Brain Imaging and Behavior
https://doi.org/10.1007/s11682-021-00516-6

ORIGINAL RESEARCH

Altered brain activity in the bilateral frontal cortices and neural correlation with cognitive impairment in schizophrenia

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Accepted: 17 July 2021

Abstract

Cognitive impairments are core aspects of schizophrenia and are highly related to poor outcomes. However, the effect of therapy on cognitive impairments remains unsatisfactory as its biological mechanisms are not fully understood. The purpose of this study was to investigate the disrupted intrinsic neural activity of the frontal areas and to further examine the functional connectivity of frontal areas related to cognitive impairments in schizophrenia. We collected brain imaging data using a 3T Siemens Prisma MRI system in 32 patients with schizophrenia and 34 age- and sex-matched healthy controls. The mean fractional amplitude of low-frequency fluctuation (mfALFF) in the frontal regions was calculated and analyzed to evaluate regional neural activity alterations in schizophrenia. Seed regions were generated from clusters showing significant changes in mfALFF in schizophrenia, and its resting-state functional connectivity (rs-FC) with other brain regions were estimated to detect possible aberrant rs-FC indicating cognitive impairments in schizophrenia. We found that mfALFF in the bilateral frontal cortices was increased in schizophrenia. mfALFF-based rs-FC revealed that decreased rs-FC between left middle frontal gyrus (MFG) and left medial superior frontal gyrus (MFSG) was associated with poor delayed memory ($r=0.566$, Bonferroni-corrected $p=0.012$). These findings demonstrate increased neural activity in the frontal cortices in schizophrenia. FC analysis revealed a diminished rs-FC pattern between the left MFG and left MSFG that was associated with cognitive impairments. These findings have provided deeper insight into the alterations in brain function related to specific domains of cognitive impairment and may provide evidence for precise interventions for cognitive deficits in schizophrenia.

Keywords Schizophrenia · Cognitive impairments · Delayed memory · Resting-state functional magnetic resonance image

Introduction

Schizophrenia is a severe mental disorder generally characterized by positive symptoms, negative symptoms, and cognitive impairments. Over 80% of patients with schizophrenia experience deficits in multiple domains of cognitive function (Bora et al., 2010). According to existing literature, cognitive impairment can be evident during the early stage of the illness (Bora & Murray, 2014) and persists over the entire course of the disease, with little- to- no responses to antipsychotic treatment. Although cognitive deficits are not directly associated with psychotic symptoms of schizophrenia, consistent cognitive deficits usually lead to functional disability and poor outcomes (Strassnig et al., 2015).

There is great difficulty in establishing clear patterns of specific deficits related to schizophrenia. Over the past few decades, emerging studies have characterized the neurobiological sources and development of cognitive impairments

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Published online: 27 August 2021

in schizophrenia. Magnetic resonance imaging (MRI) enables observation of brain-behavior relationships, providing a more efficient approach to exploring the neurobiological mechanism of cognitive deficits. Among diverse brain regions, the frontal regions are critical for cognitive function such as executive function, behavioral/emotional self-regulation and, metacognition/integration (Gläscher et al., 2019; Stuss, 2011). Cortical thickness of several regions in the frontal lobes is positively related to attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving in the transdiagnostic group of schizophrenia and bipolar disorder (Shahab et al., 2019). Gray matter alteration of the prefrontal cortex is associated with global cognitive deficits in neuropsychiatric diseases, including schizophrenia, Alzheimer's disease and Parkinson's disease, according to the literature (Chen et al., 2017; Kunst et al., 2019; Zhang et al., 2018). It was also reported that regional homogeneity in the middle frontal gyrus and superior frontal gyrus (SFG) is positively correlated with attention and vigilance impairment in schizophrenia (Yan et al., 2020). To better understand the mechanisms involved in cognitive deficits in schizophrenia, researchers studied the impact of cognitive training on brain alterations, finding that cerebral activities increased after cognitive training (Bon & Franck, 2018). Despite emerging studies aimed at clarifying the neurobiological mechanisms of cognitive impairment, how frontal regions functionally contribute to different domains of cognitive impairment in schizophrenia is still unknown.

