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Decreased regional homogeneity and increased functional connectivity of default network correlated with neurocognitive deficits in subjects with genetic high-risk for schizophrenia: A resting-state fMRI study

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ABSTRACT

The complex symptoms of schizophrenia (SCZ) have been associated with dysfunction of the default mode network (DMN). Subjects at genetic high risk (GHR) for SCZ exhibit similar but milder brain abnormalities. This study aimed to investigate functional alterations of DMN from the local to the whole and their relationships with cognitive deficits in GHR subjects. 42 GHR subjects and 38 matched healthy controls (HC) were studied by resting-state functional magnetic resonance imaging (rs-fMRI). Regional homogeneity (ReHo) analysis was performed to measure the local brain function of the DMN, derived by the group independent component analysis, and areas with aberrant ReHo were used as seeds in functional connectivity (FC). Compared with the HC group, the GHR group exhibited significantly decreased ReHo and increased FC in the fronto-limbic-striatal system within the DMN. Furthermore, a significant negative correlation was found between decreased ReHo in the right superior frontal gyrus and the delayed recall in GHR subjects. Our findings revealed decreased local function and hyper-connectivity in the fronto-limbic-striatal system of the DMN in GHR subjects, which is associated with cognitive deficits. This may improve our understanding of the neurophysiological endophenotypes of SCZ and the neural substrate underlying the cognitive deficits of the disease.

1. Introduction

SCZ is a neurodevelopmental disorder with high heritability estimated at 80% (Owen et al., 2005). However, the pathogenesis and progression patterns of SCZ are still under controversy, partly due to the uncertainty about when the disease-related abnormalities first become evident (Lawrie et al., 2007). Moreover, there are a lot of factors (i.e. medication use, long duration of untreated psychosis, unemployment, substance abuse, and institutionalization) confounding the studies centering on patients. This has led to an increased interest in subjects at genetic high risk (GHR) for SCZ, especially first-degree relatives, who have about 10-fold higher risk for developing SCZ than the general population (Gottesman and Gould, 2003). A growing body of evidence suggests that GHR subjects exhibit similar but milder brain abnormalities and cognitive deficits compared to their ill relatives, and that these abnormalities may represent genetic vulnerability for the development of SCZ (Chen et al., 2009; Spilka and Goghari, 2017; Tang et al., 2015; Villarreal et al., 2014). Study of GHR subjects may offer a window for understanding etiologic mechanisms of SCZ in spite of most confounding factors.

In the past decades, neuroimaging studies have revealed various abnormalities in brain structure and function that may lead to neurocognitive deficits in GHR subjects (Brahmbhatt et al., 2006; Hao et al., 2009; Van Buuren et al., 2011). Recently, rs-fMRI is seeing increased application since it serves as an effective technique without requiring any specific task involvement. This is more conducive to revealing the

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neural substrates of task-independent self-information processing in diseases. Some brain regions have been found to show more activity at rest, including the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and parietal cortex (Whitfield-Gabrieli et al., 2009). These areas, which form the DMN, are very similar to those associated with abnormalities in SCZ (Shenton et al., 2001). The DMN is thought to be more active at rest and associated with the construction of internal self-reference (Lin et al., 2011; Mason et al., 2007). Its dysfunction appears prominent in SCZ as indicated by clinical and neurocognitive characteristic of the disease (Anselmetti et al., 2007). Previous fMRI studies have reported abnormal functional connectivity (FC) of DMN in prefrontal areas and PCC/ACC, which were related to the positive symptoms and working memory in both SCZ patients and their unaffected siblings (Chari et al., 2019; Liu et al., 2012; Spilka and Goghari, 2017). Some studies also demonstrated altered local spontaneous neuronal activity of DMN in GHR by using fractional amplitude of low-frequency fluctuation (fALFF) and ReHo methods, these areas included inferior and middle temporal gyrus, fronto-insular gyrus, orbito-frontal and inferior occipital (Guo et al., 2014b; Liu et al., 2016). Considering that most previous rs-fMRI studies primarily focused on either certain local indicators or global functional connectivity, systematically investigating the DMN of GHR subjects from local to global might shed some new light on the disease.

