Relationships between abnormal neural activities and cognitive impairments in patients with drug-naïve first-episode schizophrenia

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Abstract

Background: Prior resting state functional magnetic resonance imaging studies via the regional homogeneity (ReHo) method have demonstrated inconsistent and conflicting results because of several confounding factors, such as small sample size, medicinal influence, and illness duration. Relationships between ReHo measures and cognitive impairments in patients with drug-naïve first-episode schizophrenia (dn-FES) are rarely reported. This study was conducted to explore the correlations between ReHo measures, cognitive deficits, and clinical symptoms in patients with dn-FES.

Methods: A total of 69 patients with dn-FES and 74 healthy controls were recruited. MATRICS Consensus Cognitive Battery (MCCB), Wechsler Adult Intelligence Scale (WAIS), and Positive and Negative Syndrome Scale (PANSS) were used to assess cognitive function, intelligence quotient (IQ), and clinical symptoms, respectively. The correlations between ReHo map and cognitive deficits, the severity of symptoms were examined using strict correlation analyses within brain areas.

Results: The ReHo values in the right middle frontal gyrus (MFG) and the superior frontal gyrus (SFG) increased in the dn-FES group, whereas the ReHo values in the right cuneus decreased. Correlation analysis showed that the ReHo values in the right MFG were positively correlated with attention/vigilance impairments, social cognition deficits, the severity of clinical manifestations.

Conclusions: These findings suggested that abnormal spontaneous activities in the right MFG reflect the illness severity and cognitive deficits, which serves as a basis for establishing the objective diagnostic markers and might be a clinical intervention target for patients with schizophrenia.

Background

Schizophrenia is a disabling mental illness that affects 0.5% of the Chinese population[1]. This complex mental illness is characterized by impairment in a broad array of domains, including perception, attention, memory, processing speed, reasoning, problem solving, and social cognition[2]. Cognitive dysfunctions are core features of schizophrenia and have a substantial influence on patients' psychosocial lives, these deficits have emerged as important targets of treatment-oriented research[3, 4].

The US National Institute of Mental Health initiative, namely, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), was designed to improve the development of cognition-enhancing treatments and enhance cognition in schizophrenia. The MATRICS consensus cognitive battery (MCCB) is a standard cognitive battery to evaluate the cognitive deficits associated with schizophrenia. MCCB contains ten tests that measure seven cognitive domains: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition[3, 4]. MCCB has been used widely in China since its clinical reliability and validity were established[5]. Patients with schizophrenia show significant cognitive deficits across multiple cognitive domains[6–8].

Functional neuroimaging technology has been widely used to study the neuronal pathophysiology of schizophrenia. Resting state functional Magnetic Resonance Imaging (rs-fMRI) is a useful non-invasive neuroimaging technique for exploring local spontaneous neural activities and studying cognitive impairment. Regional homogeneity (ReHo) is a method employed in rs-fMRI based on Kendall's coefficient of concordance to measure the temporal synchronization of the time series of each voxel with those of its adjacent neighbors[9]. It is a useful technique for discovering abnormal brain activities and determining the correlation of these differences with clinical symptoms and neurocognitive deficits. Patients with schizophrenia exhibit an increase in ReHo values in the dorsolateral prefrontal cortex (DLPFC)[10–12], the medial prefrontal cortex[13], the angular gyrus[14], the precentral gyrus[15], and the superior temporal gyrus[12]. They also experience a decrease in ReHo values in the superior temporal gyrus[12–15], occipital lobes[11, 14, 16], the parietal lobule[13, 15], the precentral lobule[12, 13], and the postcentral gyrus[12, 14, 15].

ReHo studies on schizophrenia have shown several promising findings, but such findings are inconsistent and conflicting. The reduced function of the dorsolateral prefrontal cortex plays a major role in the pathophysiology of schizophrenia and is associated with executive function deficits, response inhibition, and working memory [8, 17–19]. However, other brain areas, such as the superior temporal gyrus[12–15] and the precentral lobule[13, 15], have yielded inconsistent and controversial results, and the relationships between abnormal brain activities and cognitive impairments have not been well studied.