Resting-state functional MRI (rs-fMRI) data have been widely used for evaluating the ongoing intrinsic neural activities in the brain. The main advantage of rs-fMRI is that in addition to examining the cortex activity of participants in the resting state, it can also demonstrate spontaneous fluctuations in brain activity and provide deeper intrinsic characteristics of the brain (Fox & Raichle, 2007; Power et al., 2011). Additionally, it allows for a broader sample of schizophrenia patients using rs-fMRI scanning as participants are not asked to perform specific tasks, which could be too challenging for patients with severe symptoms to complete. In more recent years, the multiband sequence of fMRI was developed and applied, allowing the simultaneous acquisition of multiple slices (Smitha et al., 2018). Each excited slice is identically sampled so that the signal-to-noise ratio (SNR) loss is minimized.

The objective of this study was to investigate alterations in intrinsic neural activities in frontal regions related to specific domains of cognitive impairments in schizophrenia patients. We recruited patients with schizophrenia and sex- and age-matched healthy controls, using a simultaneous multislice (SMS) sequence to explore the possible frontal dysfunction associated with cognitive impairment in schizophrenia. Each subject's cognitive function was assessed using the repeatable battery for the assessment of neuropsychological status (RBANS). We hypothesize that compared to healthy controls, patients with schizophrenia have altered frontal cortex activities and impaired whole-brain rs-FC between the frontal cortex and other regions; these alterations are associated with impaired cognitive functions.

Methods

Subjects

A total of 32 patients with schizophrenia and 34 healthy controls were recruited for our study. Schizophrenia patients were recruited from the Shanghai Mental Health Center outpatient clinic and interviewed by two independent experienced psychiatrists. Each patient was diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for schizophrenia and was interviewed using the *Mini-International Neuropsychiatric Interview* (MINI). The inclusion criteria were as follows: (1) met the criteria of schizophrenia in the DSM-IV; (2) had a minimum of nine years of education; (3) was aged from 18 to 50; (3) was Chinese Han and right-handed; (4) had not taken antipsychotic medicine within two weeks; (5) without contraindications for MRI; and (6) did not have severe somatic diseases. Healthy controls were recruited from Shanghai and surrounding areas, and each of them was interviewed by a psychiatrist using the MINI. Healthy controls were free of personal or family history of mental illness. Each subject signed written informed consent before the performance of any procedures related to the study. This study was reviewed and approved by the Review Boards of the Shanghai Mental Health Center.

Demographic, clinical and cognitive assessment

All participants' demographic data, including age, sex, education level and marital status, were recorded. The duration of illness of each patient with schizophrenia was gathered and reported. Trained researchers assessed the clinical symptoms of schizophrenia using the Chinese version of the Positive and Negative Syndrome Scale (PANSS). Each subject's cognitive function was assessed using RBANS (Chinese version). The RBANS reflects five domains of cognitive function, including immediate memory, visual spanning, language, attention and delayed memory. Both scales have shown good reliability and validity in the Chinese population (He & Zhang, 2000; Zhang et al., 2008).

MRI data acquisition

All brain image data were collected on a 3T Siemens Prisma MRI system using a 64-channel radiofrequency coil. Resting-state pictures were acquired using a multiband echo planar imaging sequence. This approach provides blood oxygenation level-dependent (BOLD) signals much closer to real-time connectivity in the brain with a relatively high spatial resolution. It can also reduce scan time and increase slice coverage (Norbeck et al., 2018). The multiband acceleration factor in the present study was set as eight, meaning a simultaneous acquisition of eight slices. Additional protocol details: TR = 800 ms; TE = 30 ms; flip angle = 56°; matrix = 104 * 104; field of view (FOV) = 208 mm * 208 mm; 72 slices with no gap, voxel size = 2 mm * 2 mm * 2 mm. A total of 450 volumes were obtained during the 6 min and 10 s scans. Additionally, a high-resolution T1-weighted anatomical image (TR/TE = 2000 ms /2.32 ms, flip = 8°; 208 slices with thickness = 0.9 mm, FOV = 230 mm * 230 mm; matrix = 256 * 256) was acquired for coregistration and normalization of functional image data.