Therefore, in the present study, we used the method of ReHo to detect alterations of local neuronal activity within the DMN, which was identified by group independent component analysis (gICA) in all subjects. ReHo is a reliable and sensitive measurement that can be used to evaluate regional brain function, reflecting synchrony of low-frequency fluctuations in local brain regions, and its abnormalities may connote alterations in regulation and coordination of regional neuronal activity (van Buuren et al., 2012; Zang et al., 2004). We then used a voxel-based method to verify if there were alterations in FC between the regions with abnormal ReHo and other brain regions in the DMN. We hypothesized that cognitive deficits in GHR would be associated with aberrant DMN activities.

2. Materials and methods

2.1. Participants

42 GHR subjects were recruited from the Second Xiangya Hospital, in Changsha, Hunan, China. They were confirmed to have at least one first-degree relative who has met the DSM-IV diagnostic criteria for SCZ. In addition, 40 healthy volunteers were recruited via advertisement in the local media. The ones that had any current or history of DSM-IV Axis I disorder themselves or among their first-degree to third-degree relatives were excluded.

All subjects were 13 to 30-year-old right-handed Han Chinese with gender and age matched. Subjects were excluded if they met any of following criteria: serious somatic disease, substance abuse or dependence, mental retardation, a history of psychiatric disorders or antipsychotic treatments, head injury resulting in a sustained loss of consciousness exceeding 5 min. They were all provided an oral and written description of this study prior to solicitation of informed consent to participate (No. S009, 2018).

2.2. Neurocognitive assessment

All the subjects completed certain parts of MATRICS™ Consensus Cognitive Battery (MCCB™) (Kern et al., 2008; Nuechterlein et al., 2008) as the assessment of cognitive domains within 24 h around the MRI scan. The tests included the Hopkins Verbal Learning Test-Revised (HVLT-R) for verbal memory, the Continuous Performance Test (CPT) for sustained attention, the Trail Making Test A and B (TMTA, TMTB) for speed of processing, as well as the Chinese version of Stroop Color and Word Test (SCWT) (Biederman, 1979) for response inhibition ability.

2.3. Image acquisition

For each participant, T1*-weighted echo-planar images were acquired in the resting condition using a 3.0T magnetic resonance imager (Siemens, Skyra, Germany) equipped with a 16-channel array coil at the Magnetic Imaging Centre of Hunan Children's Hospital, Changsha, China. Participants were instructed to remain awake and still in supine position with eyes closed. Foam pads and earplugs were provided to minimize head motion and reduce scanner noise. Sequence parameters were as follows: TR = 2000 ms; TE = 30 ms; flip angle = 90°; slice number = 36; FOV = 256 × 256 mm; slice thickness = 3.4 mm; voxel size = 3.4 × 3.4 × 3.4 mm^3. Each functional run contained 250 image volumes, resulting in a functional scanning time of 508 s. For registration of functional images, a high-resolution structural image was acquired using a high-resolution sequence: TR = 2530 ms; TE = 2.33 ms; flip angle = 7°; slice number = 192; FOV = 256 × 256 mm; slice thickness = 1 mm; voxel size = 1 × 1 × 1 mm^3.

2.4. Data pre-processing

Functional MRI data were preprocessed and analyzed using Data Processing Assistant for Resting-State fMRI (DPARSF 4.1, available at http://www.restfmri.net) (Yan, 2010), running in MATLAB (version 2012a, The MathWorks, Inc., Natick, Massachusetts, United States). The first 10 time points of each subject were discarded to eliminate the non-equilibrium effects of magnetization. The image data preprocessing included slice timing, realignment, co-registration to individual structural T1 scan, segmentation into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), and spatial normalization to Montreal Neurological Institute coordinates (MNI) space by using the normalization parameters estimated in DARTEL, with a resampling voxel size of 3 mm × 3 mm × 3 mm. A temporal filter (0.01–0.08 Hz) was used to decrease the effect of low-frequency drifts and physiological high-frequency noise, and then linear trends were removed. Subsequently, Friston's 24-parameter model (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items) (Friston et al., 1996) was applied to regress out the effect of head motion. To further overcome the influence of head movement on subsequent data analysis, each bad time point was used as a separate regressor in nuisance covariates regression, where “bad” was defined as any volume with mean FD (Jenkinson) > 0.2 mm, as well as 2 forward and 1 back of these volumes (Jenkinson et al., 2002). Then, the CSF and WM signals were also removed as nuisance variables to reduce the non-neuronal BOLD fluctuation effects through linear regression. In addition, we also calculated the mean FD (Jenkinson) and found no different between two groups ($t = -0.231$, $p = 0.818$). Two participants in HC group whose translation or rotation parameters of head motion exceeded ± 1.5 mm or ± 1.5°, and mean FD Jenkinson > 0.2 mm (Yan et al., 2013) were excluded. Finally, the generated images were spatially smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel after ReHo analysis and before functional connectivity (FC) analysis.