Numerous researchers attempted to map the neuronal pathophysiology in schizophrenia, but results were contradictory. The underlying etiology and pathophysiology of schizophrenia remain unknown, and the following factors should be considered: (1) existing studies have no adequate statistical power because of a small sample size; (2) in previous studies, the main threshold setting at a low or even uncorrected level for multiple tests produces hundreds or thousands of false positives to reflect true effects; this setting should be replicated in future studies, but strict correction should be performed to prevent type I errors[20–23]; and (3) the heterogeneity of patients with schizophrenia is related to multiple episode courses, illness duration, and medical effect and causes inconsistent and contradictory findings.

In the current study, we hypothesized patients with schizophrenia exhibit common and distinct brain activities would reflect the severity of psychotic symptoms and cognitive deficits. This study was first to investigate abnormal spontaneous neural activities and their correlations with the cognitive dysfunction between patients with first-episode drug-naïve schizophrenia (dn-FES) and matching healthy controls (HC) as indexed by ReHo. It also aimed to explore the associations between signal changes and clinical symptoms and to provide more revealing and consistent findings. Finally, we aimed to ascertain which functional brain aberrations would reflect the clinical moderators including illness severity and cognitive deficit.

Methods

Participants

Eighty-seven patients who had first-episode schizophrenia and had never been medicated were recruited from Nanjing Brain Hospital between January 2017 and December 2018. The following inclusion criteria were considered: patients were in compliance with the DSM-IV diagnostic criteria for schizophrenia; and patients presented no evidence of affective disorders, head trauma, and substance abuse.

Eighty-two HC that matched in terms of age and gender were recruited in the local community, and they had no history of a major psychiatric disorder and no family history of psychotic disorder.

The general inclusion criteria for all of the groups were right handed, aged 16–45 years, and able to understand survey instructions and execute cognitive tests. The general exclusion criteria were a history of the head injury with a loss of consciousness, substance abuse, and use of drugs that might affect the functions of the central nervous system. The study was approved by the Nanjing Brain Hospital Ethics Committee. After the study was completely described, a written informed consent was obtained from all of the participants.

Neuropsychological and clinical assessments

MCCB [24, 25] was used to assess cognitive function. The present study includes nine tasks across seven cognitive domains, including speed of processing (Category Fluency, Trails A, Brief Assessment of Cognition in Schizophrenia Symbol Coding), attention/vigilance(Continuous Performance Test), working memory(Wechsler Memory Scale-III Spatial Span), verbal learning (Hopkins Verbal Learning Test–Revised), visual learning (Brief Visuospatial Memory Test–Revised),reasoning and problem solving (The Mazes test), and social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test). We corrected the original score for age, gender, and education to obtain a *T* score to evaluate cognitive function, and high scores showed a good performance. We adopted the Wechsler adult scale of intelligence[26] to test the intelligence quotient. The PANSS was used to assess the symptoms of the patients[27], and the process was carried out by two experienced psychiatrists.

Image data acquisition

MRI scanning was performed with a Siemens 3.0-T signal scanner, and a standard head coil padded with foam was used to reduce head motion and scanner noise. All of the participants laid in a supine position and were instructed to remain as still as possible, close their eyes, remain awake, and not think of anything[9, 28].Three-dimensional T1-weighted sagittal images were acquired using a brain volume sequence with the following parameters: repetition time (TR) = 2,300 ms, echo time (TE) =2.96ms, inversion time = 900 ms, flip angle (FA) = 9°, field of view (FOV) = 256 mm × 256 mm, matrix =256 × 256, slice thickness = 1 mm, 192 sagittal slices, and acquisition time = 554 s. The images were acquired using a gradient echo single-shot echo planar imaging sequence with the following parameters: TR/TE = 2,500/30 ms, FOV =224 mm × 224 mm, matrix = 64 × 64, FA = 90°, slice thickness = 3.5 mm, no gap, 37 interleaved transverse slices, 149 volumes, and acquisition time = 379s.