All subjects were instructed to keep still, with their eyes closed, remaining awake but not thinking of anything, during scanning. After scanning, each participant was asked whether they had fallen asleep or thought of anything during scanning to ensure quality.

Data preprocessing

Resting-state fMRI data were preprocessed using DPARSF (Version 4.3 Advanced Edition, http://www.rfmri.org/DPARSF) (Yan et al., 2016). The first ten time points were removed to achieve signal equilibrium. Subjects whose translational and rotational head motion exceeded the thresholds of ± 2 mm and ± 2° were excluded. Next, linear trends were removed to account for scanner drift, and multiple linear regression was performed on potential nuisance variables, including white matter, cerebrospinal fluid, and global signals. Friston-24 parameter motion correction was also applied. Individual 4D volumes were then spatially normalized to Montreal Neurological Institute (MNI) space, retaining voxel size $2mm^3$, using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL). The obtained images were smoothed with a 4-mm full-width half-maximum (FWHM) Gaussian kernel.

mfALFF analysis

fALFF represents the ratio of the regional power spectrum of low frequency to that of the whole frequency range. Fast Fourier transform (FFT) was used to convert the time series of each voxel in the brain to the frequency domain without bandpass filtering, and the power spectrum was then obtained. The square root was computed at each frequency of the power spectrum and the averaged square root was acquired across 0.01–0.08 Hz at each voxel. The average square root power across 0.01–0.08 Hz was divided by that across the entire frequency range. For each voxel, the mfALFF was obtained for standardization purposes by dividing the fALFF of each voxel by the global mean fALFF value.

mfALFF-based functional connectivity (FC) analysis

The clusters in the bilateral frontal cortices presenting mfALFF alterations in schizophrenia patients compared to the healthy controls were selected as regions of interest (ROIs) for FC analysis. The seed regions representing each ROI were defined by a sphere with a 6-mm radius and centered on the peak voxel of each cluster. To ensure that the seed region was confined to the frontal cortex, each seed was intersected with the frontal cortex mask generated from the Automated Anatomical Labeling (AAL) using WFU *Pickatlas* software (http://fmri.wfubmc.edu/software/pickatlas) (Maldjian et al. 2003). Then we extracted the mean time series for each seed region and calculated its Pearson's correlation coefficient with the time course of all the other voxels in the whole brain to generate the *r*-FC map for all subjects. Next, the correlation maps were converted to *z* values using Fisher's *r*-to-*z* transformation.

Statistical analysis

SPSS 24.0 was used for the comparison of general demographic data collected from schizophrenia patients and healthy controls with Student's t-test and chi-square tests. SPM software was used for comparison of mfALFF maps between schizophrenia patients and healthy controls. A mask of bilateral frontal cortices was applied while performing the test. FC map comparisons were also performed using the two-sample t-test. The cluster-based FWE correction was used for both mfALFF and FC analysis with the primary significance level set at $p < 0.001$. For clusters showing significant differences in mfALFF values, the mfALFF values were extracted for correlation analysis with cognitive function using partial correlation analysis. *z* scores showing significant differences between the schizophrenia group and healthy controls were also extracted. Then, the correlation between altered FC and cognitive impairment was conducted using partial correlation analysis. Bonferroni correction was then applied to all partial correlation results. In all tests above, sex, age, and education level were included as covariates to control for potential influences. The significance level was set at $p < 0.05$ after correction.