2.5. DMN identification

The group independent component analysis (gICA), a multivariate data-driven approach, was applied to extract DMN from all the subjects with the group ICA of fMRI toolbox (GIFT) (v4.0a, available at http://icatb.sourceforge.net/gift/gift_startup.php). Using the minimum description length (MDL) (Yi-Ou Li et al., 2006) criteria for preliminary dimension estimation, 22 independent components (ICs)were identified and were acquired by the infomax algorithm. Multiple runs (100 iterations) were conducted using Icasso (available at https://research.

ics.aalto.fi/ica/icasso/) to investigate the reliability of the ICs with a random initiation method (Himberg et al., 2004). Then, time-courses and spatial maps in each subject were back reconstructed (Erhardt et al., 2011). The DMN was selected by spatial correlation with the templates offered by GIFT. After the conversion of the intensity values in each spatial map to Z value, the DMN was determined by one-sample *t*-test with a $q < 0.01$ false discovery rate (FDR) correction (cluster size = 50) (Qi et al., 2012) and then used as a mask for the subsequent analysis.

2.6. ReHo analysis

ReHo analysis was performed in DPARSF software. ReHo maps of each subject were obtained on a voxel-wise basis by calculating Kendall's coefficient of concordance (KCC) between the time series of a given voxel and those of its nearest neighboring 26 voxels (Zang et al., 2004). The greater ReHo value of a given voxel means the higher degree of localized temporal synchronization within a neighboring cluster. Then, the voxel ReHo was divided by the average ReHo value of the entire brain in each subject for the purpose of standardization.

2.7. Functional connectivity analysis

To investigate whether abnormal functional connectivity (FC) existed between the brain regions that exhibited altered localized temporal synchronization (measured by ReHo) and other brain regions. Five seed regions of interest (ROIs) were used for FC analysis, which were derived from those showing significant abnormality of the ReHo values. For each subject, we first averaged the time series of voxels within each seed ROI, so as to obtain the representative time series. Then we calculated the Pearson's correlation coefficient between the representative time series of each seed ROI and every other voxel in the whole brain in the voxel-wise method. Finally, the generated correlations-coefficient maps were converted to Z values with Fisher r-to-Z transformation to improve normality.

2.8. Statistical analysis

Comparisons of demographic information (gender, age and educational years) and neurocognitive performance between two groups were performed on SPSS (IBM SPSS Statistics for Macintosh, Version 25.0., Armonk, NY: IBM Corp). Categorical variables were analyzed with the Chi-square test and continuous variables were analyzed using the independent two-sample *t*-test, with $p < 0.05$ considered significant. Significance of the alterations in brain function, including ReHo value and FC across groups, were estimated using a voxel-based independent two-sample *t*-test within the DMN mask with gender, age educational years and mean FD as nuisance covariates in DPARSF. False discovery rate (FDR) correction was applied to correct for multiple comparisons, the statistical threshold was set as $q < 0.05$ and cluster size (CZ) = 20.

In addition, to assess whether the aberrant ReHo and FC in the GHR group are correlated to neurocognitive deficits revealed above, z ReHo values and z FC values were extracted from 6 ROIs separately. Simple linear regression was applied, residuals for ReHo values and parameters of significantly different cognitive domains were calculated to exclude the effects of gender, age and education years. Since we were to analyze correlations between six brain regions and two cognitive items, Pearson bivariate correlation analysis was applied to these residuals, with a threshold of $p < 0.004$ considered significant (Bonferroni correction, $p = 0.05/(2 \times 6)$).

3. Results

3.1. Demographic and neurocognitive characteristics

The demographic and neurocognitive characteristics are summarized in Table 1and Table 2, respectively. The two groups did not differ significantly in gender ($p = 0.824$), age ($p = 0.282$) or years of education ($p = 0.599$) (Table 1). However, GHR subjects have significant poorer delayed recall performance measured by the HVLT-R test ($p = 0.041$) and longer completion time of the TMTB test ($p = 0.043$) compared with controls (Table 2).

Table 1
Demographic characteristic of included subjects.