Data preprocessing and processing

Functional images were preprocessed with the Matlab2013b platform and the Data Processing Assistant for rs-fMRI (DPARSF4.4, advanced edition)[29]. Data were calculated in an original space warped by diffeomorphic anatomical registration via an exponentiated Lie algebra (DARTEL). The first four volumes of the BOLD data were discarded for each subject to allow the signal to reach equilibrium. The remaining images were corrected for the acquisition time delay between slices. All of the subjects should have no > 2 mm maximum displacement in any plane, 2° of angular motion, and 0.2 mm mean frame-wise displacement[30]. Then, the images were spatially realigned to the first image of each dataset, and movement parameters were assessed for each subject and corrected using the Friston 24 approach [31]. Several nuisance covariates (global brain, white matter, and cerebrospinal fluid signals) were regressed out. The datasets were band-pass filtered to reduce low-frequency drift and high-frequency physiological respiratory and cardiac noise ($0.01 < f < 0.1$ Hz). ReHo was calculated on a voxel-by-voxel basis by calculating Kendall's coefficient of concordance on the basis of regional homogeneity hypothesis, which estimates similarity in the time series of a given voxel to its nearest 26 voxels[9]. Each subject's value was divided by the mean value of their whole-brain ReHo to eliminate the whole-brain effect at utmost. The standardized ReHo images were spatially smoothened with a Gaussian filter with a full width at half maximum (FWHM) of 4 mm. Finally, ReHo values were used for statistical analysis.

Statistical analysis

SPSS software (version20.0) was used to statistically analyze demographic data, clinical symptoms, IQ, and cognitive data. For continuous variables, a two-sample t-test was used to compare the differences between the two groups, and achi square test was used for categorical variables.

The ReHo maps were compared between the two groups by using the threshold-free cluster enhancement (TFCE) method with family wise-error (FWE) correction for multiple comparisons. Age, gender, education, and probability of gray matter were treated as covariates, and the threshold for significance was $p < 0.05$ [32]. In the following correlation analysis, the resultant significant ReHo map was used as inclusion masks.

Patients with schizophrenia were subjected to voxel-wise correlation analyses to explore the correlation between the ReHo map and PANSS (positive symptoms, negative symptoms, general, and all totals) and the correlation between the ReHo map and MCCB (speed of processing, verbal learning, working memory, reasoning/problem solving, visual learning, attention/vigilance, social cognition, and overall composite). In addition, age, gender, education, and illness duration were placed in the model as covariates. The permutation-based nonparametric inference was undertaken with 5,000 permutations, and significance level was thresholded for the correction of multiple comparisons by using a TFCE of 0.05.

Results

Demographic data outcome

Data from 26 subjects (18 FES and 8 HC) were excluded because of excessive head movement, and the 143 remaining subjects (69 FES and 74 HC) were used for all analysis. No significant differences were found between FES and HC groups in terms of age ($p = 0.083$) or gender ($p = 0.142$), but significant differences were observed in education ($p = 0.004$). The results of demographic data are listed in Table 1.

Group differences in ReHo

In our study, compared with the control group, the increased ReHo values were found mainly in the right MFG and the right superior frontal gyrus (SFG), where as the decreased ReHo values were observed in the right cuneus ($p < 0.05$, TFCE, FWE corrected). Age, gender, illness duration, and probability of gray matter were corrected as covariates during calculation (Figure 1, Table 2).

Correlation analyses

Voxel-wise correlation analyses between the ReHo map and PANSS scores were performed to explore the relationship between the ReHo values and the PANSS scores in the dn-FES group by setting age, gender, education, and illness duration as covariates. Positive symptoms ($r = 0.41$, $p < 0.05$, corrected by TFCE), negative symptoms ($r = 0.32$, $p < 0.05$, corrected by TFCE), and PANSS total score ($r = 0.45$, $p < 0.05$, corrected by TFCE) had a positive correlation with the ReHo value in the right MFG. The same approach was employed to investigate the relationship between the ReHo values and the MCCB in the dn-FES group. Attention/vigilance ($r = -0.30$, $p < 0.05$, corrected by TFCE), social cognition ($r = -0.38$, $p < 0.05$, corrected by TFCE), and overall composite ($r = -0.34$, $p < 0.05$, corrected by TFCE) had a negative correlation with the ReHo value in the right MFG (Tables 3 and 4).

