Psychiatry Research: Neuroimaging 290 (2019) 51–57

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Network functional connectivity analysis in individuals at ultrahigh risk for psychosis and patients with schizophrenia

Chen Xiongying[a,1], Li Xianbin[a,1], Yan Tongjun[b], Dong Qianhong[a], Mao Zhen[a], Wang Yanyan[b], Yang Ningbo[a,c], Zhang Qiumei[d,e], Zhao Wan[d], Zhai Jinguo[e], Chen Min[e], Du Boqi[d], Deng Xiaoxiang[d], Ji Feng[e], Xiang Yu-Tao[f], Song Jie[g], Wu Hongjie[g], Dong Qi[d], Chen Chuansheng[h], Wang Chuanyue[a,*], Li Jun[d,*]

[a] The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders & the Advanced Innovation Center for Human Brain Protection, Beijing Anding Hospital, School of Mental Health, Capital Medical University, Beijing, China
[b] The PLA 102nd Hospital and Mental Health Center of Military. Changzhou 213003, PR China
[c] First Affiliated Hospital of Henan University of Science and Technology, No.24 Jinghua Road, Jianxi District, Luoyang 471003, China
[d] State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, China
[e] School of Mental Health, Jining Medical University, 45# Jianshe South Road, Jining 272013, Shandong Province, PR China
[f] Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau, PR China
[g] Shengli Hospital of Shengli Petroleum Administration Bureau, Dongying 257022, Shandong province, PR China
[h] Department of Psychology and Social Behavior, University of California, Irvine, CA 92697, United States

ARTICLE INFO

Keywords:
Schizophrenia
Ultrahigh risk
Degree centrality
Functional connectivity
Network

ABSTRACT

Schizophrenia is a severe mental disorder, and the onset of which is preceded by a stage of ultrahigh risk (UHR) for developing psychosis. Therefore, analyzing individuals with UHR is essential for identifying predictive biomarkers for the onset of schizophrenia. The current study aimed to identify such biomarkers based on a voxelwise whole-brain functional degree centrality (FDC) analysis. Conjunction analysis showed that, compared with healthy controls, both UHR subjects and patients with schizophrenia showed significantly increased FDC at the medial prefrontal cortex (MPFC) and significantly decreased FDC at the right fusiform gyrus (FG). The subsequent partial correlation analysis showed significant correlations between the disorganization symptoms and FDCs at the MPFC and the right FG for both UHR subjects and patients with schizophrenia. These findings suggest that FDC within the MPFC and the right FG could be candidate biomarkers for the onset of schizophrenia.

1. Introduction

Schizophrenia is a severe mental disorder with approximately 1% lifetime prevalence throughout the world. Although the exact etiology of schizophrenia is still unknown, the dysconnectivity hypothesis, first proposed more than twenty years ago (Friston and Frith, 1995; Weinberger, 1993), has recently gained more attention among pathophysiological theories of schizophrenia. As functional connectivity analysis evolved from the seed-based to the network-based method (which involves analyzing whole-brain functional connectivity among each pair of voxels), the dysconnectivity hypothesis of schizophrenia has also shifted from focusing on specific functional connectivity (e.g., from the dorsolateral prefrontal cortex to the contralateral hippocampus; Rasetti et al., 2011) to covering whole-brain functional connectivity (Chen et al., 2015; Palaniyappan and Liddle, 2014; van Lutterveld et al., 2014; Wang et al., 2014).

Based on the graph theory, a fully connected network is defined as nodes and the connections between them (edges). Several researchers (Buckner et al., 2009; Dai et al., 2015; Liang et al., 2013; Zuo et al., 2012) have recently used a method to measure the global functional connectivity of each node by its functional degree centrality (FDC), which is the total correlation of its time series with those of the rest of the network. Unlike the traditional seed-based functional connectivity analysis, FDC is not dependent on the previous definition of seeds and can provide an unbiased approach to identify brain regions that exhibit deficient functional connectivity in patients.

* Corresponding authors.
E-mail addresses: wang_cy@ccmu.edu.cn (C. Wang), lijundp@bnu.edu.cn (J. Li).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.pscychresns.2019.06.004
Received 19 September 2018; Received in revised form 19 June 2019; Accepted 21 June 2019
Available online 25 June 2019
0925-4927/

The voxelwise FDC analysis, in which a node represents a voxel, has been used in many previous resting-state fMRI studies to detect the difference between schizophrenia patients and healthy controls (Chen et al., 2015; Lei et al., 2015; Palaniyappan and Liddle, 2014; Skatun et al., 2016; van Lutterveld et al., 2014; Wang et al., 2014). Although the brain regions that showed abnormal FDC in schizophrenia across these studies were not consistent, most of them were important brain hubs, such as the prefrontal cortex (PFC), the inferior parietal lobule (IPL), the anterior (ACC) and the posterior cingulate cortex (PCC), among others.

By contrast, little is known about the FDC deficit in individuals at ultrahigh risk (UHR) for developing psychosis. UHR is a period preceding the onset of mental disorder. Fusar-Poli and colleagues showed that 36% of UHR individuals developed psychosis within three years (2012) and 73% of those developing psychosis met the criteria for schizophrenia (2013). Given that UHR is the intermediate state between health and mental disorder, analysis of individuals with UHR provides a unique and important opportunity to identify biomarkers that are predictive of the onset of schizophrenia.

To identify FDC-based biomarkers, the current study included three groups of subjects: healthy controls, UHR subjects, and patients with schizophrenia. We first identified brain regions in which FDCs were different between UHR subjects and healthy controls. We then tested whether the same FDC-based biomarkers differentiated schizophrenia patients from healthy controls. Finally, we examined whether the FDCs of these identified brain regions were associated with the severity of positive, negative and disorganization symptoms within each group of schizophrenia patients and UHR subjects, as one study showed that disorganization symptoms were a very significant predictor of the transition from the UHR to schizophrenia (Demjaha et al., 2012). Disorganization was measured using the scale of prodromal symptoms (SOPS) in UHR subjects and by selected items of the positive and negative syndrome scale (PANSS) in schizophrenia patients.