Demographic characteristics	GHR (n = 42)	HC (n = 38)	p Value
Gender (Male/Female)	23/19	22/16	0.824[a]
Age (year)	21.310 ± 5.466	20.260 ± 2.892	0.282[b]
Education duration (year)	12.210 ± 3.660	12.580 ± 2.445	0.599[b]

[a] Pearson Chi-Square test applied, 2-sided p of Fisher's exact test provided.
[b] Independent T-test applied, Levene's test for equality of variances, 2-tailed p provided.

Table 2
Comparison of cognitive domains conducted between GHR and HC group.

Cognitive domains	GHR (n = 42)	HC (n = 38)	p Value[a]
HVLT-R			
Trial 1	7.120 ± 1.501	7.290 ± 1.930	0.659
Trial 2	9.380 ± 1.652	9.680 ± 1.544	0.400
Trial 3	10.380 ± 1.361	10.710 ± 1.088	0.238
Delayed Recall	9.570 ± 1.876	10.340 ± 1.419	**0.041***
Total Recall	26.640 ± 3.721	27.680 ± 3.863	0.223
CPT			
Vision			
Errors	10.190 ± 6.267	12.160 ± 7.240	0.198
Misses	13.170 ± 35.426	3.430 ± 4.723	0.085
Time (ms)	864.070 ± 83.329	839.73 ± 36.481	0.105
Accuracy (%)	94.412 ± 8.519	96.282 ± 2.221	0.177
Hearing			
Errors	17.120 ± 8.325	18.030 ± 10.856	0.680
Misses	19.290 ± 31.718	24.970 ± 63.749	0.616
Time (ms)	877.630 ± 75.300	887.97 ± 152.662	0.702
Accuracy (%)	91.209 ± 7.890	89.758 ± 14.735	0.585
TMT			
Part A			
Finish time (ms)	34.720 ± 17.749	32.366 ± 10.558	0.479
Error Frequency	0.210 ± 0.470	0.240 ± 0.675	0.862
Part B			
Finish time (ms)	96.000 ± 56.092	76.030 ± 26.089	**0.043***
Error Frequency	0.760 ± 1.543	0.420 ± 0.889	0.236
SCWT			
Stroop A			
Time (s)	16.601 ± 5.045	15.236 ± 5.762	0.262
Errors	0.170 ± 0.490	0.080 ± 0.359	0.368
Self-corrections	0.330 ± 0.687	0.260 ± 0.554	0.619
Stroop B			
Time (s)	18.805 ± 6.264	17.098 ± 4.099	0.150
Errors	0.070 ± 0.261	0.180 ± 1.136	0.533
Self-corrections	0.400 ± 0.701	0.240 ± 0.431	0.196
Stroop C			
Time (s)	32.165 ± 15.529	27.622 ± 7.155	0.093
Errors	0.860 ± 1.117	0.530 ± 0.951	0.160
Self-corrections	1.140 ± 1.491	0.680 ± 0.989	0.113

HVLT-R: the Hopkins Verbal Learning Test-Revised; CPT: Continuous Performance Task; TMT: Trail Making Test; SCWT: Stroop Color and Word Test.
[a] Independent T-test applied, Levene's test for equality of variances, 2-tailed p provided.

3.2. ReHo differences in DMN

The DMN mask, selected from 22 ICs by gICA, is mainly comprised of bilateral MPFC, ACC, PCC/ precuneus (PCu), inferior/lateral/medial parietal cortex, middle occipital cortex, and lateral/superior/temporal cortex (Fig. 1).

Within the DMN mask, differences of ReHo between two groups were revealed by a voxel-based independent two-sample *t*-test with FDR