Results

Demographic and clinical variables

One subject from the schizophrenia group and three subjects from the control group whose translational and rotational head motion exceeded the thresholds of ± 2 mm and ± 2° were excluded. Demographic information for the remaining 62 subjects (31 schizophrenia patients and 31 healthy controls) was compared. There was no significant difference between schizophrenia patients and healthy controls in demographic variables ($p > 0.05$). Schizophrenia patients showed significantly decreased cognitive function in multiple aspects, including immediate memory ($p < 0.001$), language ($p < 0.001$), attention ($p < 0.001$), and delayed memory ($p = 0.003$). The details are represented in Table 1.

mfALFF

Six clusters in the frontal cortex showed significantly increased mfALFF in the schizophrenia group after adjusting for sex, age, and education level. The peak voxel was chosen as the center of ROIs constructed for further analysis. Four clusters in the left frontal cortex were located in the superior frontal gyrus (SFG) (MNI: peak voxel: − 18, 60, − 10; center of ROI 1), inferior frontal gyrus (MNI: − 40, 42, − 14; center of ROI 2), dorsolateral superior frontal gyrus (MNI; peak voxel: − 14, 48, 24; center of ROI 5) and middle frontal gyrus (MNI; peak voxel: − 28, 48, 30; center of ROI 6). Two clusters in the right frontal cortex located in the middle frontal gyrus (MNI; peak voxel: 22, 60, − 14; center of ROI 3) and dorsolateral superior frontal gyrus (MNI; peak voxel: 30, 46, 8; center of ROI 4) respectively. Each ROI was constructed as a sphere centered at the peak voxel of the ROI with a 6 mm radius. See details in Fig. 1 and Table 2.

FC analysis

ROI 6 located in the left middle frontal gyrus (MFG) showed decreased rs-FC with two clusters, which were located in the left medial superior frontal gyrus (MSFG) (MNI; peak voxel: − 8, 62, 6) and the right SFG of the medial orbital (MNI; peak voxel: 10, 62, − 2). See details in Fig. 2 and Table 3.

Table 1 Demographic and clinical information

	Schizophrenia group (N = 31)	Control group (N = 31)	t/χ^2	p
Age/year	30.58 ± 9.862	26.42 ± 6.879	− 1.927	0.059
Gender/% (n)			0.000	1
Male	38.71 (12)	38.71 (12)		
Female	61.29 (19)	61.29 (19)		
Marital status/%(n)			0.622	0.430
Unmarried	58.06 (18)	67.74 (21)		
Married	41.94 (13)	32.26 (10)		
Divorced	0 (0)	0 (0)		
Widowed	0 (0)	0 (0)		
Education level/year	12.82 ± 3.765	14.32 ± 3.318	1.664	0.101
Duration of illness/month	46.68 ± 38.024			
PANSS				
Positive subscale	15.39 ± 5.783			
Negative subscale	15.87 ± 5.365			
General psychopathology subscale	32.87 ± 8.527			
PANSS total score	64.13 ± 15.905			
RBANS				
Immediate memory	71.19 ± 17.651	89.53 ± 19.186	3.879	<0.001
Visual spanning	93.35 ± 16.419	98.23 ± 16.089	1.180	0.234
Language	77.61 ± 17.169	94.77 ± 15.123	4.176	<0.001
Attention	90.81 ± 16.556	109.42 ± 13.460	4.857	<0.001
Delayed memory	79.16 ± 18.960	93.26 ± 16.307	3.138	0.003
RBANS total score	77.45 ± 15.954	95.03 ± 14.545	4.536	<0.001

PANSS positive and negative syndrome scale, *RBANS* repeatable battery for the assessment of neuropsychological status