2. Materials and methods

2.1. Subjects

The sample consisted of 30 schizophrenia patients, 30 UHR subjects and 30 healthy controls. All subjects had normal or corrected-to-normal vision and were right-handed as assessed by the Edinburgh handedness inventory. Subjects with head motions of more than 3 mm or 3° during scanning for any of the volumes were rescanned. None of the participants reported any history of hard drug use (e.g., cocaine, crack, heroin, methamphetamine, etc.). Demographic and clinical information is shown in Table 1. Both schizophrenia patients and UHR subjects were recruited from the Beijing Anding Hospital. Schizophrenia patients were diagnosed according to the consensus of two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID), and their symptoms were assessed using the positive and negative syndrome scale (PANSS). All patients were treated with stable doses of atypical antipsychotics for more than 2 weeks. Antipsychotic medications included clozapine, olanzapine, risperidone, aripiprazole, and haloperidol. No antidepressants were in use. Some patients had taken 2.5-5 mg diazepam occasionally for their insomnia. However, patients were asked not to take diazepam or other benzodiazepines at least 24 hours before the scheduled fMRI scan (an appointment would be canceled if they did). Exclusion criteria for schizophrenia patients included a history of other Axis I psychiatric disorders and severe brain injury (any closed or open injuries that might be related to current symptoms or cognitive functions), current substance abuse, and currently experiencing acute psychotic symptoms that would jeopardize the integrity of the fMRI scan. UHR subjects were diagnosed based on the consensus of two experienced psychiatrists using the Structured Interview for Prodromal Syndromes (SIPS), and their symptoms were assessed using the Scale of Prodromal Symptoms (SOPS). Exclusion criteria were the same as that used for schizophrenia patients. None of the UHR subjects were treated with antipsychotics or antidepressants. Finally, we recruited healthy controls by advertisement from the same geographical region of the schizophrenia patients and UHR subjects. All healthy controls were assessed by experienced psychiatrists to screen for any personal or family history of psychiatric disorders.

This study's protocol was reviewed and approved by the Institutional Review Board of the Institute of Cognitive Neuroscience and Learning at Beijing Normal University. All subjects were Han Chinese and gave written informed consent for this study. This study was conducted in accordance with the approved protocol.

2.2. Imaging data acquisition

All imaging data were acquired at the Brain Imaging Center of Beijing Normal University. All subjects were scanned on a Siemens 3T scanner (Siemens, Erlangen, Germany) with their head snugly fixed with straps and foam pads to restrict head movement. Resting-state images were acquired first, followed by a T1 image scan. During the resting-state fMRI data collection (lasting approximately 8 minutes), all subjects were required to keep their eyes closed, to stay still but relaxed, and not to think of anything in particular and not to fall asleep. The resting-state images were collected axially using an echo-planar imaging (EPI) sequence: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view (FOV) = 200 × 200 mm^2; matrix size = 64 × 64; axial slices = 31; 4.0 mm slice thickness without gap; voxel size = 3.125 × 3.125 × 4.0 mm^3. Structural images were acquired using a T1-weighted sagittal 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR = 2530 ms; TE = 3.45 ms; FA = 7°; FOV = 256 × 256 mm^2; matrix size = 256 × 256; slices = 176; thickness = 1.0 mm; voxel size = 1.0 × 1.0 × 1.0 mm^3.

2.3. fMRI data preprocessing

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK). Preprocessing was performed as follows: The first 10 images were discarded to ensure magnetic signal stabilization, and the remaining images were corrected for slice timing and head motion. Next, individual T1-weighted images were coregistered to the mean functional images and then segmented into gray matter, white matter, and cerebrospinal fluid. Transformations from individual native space to MNI space were computed with the DARTEL toolbox (Ashburner, 2007). Next, the functional images were resampled to voxel size 3.0 × 3.0 × 3.0 mm^3 and spatially smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel. Finally, the functional images were linearly detrended and temporally bandpass filtered (0.01-0.1 Hz) to reduce low-frequency drifts and high-frequency physiological noise. To further minimize the effects of confounding factors, the Friston 24 head motion parameters and white matter and cerebrospinal fluid signals were regressed out from each voxel's time series. The global mean signal was not regressed out because it has been suggested to reflect important neuronal activity rather than noise (Fox et al., 2009; Gotts et al., 2013; Hahamy et al., 2014; Murphy et al., 2009; Saad et al., 2013), which is consistent with some previous studies on network analysis (Guo et al., 2015; Li et al., 2018; van Lutterveld et al., 2014; Wang et al., 2015).

2.4. Functional Degree Centrality (FDC) analysis

FDC is a measure in graph theory that estimates the total functional connectivity between a voxel and the rest of the brain (Buckner et al., 2009; Zuo et al., 2012). It has often been used to identify the hub regions of the brain network (Dai et al., 2015; Liang et al., 2013; Liu et al., 2015; Rubinov and Sporns, 2010). Specifically, Pearson's correlation

Table 1
Demographic and clinical characteristics of the subjects.