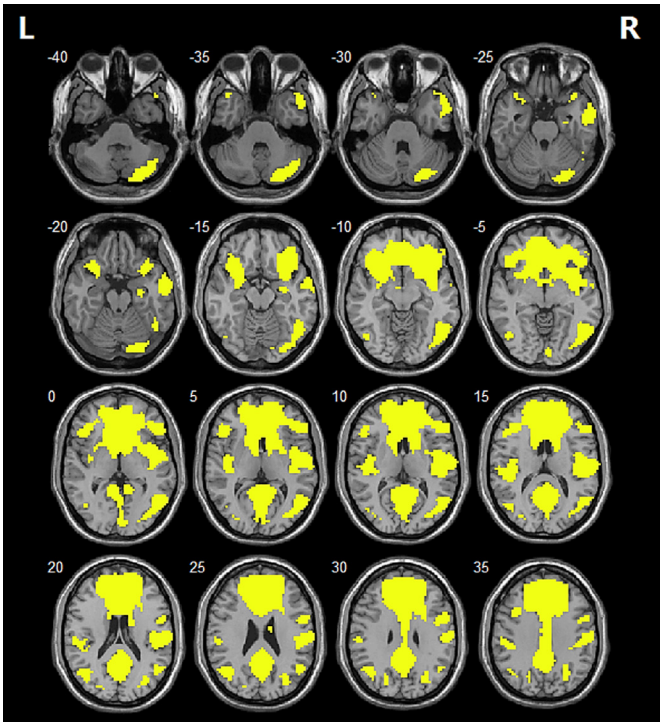

Fig. 1. Default mode network (DMN) mask derived from group independent component analysis (gICA) at resting state. Second-level within-group analyses were applied to all subjects, $q < 0.05$ with FDR correction, Cluster size = 50.

correction ($q < 0.05$, CZ = 20). Compared with the HC group, the GHR group had decreased ReHo values in the bilateral middle frontal gyrus (MFG), left ventral ACC (LVACC), right superior frontal gyrus (RSFG) and left caudate. However, no significantly increased ReHo values were observed in the GHR group relative to the HC group. The related results are presented in Table 3 and Fig. 2 (Table 3, Fig. 2).

3.3. Functional connectivity in DMN

Five regions with altered ReHo value were used as seed ROIs for FC within DMN mask. Only the connectivity between the RSFG and the left orbitofrontal gyrus (LOFG) was significantly increased in the GHR group (FDR correction, $q < 0.05$, CZ = 20) (Table 4, Fig. 3). In contrast, we failed to find any significantly decreased FC among any two brain regions in the GHR group compared to that in the HC group.

3.4. Relations between abnormal brain activity and neurocognitive deficits

With respect to potential relations between abnormal brain activity and neurocognitive deficits in GHR subjects, five z ReHo values and one z FC value extracted from six ROIs were correlated with delayed recall measured by the HVLT-R test and completion time of the TMTB test.

The ReHo values in RSFG were negatively correlated with the delayed recall ($r = -0.443$, $p = 0.003$) and the ReHo values in right MFG had a negative relationship with the delayed recall ($r = -0.317$, $p = 0.041$) (Fig. 4). However, no correlations were found between abnormal FC and neurocognitive deficits in the present study. After Bonferroni correction, only the relationship between decreased ReHo value in RSFG and delayed memory survived.

4. Discussion

In the current study, we systematically examined the DMN characteristics in individuals with genetic high risk for SCZ and HCs. The findings of the study suggested that GHR subjects may have reduced regional temporal synchronization and hyper-connectivity in the DMN. In addition, GHR subjects may also have some degree of cognitive deficit, mainly manifesting as delayed recall impairment and slow processing speed. Furthermore, there was a relationship between abnormal brain activities and neurocognitive deficits. To the best of our knowledge, the present study is the first study exploring the abnormal function of DMN from the local to the whole systematically, and the relationship between these alterations and neurocognitive deficits in the GHR group.

We found that compared to the HC group, the GHR group showed significantly decreased ReHo in the bilateral MFG, RSFG and LACC. These areas belong to the fronto-limbic system, which is thought to be involved in cognitive and emotional processing (Ruiz et al., 2013; Schott et al., 2015). Prior studies have confirmed that the dysfunction of the fronto-limbic system may result in psychiatric symptoms and cognitive deficits that are similar to those found in SCZ (Eack et al., 2016). The similar but milder pattern of brain abnormalities was reported in GHR subjects (Guo et al., 2015; Hart et al., 2013). Structural MRI studies have reported that reductions in the inferior frontal cortex, ACC, and paracingulate sulcus (Harms et al., 2010; Li et al., 2012) were shared by patients with SCZ and their unaffected siblings, and that reductions in the ventromedial prefrontal and frontal pole in GHR subjects were particularly associated with genetic susceptibility and progression of SCZ (Byun et al., 2012; Rosso et al., 2010). Additionally, functional MRI studies have consistently demonstrated abnormal activities and connections of the prefrontal and limbic regions within DMN in both resting and task-related state. Jang et al. (2011) found reduced FC in the prefrontal areas and ACC/PCC, and the degree of the reduction was positively correlated with genetic loading. Whitfield-Gabrieli et al. (2009) revealed hyperactivity and hyper-connectivity within DMN, including MPFC, PCC/PCu and ACC in patients with SCZ and their unaffected siblings, in which the MPFC abnormalities were associated with working memory performance and clinical symptoms. Furthermore, a recent resting study in GHR subjects showed altered spontaneous neuronal activity in middle temporal, orbito-frontal, inferior occipital and fronto-insular gyrus measured by ALFF and ReHo (Liu et al., 2016). Therefore, it has been proven that there are widespread abnormalities in the fronto-limbic system in SCZ patients and GHR subjects. Our findings add to the previous evidence and suggest a general decreased regional homogeneity of the fronto-limbic system within the DMN in GHR subjects. The decreased ReHo in bilateral MFG, RSFG and LACC may indicate that GHR subjects had abnormal