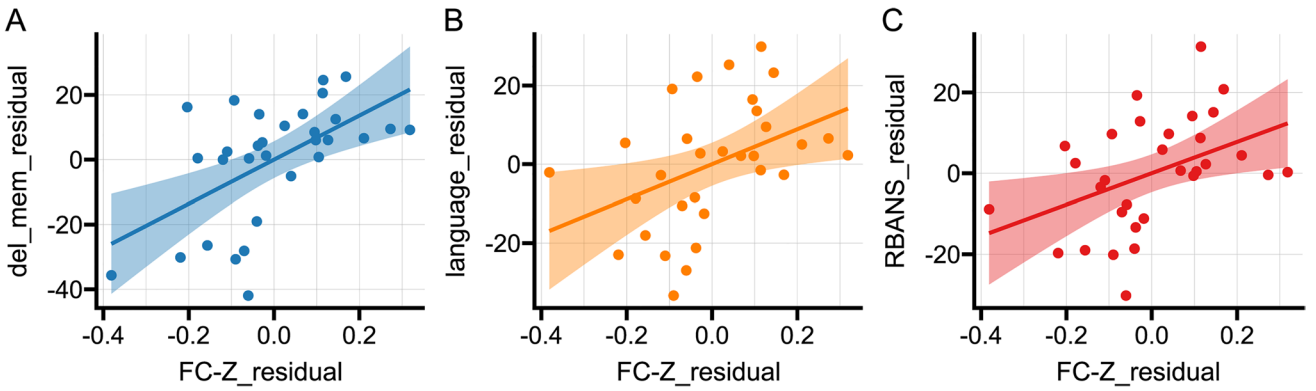

Fig. 1 mfALFF alterations in schizophrenia patients compared to healthy controls. **A** Shows the distribution of mfALFF values of the six clusters in schizophrenia patients and healthy controls. The x axis shows the mfALFF values of the six clusters. **B** Shows the spatial locations of six ROIs derived from clusters that show significantly increased mfALFF in schizophrenia. Abbreviations: *SZ* schizophrenia, *HC* healthy controls

Table 2 Clusters exhibiting significantly increased mfALFF in schizophrenia ($p < 0.05$, cluster-based FWE corrected)

	Location of peak voxels/ AAL	Coordinates of peak voxels			Cluster size
		X	Y	Z	
Cluster 01	Frontal_Sup_Orb_L	− 18	60	− 10	275
Cluster 02	Frontal_Inf_Orb_L	− 40	42	− 14	67
Cluster 03	Frontal_Mid_Orb_R	22	60	− 14	77
Cluster 04	Frontal_Sup_R	30	46	8	37
Cluster 05	Frontal_Sup_L	− 14	48	24	51
Cluster 06	Frontal_Mid_L	− 28	48	30	39

AAL the Automated Anatomical Labeling

Relationship between mfALFF/FC and cognitive function

The partial correlation analysis revealed that rs-FC between the left MFG and left MSFG was positively related to delayed memory in the schizophrenia group ($r = 0.566$, Bonferroni-corrected $p = 0.012$). The rs-FC between the left MFG and left MSFG also showed a positive relationship with language ($r = 0.422$, $p = 0.025$), but the relationship did not remain after Bonferroni correction (Bonferroni-corrected $p = 0.15$). No significant association between altered mfALFF and cognitive function was observed. Details are shown in Table 4 and Fig. 3.

Discussion

To the best of our knowledge, this is the first study to reveal decreased rs-FC between the left MFG and MSFG as a specific rs-FC mode that is positively correlated with deficits in delayed memory. Our findings provide deeper insight into the alterations in brain function that are related to specific domains of cognitive impairment and may provide evidence for precise intervention in cognitive deficits in schizophrenia.

Increased mfALFF in frontal regions in schizophrenia

It has been recognized that the frontal cortex is in charge of higher-order functions. More importantly, frontal dysfunction is involved in many aspects of schizophrenia, including hallucination (Qiu et al., 2018) and suicidal ideation (Minzenberg et al., 2014). A genetic study identified schizophrenia-related alterations in polyadenylated RNAs in the dorsolateral prefrontal cortex (DLPFC) (Jaffe et al., 2018). Important networks and brain circuits, such as the default-mode network and cortico-cerebellar-striatal-thalamic loop containing frontal regions, are involved in psychiatric symptoms and cognitive impairment in schizophrenia (Rotarska-Jagiela et al., 2010; Sheffield & Barch, 2016).