	Mean ± SD Schizophrenia	UHR	Healthy Control	F or x^2	*P*
Gender (M/F)	22/8	14/16	17/13	4.49	0.11
Age (y)	25.77 ± 7.06	23.67 ± 4.01	25.00 ± 3.69	1.28	0.28
Education (y)	12.6 ± 3.29	13.70 ± 2.34	14.07 ± 2.66	2.24	0.11
[a]Medicine	9.016 ± 7.71	-	-	-	-
Illness duration (m)	51.53 ± 50.53	-	-	-	-
Inpatient times	1.43 ± 0.97	-	-	-	-
PANSS				-	-
Positive scores	23.80 ± 6.84	-	-	-	-
Negative scores	22.13 ± 7.31	-	-	-	-
General psychopathology scores	42.43 ± 7.98	-	-	-	-
[b]Disorganization	7.87 ± 3.35	-	-	-	-
Total scores	88.03 ± 16.21	-	-	-	-
SIPS				-	-
Positive symptom score	-	5.00 ± 4.13	-	-	-
Negative symptom score	-	6.26 ± 5.41	-	-	-
General symptom score	-	3.23 ± 3.35	-	-	-
Disorganized symptom score	-	2.80 ± 2.83	-	-	-
Total scores	-	17.30 ± 13.32	-	-	-

UHR, ultrahigh risk subjects.
[a] Chlorpromazine equivalents.
[b] The score consists of items of conceptual disorganization, difficulty in abstraction, and poor attention.

coefficients were computed in all possible pairs of voxels, which resulted in a whole-brain functional connectivity matrix. This step was restricted to a predefined gray matter mask that was the same as in previous studies (Zhou et al., 2014; Zuo et al., 2012). The FDC for a given voxel was calculated using the following equation (Buckner et al., 2009; Zuo et al., 2012):

$$FDC(i) = \sum_{j=1,\, j\neq i}^{N_{voxels}} r_{ij}, \quad r_{ij} > r_0$$

where r_{ij} was Pearson's correlation coefficient between voxel i and voxel j, and r_0 was a correlation threshold that was used to eliminate possible spurious correlations arising from noise. In this study, $r_0 = 0.2$. Different correlation thresholds did not change the connection pattern significantly, which is consistent with previous reports (Dai et al., 2015; Liu et al., 2015). The FDC map for each individual was then produced. Finally, the FDC map was standardized to a z-score map and was used in the subsequent statistical analysis (Buckner et al., 2009; Liu et al., 2015; Zhou et al., 2016). The z-score standardization is calculated using the following formula:

$$z_i = \frac{x_i - \mu}{\sigma}, \quad 1 \le i \le N$$

where μ and σ are the mean and SD, respectively, of the FDC map.

2.5. Statistical analysis

Demographic information was compared between the three groups by a Chi-square test (for gender) or one-way ANOVA (for the other variables). We first compared between UHR subjects and healthy controls across the whole brain and then compared between schizophrenia patients and healthy controls. We also did a conjunction analysis to identify the common FDC deficit between the two comparisons. The conjunction analysis, or the conjoint testing for the same effect in different subjects, has been widely used in previous fMRI studies (Friston et al., 1999). To correct for multiple comparisons in all these analyses, significance was determined using a voxel-level threshold of $P < 0.005$ and cluster-level familywise error (FWE) corrected $P < 0.05$.

Finally, we extracted the mean FDC within each significant cluster in the above conjunction analysis and tested the association with the symptoms (positive, negative and disorganization) using the partial correlation analysis. For UHR subjects, disorganization was measured using the score of the disorganization subscale within SOPS/SIPS. Age and gender were controlled for in the correlation analysis of UHR subjects. For schizophrenia patients, disorganization was measured by the sum of three items (P2 conceptual disorganization, N5 difficulty in abstraction, and G11 poor attention) of the PANSS (Rodriguez-Jimenez et al., 2013; Wallwork et al., 2012). In the correlation analysis of schizophrenia patients, age, gender, and medicine dose were added as control variables.

3. Results

As shown in Table 1, all demographic and clinical characteristics were comparable across the three groups. The mean FDC map for each

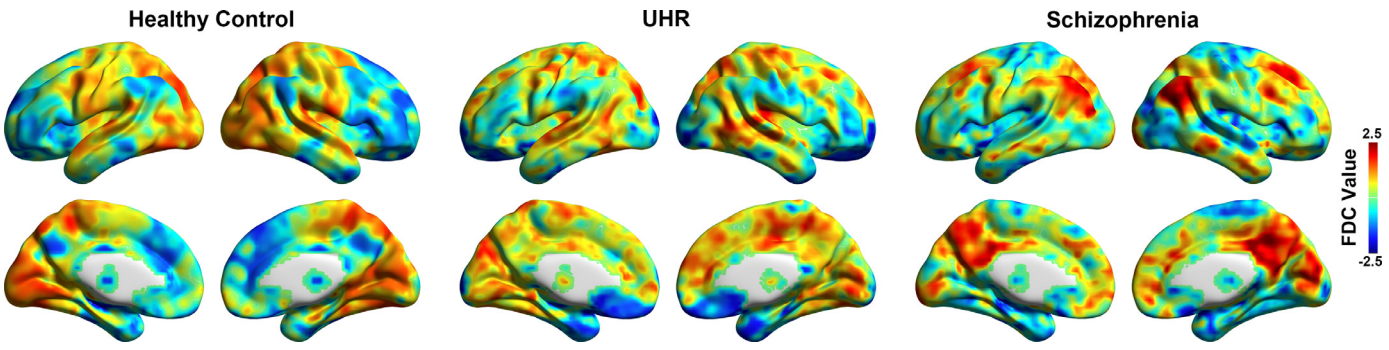

Fig. 1. Mean FDC maps within healthy controls, UHR subjects, and schizophrenia patients. UHR: ultrahigh risk subjects.