Table 3
Regions with ReHo differences in GHR and HC subjects in DMN.

Brain regions (GHR < HC)	Cluster size	Peak coordinate (MNI)			Peak T value	Cohen's *d*
		x	y	z		
Left Ventral Anterior Cingulate Cortex, LVACC	20	−6	30	12	4.573	1.117
Left Caudate	39	−6	0	0	4.664	1.136
Left Middle Frontal Gyrus, LMFG	35	−24	45	15	5.047	1.205
Right Middle Frontal Gyrus, RMFG	20	24	51	6	4.176	0.991
Right Superior Frontal Gyrus, RSFG	20	21	48	27	4.07	1.039

ReHo: Regional homogeneity; GHR: genetic high risk; HC: healthy control; x, y, z: coordinates of peak locations in the Montreal Neurological Institute (MNI) space.

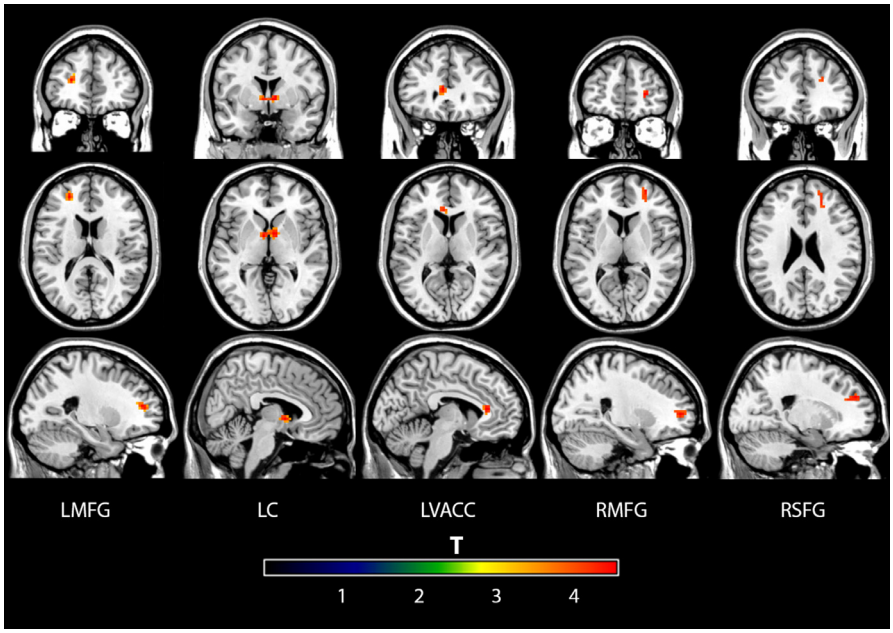

Fig. 2. Brain regions with significantly altered regional homogeneity (ReHo) value within the DMN in GHR group compared to HC group. Voxel-based independent two-sample *t*-test analyses were applied, $q < 0.05$ with FDR correction, Cluster size = 20.

regulation and coordination of localized neuronal activity in the fronto-limbic system within the DMN. In addition, we found GHR subjects showed significant impairments in long-term memory and processing speed, and observed a significant correlation between the ReHo value in RSFG and long-term memory performance. Aberrant ReHo values in the right MFG also exhibited a trend of correlation with long-term memory in the GHR group, although it was not corrected. Thus, in the present study, we not only found abnormalities in the fronto-limbic system, but further confirmed that these abnormalities may be related to the cognitive deficits in the GHR group. It suggested that incoherent neuronal activity of the fronto-limbic system within DMN might be a marker of SCZ-related abnormal brain activity that correlated to psychopathology and neurocognitive deficits.