Consistent with the literature indicating frontal dysfunction in schizophrenia, we observed widespread increased mfALFF in the frontal cortex in schizophrenia. Considering the roles of the frontal regions in cognitive function, which are reported to be impaired in schizophrenia in the present and previous studies, it is possible that the increased mfALFF is part of the ongoing compensating processes that attempt to restore the function of frontal regions and disrupted cognitive function in schizophrenia. However, limited by a lack of correlation with clinical symptoms, these alterations should be carefully explained.

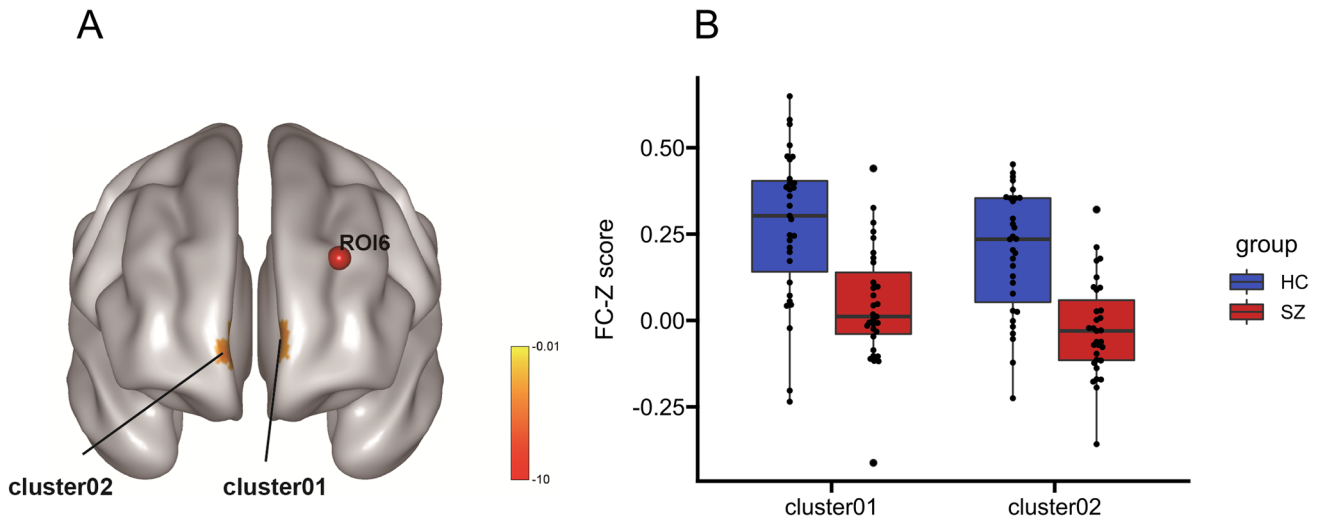

Fig. 2 **A** Shows clusters exhibiting decreased rs-FC with ROI 6. **B** Shows a comparison of rs-FC between the schizophrenia group and the control group. The y axis shows the values extracted from the z transformed rs-FC. *SZ* schizophrenia, *HC* healthy controls

Table 3 Clusters showing significantly decreased rs-FC with ROI6 ($p < 0.05$, cluster-based FWE corrected)

	Location of peak voxels/ AAL	Coordinates of peak voxels			Cluster size
		X	Y	Z	
Cluster 01	Frontal_Sup_Medial_L	− 8	62	6	118
Cluster 02	Frontal_Med_Orb_R	10	62	− 2	187

AAL the Automated Anatomical Labeling

Decreased resting-state FC (rs-FC) of frontal regions in schizophrenia

In recent years, researchers have become increasingly convinced that alterations in FC between different regions are more illustrative than regional activity changes in neuropsychiatric manifestations.

We analyzed rs-FC between ROI seed regions and other voxels in the whole brain and found that rs-FC within the frontal lobe was decreased. Specifically, rs-FC between the left middle frontal gyrus (MFG) seed region and the left MSFG and right SFG decreased. More importantly, lower rs-FC between the left MFG and left MSFG indicated more severe cognitive impairments, especially in delayed memory and language. This is consistent with one previous study that revealed an underconnectivity pattern within the prefrontal cortex relating to cognitive function (Cole et al., 2011). Together the evidence suggests that the reduced functional connectivity within frontal regions may be attributed to disease processes, especially cognitive impairment.