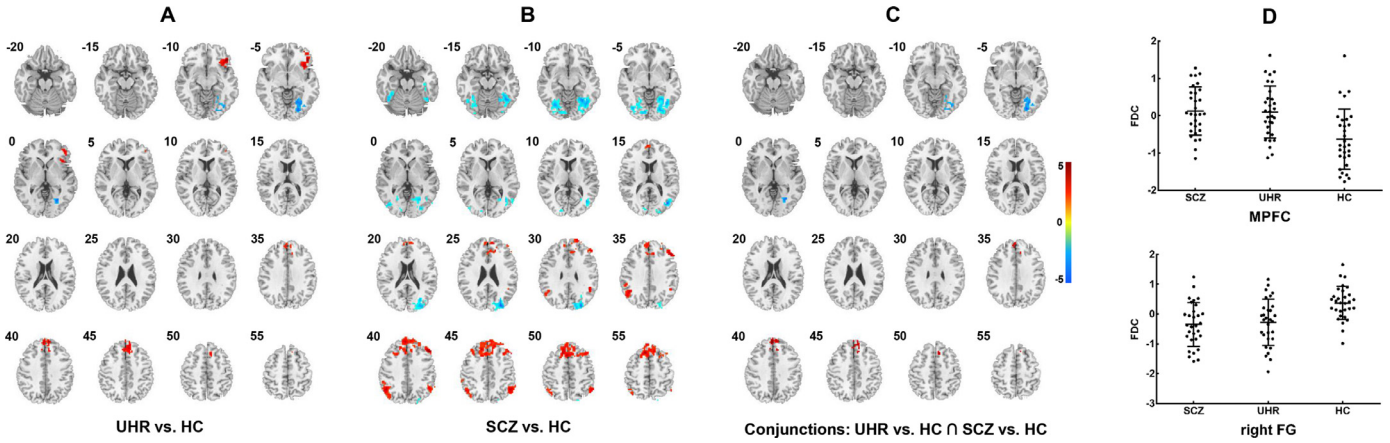

Fig. 2. The significant differences between groups. A: comparison between UHR subjects and healthy controls; B: Comparison between schizophrenia patients and healthy controls; C: conjunction analysis showing the deficits shared between UHR subjects and schizophrenia patients when compared with healthy controls; D: Scatter plot showing the FDC values for each significant cluster extracted from the conjunction analysis. HC: healthy controls; SCZ: schizophrenia.

Table 2
Regions showing FDC differences between groups.

Comparison	Region	Number of voxels	Peak MNI coordinates *x y z*	Peak *T*	FWE *P*
UHR vs. HC					
UHR > HC	MPFC	151	6 51 42	4.22	0.005
	VLPFC	136	45 33 -6	4.67	0.009
UHR < HC	FG_R	106	24 -66 -3	3.77	0.032
SCZ vs. HC					
SCZ > HC	MPFC	792	-9 27 54	4.47	0.000
	DLPFC	148	48 30 39	5.25	0.005
	IPL_L	204	-45 -54 -33	4.26	0.001
	IPL_R	123	51 -57 45	4.07	0.015
SCZ < HC	FG_L	305	-39 -75 -3	4.79	0.000
	FG_R	767	27 -84 24	5.13	0.000
Conjunction analysis					
SCZ>HC∩UHR>HC	MPFC	98	6 51 42	3.84	0.045
SCZ<HC∩UHR<HC	FG_R	101	24 -81 -6	3.69	0.040

UHR: ultrahigh risk subjects; HC: healthy controls; SCZ: schizophrenia.

group is shown in Figure 1. The direct comparison between UHR subjects and healthy controls showed significantly increased FDC in UHR subjects in the right ventrolateral prefrontal cortex (VLPFC, $T = 4.67$, FWE corrected $P = 0.009$) and medial prefrontal cortex (MPFC, $T = 4.22$, FWE corrected $P = 0.005$). UHR subjects also showed significantly decreased FDC in the right FG ($T = 3.77$, FWE corrected $P = 0.032$; see Figure 2.A and Table 2).

Compared to healthy controls, schizophrenia patients showed significantly increased FDC in the MPFC ($T = 4.47$, FWE corrected $P < 0.001$). A cluster within the dorsolateral prefrontal cortex (DLPFC, $T = 5.25$, FWE corrected $P = 0.005$) also showed significantly increased FDC in schizophrenia patients, although the right VLPFC ($T = 4.22$, FWE corrected $P = 0.054$), which differed between UHR subjects and healthy groups, did not differ between schizophrenia patients and healthy individuals. In addition, significantly increased FDC was also found in schizophrenia patients in both sides of the IPL (for the left side, $T = 4.26$, FWE corrected $P = 0.001$; for the right side, $T = 4.07$, FWE corrected $P = 0.015$). Two brain regions showed decreased FDC in schizophrenia patients: the right FG ($T = 5.13$, FWE corrected $P < 0.001$), and the left FG ($T = 4.79$, FWE corrected $P < 0.001$; see Figure 2.B and Table 2).

A conjunction analysis of the two comparisons (UHR subjects vs. healthy controls, schizophrenia patients vs. healthy controls) identified two significant areas: the MPFC ($T = 3.84$, FWE corrected $P = 0.045$) and the right FG ($T = 3.69$, FWE corrected $P = 0.040$; see Figure 2.C and Table 2). The other two areas, the right VLPFC (cluster size = 33 voxels, $T = 3.79$, FWE corrected $P > 0.05$, peak voxel MNI coordinates: $x = 42$, $y = 45$, $z = -3$) and the right DLPFC (cluster size = 31 voxels, $T = 3.80$, FWE corrected $P > 0.05$, peak voxel MNI coordinates: $x = 42$, $y = 36$, $z = 39$) were not significant after the correction for multiple comparisons.

Further confirming the results from the group comparisons, we found significant positive correlations between the disorganization symptoms and FDC in the MPFC (for UHR subjects, $r = 0.569$, $P = 0.001$ and schizophrenia patients, $r = 0.410$, $P = 0.025$) and significant negative correlations between disorganization symptoms and FDC in the right FG (for UHR subjects, $r = -0.380$, $P = 0.039$ and schizophrenia patients, $r = -0.406$, $P = 0.026$; see Figure 3). However, there was no significant correlation between FDC and positive or negative symptoms (see supplementary Table S1).