We also observed significantly decreased ReHo in the caudate in the GHR group relative to the HC group. The caudate, as part of the striatum, is dominated by dopaminergic neurons and commonly reported in SCZ and GHR studies, mainly because of the dopaminergic dysfunction hypothesis in SCZ (Heinz and Schlagenhauf, 2010). Positron emission tomography (PET) studies have found increased caudate-putamen presynaptic dopamine synthesis capacity (Huttunen et al., 2008) and caudate dopamine D2 receptor (Hirvonen et al., 2005) in both SCZ patients and GHR subjects. In a structural MRI study, GHR subjects showed shape abnormalities in the caudate, putamen and pallidum that were intermediate between SCZ patients and healthy controls (Mamah et al., 2008). A large number of task-related and resting fMRI studies have also revealed the altered caudate function in GHR subjects. For example, Gromann et al. (2014) found reduced activation in the right caudate, left insular and putamen during a reward task in GHR group. Solé-Padullés et al. (2016) reported that GHR subjects exhibited reduced connectivity in the left caudate nucleus and ACC, and also showed a positive correlation between connectivity in

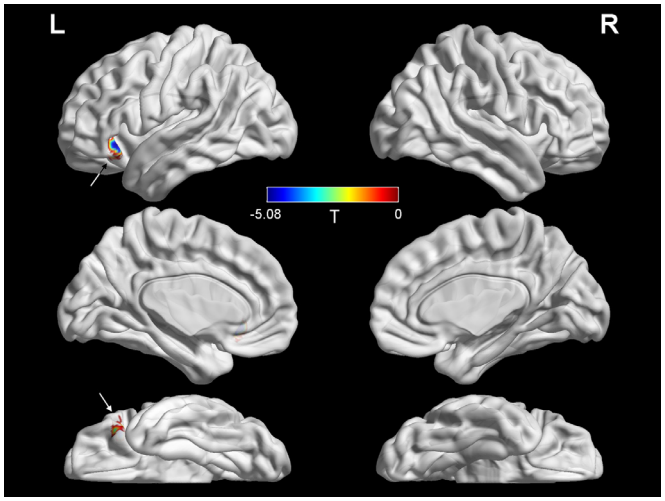

Fig. 3. Brain regions with significantly altered functional connectivity (FC) within the DMN in GHR group compared to HC group. Voxel-based independent two-sample *t*-test analyses were applied, height threshold $q < 0.05$ with FDR correction, Cluster size = 20.

the left basal ganglia network and grey matter volume in the left caudate. Besides, similarly inefficient fronto-striatal pattern during working memory in SCZ and their unaffected siblings was also reported (Diwadkar et al., 2012). In this study, we also observed decreased ReHo in the left caudate in the GHR group, which supported the results in previous studies. Moreover, the caudate was confirmed anatomically and functionally connected with VACC and their functional pathway was involved in cognitive control (Di Martino et al., 2008;

Table 4
Regions with FC differences in GHR and HC subjects in DMN.

Seed area	Brain regions with altered functional connectivity (GHR > HC)	Cluster size	Peak coordinate (MNI)			Peak T value	Cohen's *d*
			x	y	z		
Right Superior Frontal Gyrus, RSFG	Left Orbital Frontal Gyrus, LOFG	46	−36	27	−6	−5.08	1.152

FC: functional connectivity; GHR: genetic high risk; HC: healthy control; x, y, z: coordinates of peak locations in the Montreal Neurological Institute (MNI) space.