Discussion

In the present study, the dn-FES group showed severe and widespread cognitive deficits in all domains, and this observation was consistent with previous studies that used the same instrument [33–35]. Schizophrenia has distinct cognitive impairments, including speed of processing [36], working memory [37], verbal learning [38], reasoning/problem solving [39], visual learning [40], attention/vigilance [41], and social cognition [42]. Our results showed that cognitive deficits were present at the onset of schizophrenia without considering the several factors, such as long-term antipsychotic treatment, prolonged illness course.

We observed an increase in ReHo values in the right middle frontal gyrus (MFG, Brodmann Areas 10, BA10) and superior frontal gyrus (SFG, BA9) and a decrease in ReHo values in the right cuneus in patients with dn-FES as compared with healthy controls. The prefrontal cortex (PFC) is involved in the modulation of decision-making and executive control for an appropriate behavior by integrating sensory and emotional information [43, 44]. The frontal cortex lesion is related to behavioral impairments, such as inflexibility, social inappropriateness, isolation, and apathy [45]. The right MFG has been well studied and may play a major role in integrating visual, auditory, and somatic information to obtain an extensive and generalized interpretation of the environment [46]. Nevertheless, many research results are not entirely

consistent or even contrary. For instance, researchers have reported increased ReHo in the frontal lobe[12, 47, 48], but others have failed to repeat the results and have even found decreased ReHo values in the frontal lobe[49]. Several factors, such as head motion regression model, cultural backgrounds, illness courses, illness heterogeneity, experimental parameters, and statistical methods, may be considered. The cuneus belongs to the visual cortex which is involved in visual processing and associated with attention and working memory, the abnormal regional spontaneous activity in the cuneus at early stages of schizophrenia may cause higher-level cognitive impairment[50]. Our results were partially consistent with previous findings found that ReHo values decreased in the right cuneus in patients with schizophrenia[14, 48]. We proposed that the disruption of the local synchronization of the spontaneous activity in these brain areas was related to the psychopathology of schizophrenia. Especially, such common frontal aberrations may be concerned with vulnerability to psychosis.

The correlation analysis showed that the ReHo values in the right MFG were positively correlated with the severity of clinical manifestations (positive symptoms, negative symptoms, and PANSS total score) in patients with dn-FES. These results are partially consistent with previous studies[47, 51, 52]. Decreased gray matter volumes in right MFG and SFG were associated with the total PANSS scores in patients with FES[52]. Neuroimaging studies have indicated that right MFG aberrations possibly play an important role in the emergence of the psychotic symptoms of auditory hallucinations, thought disorder, and positive psychotic symptoms in schizophrenia[47]. Frontal lobe dysfunction is possibly correlated with the occurrence of negative symptoms, especially in the right MFG, which is particularly vulnerable to long-term effects of schizophrenia[51]. The right MFG has a partial overlapping brain area with the medial prefrontal cortex (MPFC), and a study on adolescent-onset schizophrenia has also shown that ReHo values in the right MPFC increased[53]. Another study has found that concomitant structural and causal connectivity deficits in MPFC are correlated with the negative symptoms of schizophrenia[54]. Similarly, our results also found that negative symptoms are positively correlated with the ReHo values in the right MFG in the early stage of patients with dn-FES. In summary, we found that the ReHo values in the right MFG were associated not only with positive symptoms but also with negative symptoms in dn-FES. The increased ReHo values in the frontal regions are thought to underlie the manifestation of the psychotic symptoms in schizophrenia. However, considering that the data on the relationship between ReHo values and clinical variables in dn-FES are sparse, these findings may need further validation.