4. Discussion

This study, for the first time, included UHR subjects in addition to schizophrenia patients and healthy controls to identify brain network-based biomarkers relevant to the onset of schizophrenia. Significantly increased FDC within the MPFC and significantly decreased FDC within the right FG differentiated both UHR subjects and schizophrenia patients from healthy controls. Furthermore, both increased FDC within the MPFC and decreased FDC within the right FG were correlated with the severity of the symptoms of disorganization (a strong predictor for the transition from the UHR stage to the onset of schizophrenia; Demjaha et al., 2012) in both UHR subjects and schizophrenia patients. All these results suggest that global functional dysconnectivity within the MPFC and the right FG may be candidate biomarkers for the onset of schizophrenia.

FG is an important part of the ventral visual system and is specialized for object recognition, especially facial recognition, as shown by both animal and human studies (Lafer-Sousa et al., 2016; Tanaka, 1997). Object recognition is a primary end state of visual processing and a critical precursor for high-level cognitive processing such as attentional control, working memory, reasoning, and emotion (Peissig and Tarr, 2007). FG occupies an important position within the whole-brain network and is a high FDC hub in the normal brain network (Achard et al., 2012; Dai et al., 2015). Our study confirmed the important role of FG in healthy controls and found significantly decreased FDC in the FG in UHR subjects and schizophrenia patients (see Figure 1). These results are consistent with previous studies that reported significantly decreased FDC in the visual pathway (including the FG) in schizophrenia patients (Skatun et al., 2016; Wang et al., 2014).

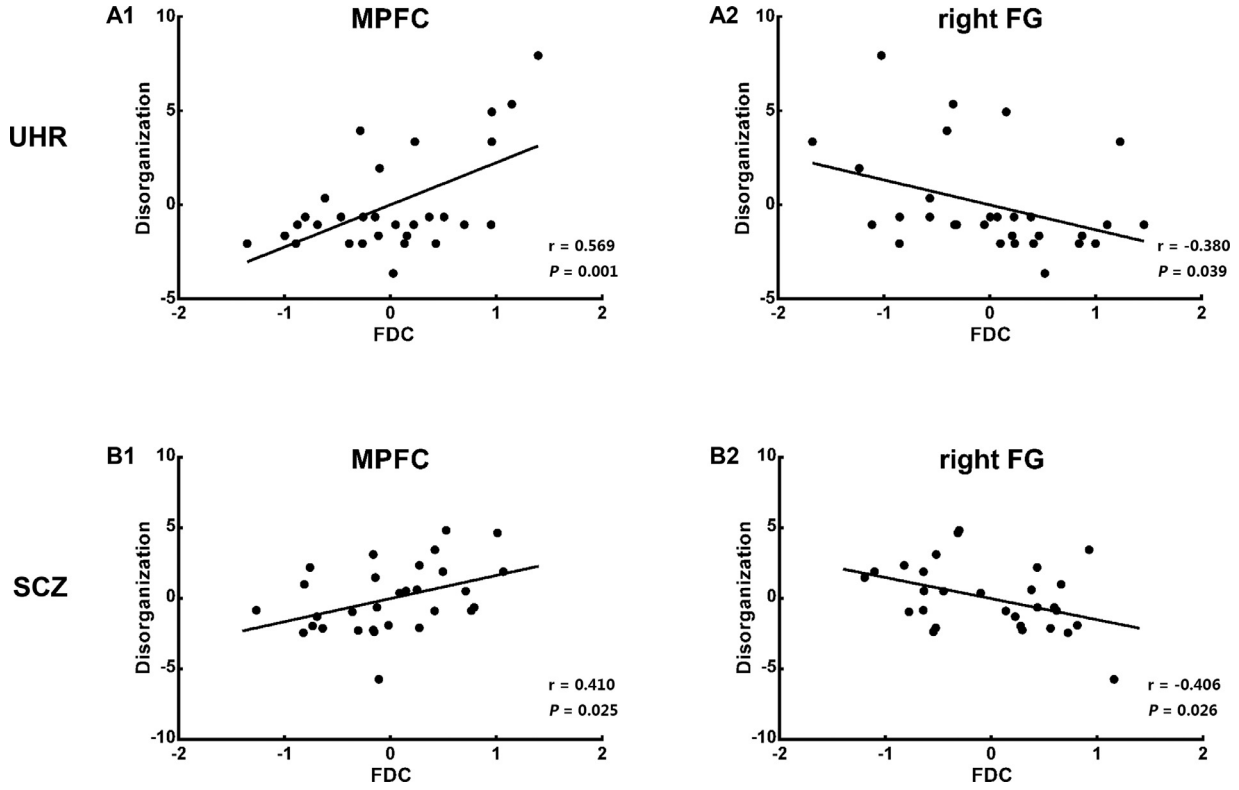

Fig. 3. Correlations between disorganization symptoms and the mean FDC extracted from each significant cluster. The upper panels show the correlations in UHR subjects (panels A1-A2), and the lower panels show the correlations in schizophrenia patients (panels B1-B2).

Decreased FDC in the FG may result in a failure to communicate the processed visual information with other regions, which may be one of the sources of impairments in schizophrenia. Furthermore, the significant correlations between the decreased FDC of the FG and the high score of disorganization symptoms in both schizophrenia patients and UHR subjects was also consistent with previous behavioral studies that showed a link between facial recognition deficit and symptoms of disorganization (Cohen et al., 2009; Eack et al., 2010; Guillaume et al., 2007; Ventura et al., 2013).