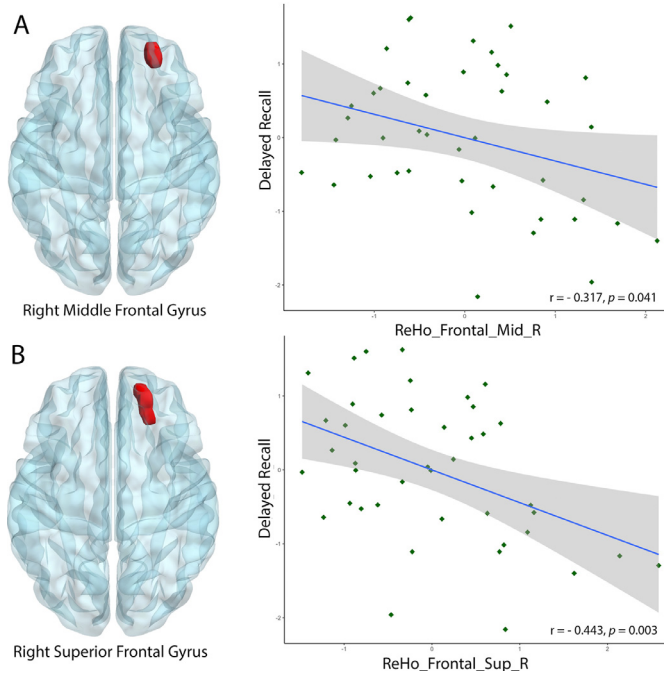

Fig. 4. Scatter plots showing significant negative correlations between delayed recall performance and ReHo values in (A) right superior frontal gyrus ($r = -0.443$, uncorrected $p = 0.003$, significant with Bonferroni correction), (B) right middle frontal gyrus ($r = -0.317$, uncorrected $p = 0.041$).

Haber, 2003). Therefore, together with the abnormal incoherent neuronal activity of fronto-limbic system in our study, we can reasonably speculate that the fronto-limbic-striatal system may play a key role in the DMN abnormality and possibly serve as a promising candidate for a neurophysiological endophenotype of SCZ.

Another noteworthy finding in this study is the hyper-connectivity of the frontal area within DMN in the GHR group. We observed that GHR subjects had increased FC between the RSFG and LOFG compared to the HC group, which was similar to the previous research that found hyper-connectivity in DMN (Chai et al., 2011; Mannell et al., 2010; Mingoia et al., 2012; Salvador et al., 2010; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). Orbitofrontal gyrus was thought to be involved in emotional processing, decision-making and goal-directed behavior (Kringelbach, 2005; Walton et al., 2004), and might be associated with schizophrenic thought disorder. Our findings might support the earlier hypothesis that prefrontal hyper-connectivity is a compensatory mechanism for the dysregulated inhibitory brain circuits in SCZ spectrum disorders. This compensatory response could temporarily lead to better functioning. However, long-term compensatory responses might cause neurotoxic effects resulting in brain dysfunction (Weinberger and McClure, 2002), which could be one of the reasons for widespread decreased FC across the frontal and limbic networks in SCZ patients (Rădulescu and Mujica-Parodi, 2008). Besides, the increased FC between RSFG and LOFG probably indicated the dysfunction in interhemispheric coordination within DMN in GHR subjects, which was often reported in SCZ patients and GHR subjects (Guo et al., 2014a; Hoptman et al., 2012). Unfortunately, we did not find any significant relationships between the abnormal FC and neurocognitive performance in GHR group. This is probably because the abnormal FC in GHR subjects restricted to certain regions, rather than extensive alterations, which were inadequate to affect the cognitive performance.

5. Limitation

There are some limitations in this study that should be improved in future studies. Firstly, the modest sample size may limit statistical power; More GHR subjects need to be recruited in further study to verify the results of the study. Secondly, the study did not include the related SCZ patients, so we did not know whether similar reduced regional homogeneity and hyper-connectivity in the fronto-limbic-striatal system within DMN could be also observed in the SCZ patients. In addition, our findings are only based on the BOLD signal of fMRI, while a combination of structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS) and electroencephalogram (EEG) might make the results more reliable. Finally, we cannot confirm whether the altered brain activities in the study are associated with the onset of SCZ. Future longitudinal multimodal studies involving SCZ patients and individuals at ultra-high-risk state for SCZ may be able to overcome these limitations.

6. Conclusion

Consistent with the hypothesis, reduced regional homogeneity was observed in the fronto-limbic-striatal system within the DMN in GHR subjects, including the bilateral MFG, LVACC, RSFG and left caudate. Another finding was an increased FC between RSFG and LOFG in the GHR group, which is postulated to be a compensatory response. In addition, we also found the impairment of long-term memory and processing speed in GHR subjects and observed a significant negative correlation between decreased ReHo values in RSFG and long-term memory. Overall, this study indicates that GHR subjects exhibit abnormalities from local brain activities to global FC in the fronto-limbic-striatal system within DMN, which were also associated with observed neurocognitive deficits. These findings should provide fresh insight into understanding the neurophysiological endophenotypes of SCZ and the neural substrate underlying the cognitive deficits of the disease.

Author contributions

XC, YH supervised this study. XM performed the analysis. XM and WZ wrote the paper. CL and KJ carried out the scanning process. XM, WZ, ZL and JT contributed to the discussion of the results. YH, ZL, LY, LO and XM collected the data. All co-authors revised and approved the version to be published.

Declaration of Competing Interest

All co-authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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