The correlation analysis showed that ReHo values in the right MFG were negatively correlated with MCCB overall composite performance, social cognitive presentation, and attention/vigilance. A structural MRI study has found a thinner MFG cortex in patients with schizophrenia, and the decreased cortical thickness in this region is relevant to cognitive impairments[55]. This brain area has input and output connectivities with the supramodal cortex and functions as a mediator of information processing or transfer during multiple cognitive operations[46]. The right MFG region is involved in higher cognitive functions, such as multitasking, planning of future actions, strategic processes in memory recall, various executive functions, and social cognition[56]. Moreover, the ReHo values of the right MFG were negatively correlated with social cognition in our study. Social cognitive deficits in schizophrenia are broad, thereby imposing a huge burden on functional recovery. Severe social cognitive deficits exist in patients with

schizophrenia, and social cognitive deficits were associated with the abnormal spontaneous activity of the MPFC[57]. The PFC is an important regulator in social cognition, the disruptions in prefrontal microcircuitry is thought to play an essential role in the pathophysiology of schizophrenia with social deficits[58]. In this study, we found that the ReHo values of the right MFG were negatively correlated with attention impairment. Attention deficit is a core feature and endophenotype of schizophrenia, which has yielded extensive research[59, 60]. The right MFG is considered the connecting area of the ventral and dorsal attention networks, which play a prominent role in attention regulation[47].

Our study found an increased ReHo values in the right SFG. A meta-analysis also showed that ReHo in the SFG is increased in both patients with first-episode and treated schizophrenia [12]. The SFG is an important component of the DLPFC[61, 62]. The DLPFC is well-known for its involvement in executive functions, but it is also involved in risky and moral decision-making[63], working memory[64], and social cognition[65]. Abnormal neuronal activity in DLPFC is associated with auditory hallucinations in schizophrenia[66–69] and advanced cognitive function[70]. However, in our study, the ReHo values in DLPFC were not significantly correlated with MCCB and PANSS in the dn-FES group, which is related to many factors, including size and heterogeneity of samples and different indicators of spontaneous brain activity.

Limitations

Current research has several limitations that should be improved in future research. First, our sample size is insufficient, but it is already more than most fMRI studies in first-episode schizophrenia to date, and our results could accept more stringent multiple comparison corrections. Second, we did not perform follow up these patients with schizophrenia. Hence, we could not determine the exact characteristics of brain changes and cognitive outcomes in schizophrenia and whether abnormal ReHo was a cause or a consequence of schizophrenia. Lastly, some patients who were unable to keep the head or continue to complete all the cognitive tests were excluded from the study lead to our results are not representative of all patients with schizophrenia.

Conclusions

In conclusion, these findings indicate that increased ReHo values in the right MFG and SFG are present even at the early stage of patients with drug-naïve first-episode schizophrenia, The frontal aberrations may be concerned with vulnerability to psychosis. The abnormal regional spontaneous neuronal activities revealed by ReHo values in the right MFG are related not only to the negative and positive symptoms of schizophrenia but also to attention and cognition deficits, these functional brain changes may reflect a clinical moderators including illness severity and cognitive deficits. This finding suggests that the altered spontaneous brain activities in frontal cortex may reflect the neuropathological characteristics of schizophrenia, and it also serves as a basis for establishing the objective diagnostic markers or a clinical intervention target.

Declarations

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Authors' contributions

N.Z. and S.X. designed the study. M.Z. and S.L. collected the data. W.Y., R.Z. and W.L. analyzed the data and wrote the manuscript. N.Z. and S.X. revised the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

The data sets used and /or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All research procedures were approved by the Medical Research Ethics Committee of Nanjing Brain Hospital, and were conducted in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent of the schizophrenic patient was obtained from his/her legally authorized representative and the control provided written informed consent himself/herself after totally understanding the purpose of our study.

Consent for publication

Not applicable.

Competing interests

The 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.