The MFG is a part of the DLPFC, a key region linked to cognitive and executive function. Previous evidence has established that MFG is involved in a variety of neural/psychological processes, including language, emotional and cognitive processes (Abrahams et al., 2003; Geva et al., 2011; Leung et al., 2002; Müller et al., 2013; Puy et al., 2018). In schizophrenia, the increased resting-state cerebral blood flow in the left MFG predicted poor communication skills (Cantisani et al., 2018). It is possible that the observed hyperperfusion in the left MFG is a compensatory process in the early stage of the illness. An attenuated response in the MFG was found during humor processing using the task paradigm in patients with schizophrenia spectrum disorders (Adamczyk et al., 2017; Berger et al., 2018), suggesting that aberrant MFG activation may be involved in social dysfunction and may further influence the social/functional outcome of schizophrenia (Cantisani et al., 2018). The role of MFG in empathy was also confirmed in studies using emotional-communicative (EC) pain paradigms (Xiong et al., 2019).

Table 4 Correlation coefficient of rs-FC between ROI 6 and cluster 01 (Bonferroni corrected)

	r	*p*	Bonferroni-corrected *P*
Immediate memory	0.348	0.070	0.42
Visuospatial skill	0.019	0.922	>0.999
Language	0.422	0.025	0.150
Attention	0.155	0.431	>0.999
Delayed memory	0.566	0.002	0.012
RBANS total score	0.421	0.026	0.156