The MPFC is the other important network-based biomarker found in this study (increased FDC was significantly correlated with disorganization symptoms for both schizophrenia patients and UHR subjects). The MPFC, an important component of the default mode network (DMN), is also one of the most important hubs in the whole-brain network. It requires more cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism (Liang et al., 2013; Tomasi et al., 2013) to support information exchange across brain regions. The even higher energy demand of this region, as reflected by the increased FDC in the MPFC, may result in a huge burden for the whole-brain network and a weak point that is vulnerable to many disease-related risk factors. To our knowledge, increased FDC within the MPFC in schizophrenia patients has been reported in at least two previous resting-state fMRI studies that also performed whole-brain voxelwise FDC analysis (Chen et al., 2015; Skatun et al., 2016). Some other studies reported increased FDC of schizophrenia in other DMN hubs such as the PCC, precuneus, and hippocampus, although they did not find significant results in the MPFC (Palaniyappan and Liddle, 2014; van Lutterveld et al., 2014). Altered functional connectivity in the MPFC may still contribute to the disorganization symptoms of schizophrenia, as suggested by the current study. As an important component of the DMN, the MPFC is activated in a resting state or when the mind is involved in tasks that direct attention away from external stimuli (Andreasen et al., 1995). The internal mentation hypothesis has been proposed to highlight the importance of the DMN in internally directed cognitive processes. The overactive DMN may strengthen this process and further produce internal, introspective thoughts or disorganization symptoms.

In addition to the FG and MPFC, we found brain regions in which increased FDC was specific to either schizophrenia patients (including the DLPFC and IPL) or UHR subjects (including the VLPFC). All of these regions belong to the central executive network. During central executive processing, information from the posterior cortex (including the FG) that is received and maintained by the VLPFC will be further processed by the DLPFC and IPL (Rowe et al., 2000; Wagner et al., 2001). Due to the close relationship between the visual pathway and the central executive network (Chadick and Gazzaley, 2011), increased FDC of the central executive network in schizophrenia patients or UHR subjects may be a reactive response to the lack of correct and adequate visual information. The central executive network plays an important role in high-level cognitive functions such as working memory and attentional control, which are the core cognitive functions impaired in schizophrenia. These stage-specific FDC changes seem to suggest that deficits in higher-order processing become more evident after UHR transitions to psychosis. In previous studies, some researchers have also reported increased FDC in the central executive network in schizophrenia patients, although other studies reported decreased FDC in the same network. For example, in addition to decreased FDC within the visual pathway, Skatun and colleagues (2016), similar to this study, also reported increased FDC in the frontal (both lateral and medial parts) and parietal cortices in schizophrenia patients. Moreover, Chen et al. (2015) reported increased FDC within the prefrontal cortex (including the DLPFC and VLPFC) in schizophrenia patients. Using 90 automatic anatomical labeling (AAL) regions as ROIs, Li et al. (2017) performed a whole-brain functional connectivity analysis on all ROI pairs (4005 pairs in total) and found that most functional connectivity changes of schizophrenia patients and UHR subjects when compared with healthy controls were located in the VLPFC. Further analysis showed that functional connectivity of the VLPFC in schizophrenia patients and UHR subjects was mostly increased. It is also worth

mentioning that this study analyzed relationships between functional connectivity within the fronto-parietal central executive network and the disorganization symptoms and reported positive correlations.

Our findings suggest that the global functional dysconnectivity within the MPFC and the right FG could be candidate biomarkers for the onset of schizophrenia. However, whether or not these biomarkers are specific to schizophrenia requires more research, especially in comparison to mental disorders that also show disorganization symptoms, such as anxiety disorders, depressive disorders, and attention deficit hyperactivity disorder.

5. Conclusions

In conclusion, this is the first study to focus on the comparison of voxelwise whole-brain FDC with graph theory across healthy controls, UHR subjects and schizophrenia patients. The global functional dysconnectivity at some important brain hubs (especially the MPFC and the right FG) were found in both the UHR subjects and schizophrenia patients, and these altered FDCs were significantly correlated with disorganization symptoms. These findings shed some new light on our understanding of the underlying pathophysiological mechanisms of schizophrenia, and provide evidence that the FDC deficits at the MPFC and the right FG could be used as candidate biomarkers related to the conversion of schizophrenia.

Acknowledgements

The authors would like to thank all the volunteers. This work was supported by the National Natural Science Foundation of China (81571045, 31771242, 81471365, and 81601169), the National Key Basic Research Program of China (2014CB846103), the Major Brain Program of Beijing Science and Technology plan (Z161100002616017), the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201807, XLMX201807), the Capital's Funds for Health Improvement and Research (2018-2-2123), the Beijing Municipal Science & Technology Commission (D171100007017001 and Z161100000216151), the National Science and Technology Major Project for IND (investigational new drug, 2018ZX09201-014), and the Leading Technological Talents of the Capital Program (Z181100006318009).

We would also like to thank Yi-lang Tang, M.D., Ph.D., (Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA) for his comments on and editing of the manuscript.

Financial Disclosures

The authors declare no competing financial interests in relation to this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.06.004.

References

Achard, S., Delon-Martin, C., Vertes, P.E., Renard, F., Schenck, M., Schneider, F., Heinrich, C., Kremer, S., Bullmore, E.T., 2012. Hubs of brain functional networks are radically reorganized in comatose patients. Proc. Natl. Acad. Sci. U S A 109 (50), 20608–20613. https://doi.org/10.1073/pnas.1208933109.

Andreasen, N.C., Arndt, S., Alliger, R., Miller, D., Flaum, M., 1995. Symptoms of schizophrenia. Methods, meanings, and mechanisms. Arch. Gen. Psychiatry 52 (5), 341–351. https://doi.org/10.1001/archpsyc.1995.03950170015003.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38 (1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J. Neurosci. 29 (6), 1860–1873. https://doi.org/10.1523/JNEUROSCI.5062-08.2009.

