributes to mentalizing and autobiographical thought, possibly by retrieving stored conceptual knowledge about one's self and/or other people (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014a; Andrews-Hanna et al., 2014b). Patients with schizophrenia have difficulties getting a clear and stable representation of their selves (Berna et al., 2016). Previous studies found that patients with schizophrenia show impaired autobiographical memory (Berna et al., 2017; Ricarte et al., 2017) in regard to personal episodic memories from their recent life (Alexiadou et al., 2018), and theory of mind (TOM) deficiencies have been observed in first episode psychosis, particularly in schizophrenia (Lindgren et al., 2018). These self-related or autobiographical memory abnormalities might be induced by abnormalities of the MTL and dMPFC subsystems of the DMN.

The negative correlation between the degree centrality of the aMPFC and clinical symptoms measured by PANSS indicate that a dysfunctional aMPFC (belonging to the core subsystem of the DMN) might induce severe positive symptoms. In addition, suspicion/victimization, an important domain of positive symptoms, showed a negative correlation with the degree centrality of the aMPFC, suggesting an important role of the aMPFC, especially regarding positive symptoms, in the pathophysiology of schizophrenia. Moreover, a dysfunctional core subsystem might induce severe tension, which is related to depression and anxiety.

Midline structures, including the PCC region, showed significantly reduced degree centrality at an uncorrected $P < 0.05$. Recent neuroimaging evidence (Park et al., 2008; Taylor et al., 2007) suggests that processes (concerning self-referential processing and social cognition) relying upon these midline structures (Northoff and Bermpohl, 2004; van der Meer et al., 2010) may be affected in schizophrenia. Gusnard and Raichle (Gusnard and Raichle, 2001) argued that the MPFC is associated with self-generated thoughts, intended speech, and emotions, which are deficient in patients with schizophrenia (Frith, 1996). Abnormalities in connectivity, activity, metabolism, and grey matter volume in the PCC were also identified in previous studies (Bluhm et al., 2007; Calabrese et al., 2008; Garrity et al., 2007; Shimizu et al., 2007; Whitfield-Gabrieli et al., 2009). These functional and structural alterations support the neural disconnection hypothesis for schizophrenia (Park and Thakkar, 2010). The functions of the DMN include monitoring internal thoughts and providing cognitive flexibility for self-relevant mental simulations (Buckner et al., 2008), and our findings may thus reflect a deficit in the ability of the DMN to allocate resources properly between internal thoughts and external stimuli in patients with schizophrenia.

Several methodological issues must be considered when interpreting our findings. Firstly, a vertex-based whole brain functional connectivity analysis was conducted in this study. Consistent with the volume-based functional connectivity method used by Andrew-Hanna et al. 2010 (Andrews-Hanna et al., 2010), the PCC exhibited the highest betweenness centrality in healthy controls. Secondly, spatial correlations for each pair of the 11 RSFC maps were calculated, indicating similarities between seed functions. A higher correlation coefficient between two seeds indicates a high possibility of the two seeds belonging to the same function system (i.e., lower functional fractionation).

The current study has several limitations. Participants from site 2 were not fully matched in age and education. We repeated the analysis with and without age and education as covariates, however, and found that the main results were similar. Furthermore, the scanners at the three sites represent different types of 3T scanners, which might have induced some additional noise. We controlled for this noise to a certain extent by entering the three sites as covariates into the analyses. Additionally, correlations between aberrant connectivity and cognition in schizophrenia should be explored in future studies. Since subsystems of the DMN exhibit distinct functional contributions to cognition in healthy participants (Andrews-Hanna et al., 2010), more domains of cognition and behavior should be examined in schizophrenia, especially how self-referential processing correlates with DMN abnormalities.

In conclusion, this study demonstrates reduced functional integration between subsystems of the default network in first episode schizophrenia. Hypo-connectivity identified by pattern correlation between different default network components implies that communication and coordination throughout the dissociated components are disrupted in schizophrenia. The associations between the hyper-fractionation and clinical symptoms further suggests a role of the high fractionation in DMN in the abnormal neuropathology observed in schizophrenia.

Data access and responsibility

The first author, Fengmei Fan, has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions

Conceived and designed the study: Yunlong Tan, Shuping Tan, Zhiren Wang, Fude Yang, Xi-Nian Zuo.

Collected the data: Yunlong Tan, Hong Xiang, Shuping Tan, Zhiren Wang, Hua Guo, Hongzhen Fan.

Analyzed the data: Fengmei Fan, Hongzhen Fan, Shuping Tan, Xi-Nian Zuo, L.Elliot Hong.

Contributed reagents/materials/analysis tools: Fengmei Fan, Xi-Nian Zuo, Hongzhen Fan.

Wrote the paper: Fengmei Fan, L.Elliot Hong, Yunlong Tan, Shuping Tan, Xi-Nian Zuo.

Declaration of Competing Interest

The authors have declared that no conflicting interests exist.

Acknowledgments

The study was supported by National Natural Science Foundation of China (No. 81401115, 81761128021, 31671145), National Institutes of Health grant (R01MH112180), and Beijing Municipal Administration of Hospitals' Youth Programme (QML20172001). Funders have no role in study design, data collection and analysis, interpretation, or decision to publish, or preparation of the manuscript.

The authors are grateful to all the volunteers and patients for their participation in the study. We thank Yunhui Wang, Bingjie Wang from Beijing Huilongguan Hospital, Shiyou Tang from Chongqing Three Gorges Central Hospital, Ping Wan and Dong Wei from Zhumadian Psychiatry Hospital for their assistance in collecting data and Yong He from Beijing Normal University for his comments in the statistical analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.038.

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