Abbreviations

BA: Brodmann areas; DLPFC: Dorsolateral prefrontal cortex; dn-FES; Drug-naive first-episode schizophrenia; FWE; family wise-error; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery; MPFC: medial prefrontal cortex; MFG: Middle frontal gyrus; PANSS: Positive and Negative Syndrome Scale; ReHo: Regional Homogeneity; rs-fMRI: Resting state functional Magnetic resonance imaging; SFG: Superior frontal gyrus; TFCE: threshold-free cluster enhancement; WAIS: Wechsler Adult Intelligence Scale;

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Tables

Table 1. Demographic data, IQ, MCCB scores, and clinical information in patients and health controls

	dn-FES (n=69)	HC (n=74)	t/X ²	p
Age(years, mean±SD)	24.22±7.08	26.27±6.97	1.747	0.083
Sex (male/female)	50/19	45/29	1.475	0.142
Education(years, mean±SD)	13.23±2.81	14.69±3.10	2.939	0.004
DUP(months, mean±SD)	13.74±11.76	NA		
PANSS				
Positive symptoms	24.42±3.88	NA		
Negative symptoms	17.58±4.10	NA		
General	42.19±3.55	NA		
All totals	84.19±8.25	NA		
Cognition				
Speed of processing	35.42±10.79	51.22±8.46	9.777	<0.001
Verbal learning	35.51±11.07	46.35±9.78	6.232	<0.001
Working memory	34.22±8.92	45.12±7.10	8.116	<0.001
Reasoning/problem solving	42.90±11.56	53.53±8.17	6.383	<0.001
Visual learning	39.45±11.91	50.55±7.87	6.620	<0.001
Attention/vigilance	35.04±11.49	48.03±7.22	8.149	<0.001
Social cognition	32.68±11.28	37.81±9.34	2.970	0.004
overall composite	28.07±12.27	45.97±8.13	10.35	<0.001
IQ	104.28±11.81	115.55±8.30	6.643	<0.001

dn-FES, drug-naive first-episode schizophrenia; HC, healthy controls; DUP, duration of untreated psychosis; NA, not applicable.

p < 0.05 represents a significant difference

Table 2. Regions with ReHo differences in FES and HC subjects

	Brain regions	Brodmann area	Cluster (voxel)	MNI coordinates (mm)			T
				X	Y	Z	
FES>HC	Right middle frontal gyrus	10	66	42	60	12	4.9826
	Right superior frontal gyrus	9	37	27	45	42	4.4386
FES<HC	Right cuneus	17	17	9	-84	39	-5.2639

Statistically significant differences in ReHo between two groups were defined at p< 0.05. Data were TFCE- and FWE corrected. Data were TFCE corrected after age, gender, education, illness duration, and probability of gray matter were corrected.

Table 3. Significant correlations between PANSS and ReHo in patients with schizophrenia

Brain regions	PANSS	Brodmann area	Cluster (voxel)	MNI coordinates (mm)			Correlation coefficient r
				X	Y	Z	
Right middle frontal gyrus	positive symptoms	10	53	36	60	15	0.41
Right middle frontal gyrus	negative symptoms	10	18	36	60	9	0.32
Right middle frontal gyrus	total score	10	42	36	60	12	0.45

Significant correlations between PANSS and ReHo were defined at p < 0.05. Data were TFCE corrected after age, gender, education, and illness duration were corrected.

Table 4. Significant correlations between MCCB and ReHo in patients with schizophrenia

Brain regions	MCCB	Brodmann area	Cluster (voxel)	MNI coordinates (mm)			Correlation coefficient <i>r</i>
				X	Y	Z	
Right middle frontal gyrus	Attention/vigilance	10	10	36	57	12	-0.30
Right middle frontal gyrus	Social cognition	10	15	39	57	9	-0.38
Right middle frontal gyrus	Overall composite	10	10	39	57	9	-0.34

Significant correlations between MCCB and ReHo were defined at $p < 0.05$. Data were TFCE corrected after age, gender, education, and illness duration were corrected.

Figures

Figure 1

Brain regions with significantly altered ReHo between patients with dn-FES and HC. Brain regions with significantly altered ReHo between patients with dn-FES and HC.