Chadick, J.Z., Gazzaley, A., 2011. Differential coupling of visual cortex with default or frontal-parietal network based on goals. Nat. Neurosci. 14 (7), 830–832. https://doi.org/10.1038/nn.2823.

Chen, C., Wang, H.L., Wu, S.H., Huang, H., Zou, J.L., Chen, J., Jiang, T.Z., Zhou, Y., Wang, G.H., 2015. Abnormal Degree Centrality of Bilateral Putamen and Left Superior Frontal Gyrus in Schizophrenia with Auditory Hallucinations: A Resting-state Functional Magnetic Resonance Imaging Study. China Med. J. (Engl) 128 (23), 3178–3184. https://doi.org/10.4103/0366-6999.170269.

Cohen, A.S., Nienow, T.M., Dinzeo, T.J., Docherty, N.M., 2009. Attribution biases in schizophrenia: relationship to clinical and functional impairments. Psychopathology 42 (1), 40–46. https://doi.org/10.1159/000173702.

Dai, Z., Yan, C., Li, K., Wang, Z., Wang, J., Cao, M., Lin, Q., Shu, N., Xia, M., Bi, Y., He, Y., 2015. Identifying and Mapping Connectivity Patterns of Brain Network Hubs in Alzheimer's Disease. Cereb. Cortex 25 (10), 3723–3742. https://doi.org/10.1093/cercor/bhu246.

Demjaha, A., Valmaggia, L., Stahl, D., Byrne, M., McGuire, P., 2012. Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. Schizophr. Bull. 38 (2), 351–359. https://doi.org/10.1093/schbul/sbq088.

Eack, S.M., Mermon, D.E., Montrose, D.M., Miewald, J., Gur, R.E., Gur, R.C., Sweeney, J.A., Keshavan, M.S., 2010. Social cognition deficits among individuals at familial high risk for schizophrenia. Schizophr. Bull. 36 (6), 1081–1088. https://doi.org/10.1093/schbul/sbp026.

Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009. The global signal and observed anticorrelated resting state brain networks. J. Neurophysiol. 101 (6), 3270–3283. https://doi.org/10.1152/jn.90777.2008.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci. 3 (2), 89–97.

Friston, K.J., Holmes, A.P., Price, C.J., Buchel, C., Worsley, K.J., 1999. Multisubject fMRI studies and conjunction analyses. Neuroimage 10 (4), 385–396. https://doi.org/10.1006/nimg.1999.0484.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., Martin, A., 2013. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front Hum. Neurosci. 7 (356), 1–20. https://doi.org/10.3389/fnhum.2013.00356.

Guillaume, F., Guillem, F., Tiberghien, G., Martin, F., Ganeva, E., Germain, M., Pampoulova, T., Stip, E., Lalonde, P., 2007. Use of the process dissociation procedure to study the contextual effects on face recognition in schizophrenia: familiarity, associative recollection and discriminative recollection. Psychiatry Res. 149 (1-3), 105–119. https://doi.org/10.1016/j.psychres.2006.03.015.

Guo, W., Liu, F., Zhang, Z., Liu, G., Liu, J., Yu, L., Xiao, C., Zhao, J., 2015. Increased Cerebellar Functional Connectivity With the Default-Mode Network in Unaffected Siblings of Schizophrenia Patients at Rest. Schizophr. Bull. 41 (6), 1317–1325. https://doi.org/10.1093/schbul/sbv062.

Hahamy, A., Calhoun, V., Pearlson, G., Harel, M., Stern, N., Attar, F., Malach, R., Salomon, R., 2014. Save the global: global signal connectivity as a tool for studying clinical populations with functional magnetic resonance imaging. Brain Connect. 4 (6), 395–403. https://doi.org/10.1089/brain.2014.0244.

Lafer-Sousa, R., Conway, B.R., Kanwisher, N.G., 2016. Color-Biased Regions of the Ventral Visual Pathway Lie between Face- and Place-Selective Regions in Humans, as in Macaques. J. Neurosci. 36 (5), 1682–1697. https://doi.org/10.1523/JNEUROSCI.3164-15.2016.

Lei, W., Li, M., Deng, W., Zhou, Y., Ma, X., Wang, Q., Guo, W., Li, Y., Jiang, L., Han, Y., Huang, C., Hu, X., Li, T., 2015. Sex-Specific Patterns of Aberrant Brain Function in First-Episode Treatment-Naive Patients with Schizophrenia. Int. J. Mol. Sci. 16 (7), 16125–16143. https://doi.org/10.3390/ijms160716125.

Li, R.R., Lyu, H.L., Liu, F., Lian, N., Wu, R.R., Zhao, J.P., Guo, W.B., 2018. Altered functional connectivity strength and its correlations with cognitive function in subjects with ultra-high risk for psychosis at rest. CNS Neurosci. Therapeutics 24 (12), 1140–1148. https://doi.org/10.1111/cns.12865.

Li, T., Wang, Q., Zhang, J., Rolls, E.T., Yang, W., Palaniyappan, L., Zhang, L., Cheng, W., Yao, Y., Liu, Z., Gong, X., Luo, Q., Tang, Y., Crow, T.J., Broome, M.R., Xu, K., Li, C., Wang, J., Liu, Z., Lu, G., Wang, F., Feng, J., 2017. Brain-Wide Analysis of Functional Connectivity in First-Episode and Chronic Stages of Schizophrenia. Schizophr. Bull. 43 (2), 436–448. https://doi.org/10.1093/schbul/sbw099.

Liang, X., Zou, Q., He, Y., Yang, Y., 2013. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. Proc. Natl. Acad. Sci. U S A 110 (5), 1929–1934. https://doi.org/10.1073/pnas.1214900110.

Liu, W., Liu, H., Wei, D., Sun, J., Yang, J., Meng, J., Wang, L., Qiu, J., 2015. Abnormal degree centrality of functional hubs associated with negative coping in older Chinese adults who lost their only child. Biol. Psychol. 112, 46–55. https://doi.org/10.1016/j.biopsycho.2015.09.005.

Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44 (3), 893–905. https://doi.org/10.1016/j.neuroimage.2008.09.036.

Palaniyappan, L., Liddle, P.F., 2014. Diagnostic discontinuity in psychosis: a combined study of cortical gyrification and functional connectivity. Schizophr. Bull. 40 (3), 675–684. https://doi.org/10.1093/schbul/sbt050.

Peissig, J.J., Tarr, M.J., 2007. Visual object recognition: do we know more now than we did 20 years ago? Annu. Rev. Psychol. 58, 75–96. https://doi.org/10.1146/annurev.psych.58.102904.190114.

Rasetti, R., Sambataro, F., Chen, Q., Callicott, J.H., Mattay, V.S., Weinberger, D.R., 2011. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. Arch. Gen. Psychiatry 68 (12), 1207–1217. https://doi.org/10.1001/archgenpsychiatry.2011.103.

Rodriguez-Jimenez, R., Bagney, A., Mezquita, L., Martinez-Gras, I., Sanchez-Morla, E.M., Mesa, N., Ibanez, M.I., Diez-Martin, J., Jimenez-Arriero, M.A., Lobo, A., Santos, J.L., Palomo, T., Parg, 2013. Cognition and the five-factor model of the positive and negative syndrome scale in schizophrenia. Schizophr. Res. 143 (1), 77–83. https://doi.org/10.1016/j.schres.2012.10.020.

Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S., Passingham, R.E., 2000. The prefrontal cortex: response selection or maintenance within working memory? Science 288 (5471), 1656–1660.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52 (3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003.

Saad, Z.S., Reynolds, R.C., Jo, H.J., Gotts, S.J., Chen, G., Martin, A., Cox, R.W., 2013. Correcting brain-wide correlation differences in resting-state FMRI. Brain Connect 3 (4), 339–352. https://doi.org/10.1089/brain.2013.0156.

Skatun, K.C., Kaufmann, T., Tonnesen, S., Biele, G., Melle, I., Agartz, I., Alnaes, D., Andreassen, O.A., Westlye, L.T., 2016. Global brain connectivity alterations in patients with schizophrenia and bipolar spectrum disorders. J. Psychiatry Neurosci. 41 (5), 331–341. https://doi.org/10.1503/jpn.150159.

Tanaka, K., 1997. Mechanisms of visual object recognition: monkey and human studies. Curr. Opin. Neurobiol. 7 (4), 523–529.

Tomasi, D., Wang, G.J., Volkow, N.D., 2013. Energetic cost of brain functional connectivity. Proc. Natl Acad. Sci. U S A 110 (33), 13642–13647. https://doi.org/10.1073/pnas.1303346110.

van Lutterveld, R., Diederen, K.M., Otte, W.M., Sommer, I.E., 2014. Network analysis of auditory hallucinations in nonpsychotic individuals. Hum. Brain Mapp. 35 (4), 1436–1445. https://doi.org/10.1002/hbm.22264.

Ventura, J., Wood, R.C., Jimenez, A.M., Hellemann, G.S., 2013. Neurocognition and symptoms identify links between facial recognition and emotion processing in schizophrenia: meta-analytic findings. Schizophr. Res. 151 (1-3), 78–84. https://doi.org/10.1016/j.schres.2013.10.015.

Wagner, A.D., Maril, A., Bjork, R.A., Schacter, D.L., 2001. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral Prefrontal cortex. Neuroimage. 14 (6), 1337–1347. https://doi.org/10.1006/nimg.2001.0936.

Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr. Res. 137 (1-3), 246–250. https://doi.org/10.1016/j.schres.2012.01.031.

Wang, D., Zhou, Y., Zhuo, C., Qin, W., Zhu, J., Liu, H., Xu, L., Yu, C., 2015. Altered functional connectivity of the cingulate subregions in schizophrenia. Transl. Psychiatry 5, e575. https://doi.org/10.1038/tp.2015.69.

Wang, X., Xia, M., Lai, Y., Dai, Z., Cao, Q., Cheng, Z., Han, X., Yang, L., Yuan, Y., Zhang, Y., Li, K., Ma, H., Shi, C., Hong, N., Szeszko, P., Yu, X., He, Y., 2014. Disrupted resting-state functional connectivity in minimally treated chronic schizophrenia. Schizophr. Res. 156 (2-3), 150–156. https://doi.org/10.1016/j.schres.2014.03.033.

Weinberger, D.R., 1993. A connectionist approach to the prefrontal cortex. J. Neuropsychiatry Clin. Neurosci. 5 (3), 241–253. https://doi.org/10.1176/jnp.5.3.241.

Zhou, C., Hu, X., Hu, J., Liang, M., Yin, X., Chen, L., Zhang, J., Wang, J., 2016. Altered Brain Network in Amyotrophic Lateral Sclerosis: A Resting Graph Theory-Based Network Study at Voxel-Wise Level. Front Neurosci. 10, 204. https://doi.org/10.3389/fnins.2016.00204.

Zhou, Y., Wang, Y., Rao, L.L., Liang, Z.Y., Chen, X.P., Zheng, D., Tan, C., Tian, Z.Q., Wang, C.H., Bai, Y.Q., Chen, S.G., Li, S., 2014. Disrupted resting-state functional architecture of the brain after 45-day simulated microgravity. Front. Behav. Neurosci. 8, 200. https://doi.org/10.3389/fnbeh.2014.00200.

Zuo, X.N., Ehmke, R., Mennes, M., Imperati, D., Castellanos, F.X., Sporns, O., Milham, M.P., 2012. Network centrality in the human functional connectome. Cereb. Cortex 22 (8), 1862–1875. https://doi.org/10.1093/cercor/bhr269.