RBANS repeatable battery for the assessment of neuropsychological status

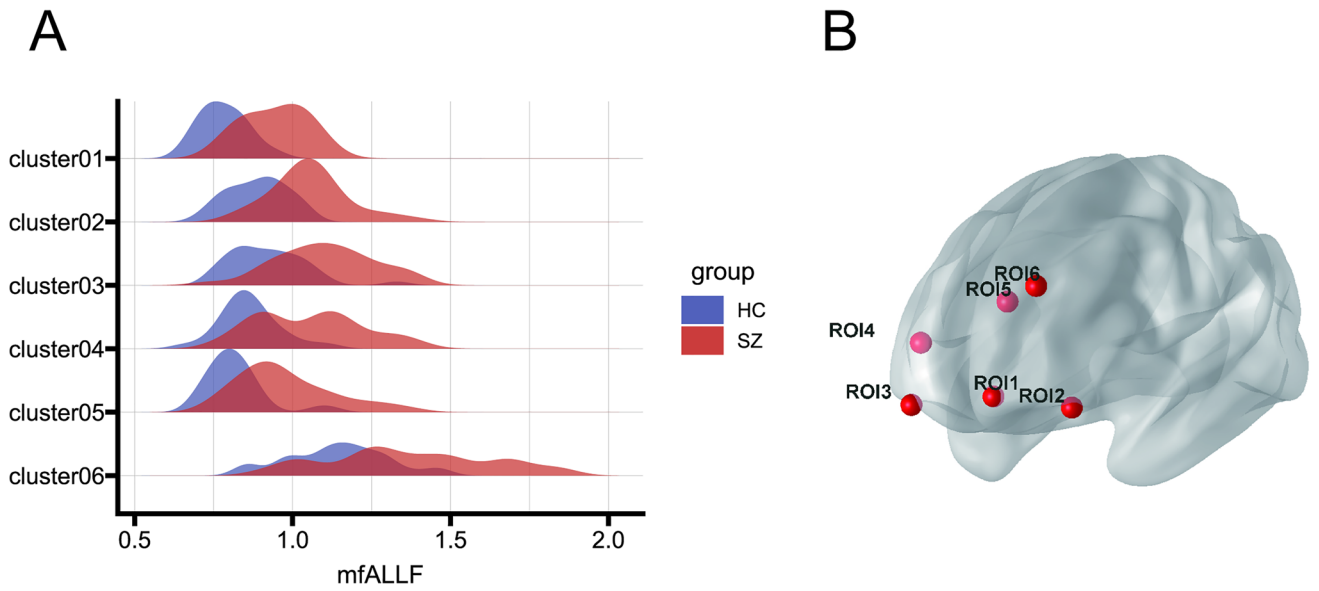

Fig. 3 rs-FC between the left MFG and MSFG is positively correlated with delayed memory. The residual rs-FC, residual delayed memory, residual language, and residual RBANS total score were used in the scatter plot

Moreover, the left MFG and left inferior parietal region were discernible as a subnetwork during the processing of audiovisual stimuli and were dysregulated in schizophrenia, which was also related to impaired memory and emotional processing (Müller et al., 2013). Although numerous studies have indicated changes in the MFG in schizophrenia, little research to date has investigated FC alterations between the MFG and other brain regions in schizophrenia. The left MFG was chosen as a seed region in our study, and its rs-FC with the left MSFG decreased and negatively correlated with delayed memory and probably with language in schizophrenia.

The left MSFG is a region of the default mode network (DMN) and plays a vital role in schizophrenia. A previous study reported a link between left MSFG and self-esteem, which is essential for the maintenance of social functions and interpersonal relationships (Kawamichi et al., 2018). In addition, it was found that changes in FC between left MSFG and other brain regions were related to deficits in activating sensory and motor regions (Weissman et al., 2004), impairments in processing internal signals (Manoliu et al., 2014), and defective attention (Corbetta et al., 2000). These findings implicated that left MSFG is crucial in maintaining high-level functions of the brain, and its disorganization might lead to symptoms in schizophrenia. A more interesting finding is that the increased FC between the right SFG and thalamus induced by exercise is associated with better cognitive performance (Gravesteijn et al., 2020), adding to the existing evidence that suggests a link between the SFG and cognitive function.

In general, therefore, it seems that the MFG and MSFG are both critical for complex and high-level cognitive functions. The present findings extend our knowledge of rs-FC between the left MFG and left MSFG in schizophrenia, especially its association with delayed memory and language. Impaired delayed memory refers to the process of faulty encoding and rapid forgetting, and its mechanism is still unclear (Ally et al., 2013). According to a previous study, poor delayed memory is associated with a thinner frontal cortex in aging adults (Armstrong et al., 2013). Herein, we identified that lower rs-FC between the left MFG and left SFG of the medial part indicates poorer delayed memory. This finding presents new evidence for the neural mechanism of impaired delayed memory in schizophrenia. Additionally, the present result indicates that language deficit in patients with schizophrenia is related to the decreased rs-FC between the left MFG and MSGF, although the p value of the correlation coefficient did not survive the Bonferroni correction. The deficit in language is a domain in cognitive impairment in schizophrenia identified using RBANS in the present study. Some researchers claimed that language abnormalities are an expression of disorganized thinking, impaired semantic memory and other nonverbal cognition in schizophrenia (Little et al., 2019). The present result referring to language is reasonable as MFG is established as essential for language and is comparable to Broca's area in its ability to indicate hemispheric dominance for language (Dong et al., 2016). However, there is still a need for additional investigations to develop a full picture of brain dysfunction attributed to language impairment in schizophrenia.

Limitations

This study was limited in several ways. First, the present study was a cross-sectional design, so causality could not be stated. Furthermore, it is hard to understand whether aberrant resting-state regional neuroactivity and rs-FC between brain regions are state or trait indicators. Further longitudinal studies are needed. Second, the sample size was relatively modest and it is in need of replication in larger samples. Third, we mainly focused on intrinsic neural activity within the frontal cortex. Therefore, alterations in other brain regions relating to cognitive impairment in schizophrenia might be neglected.

Conclusion

These findings demonstrate increased neural activity in the frontal cortices in schizophrenia. rs-FC analysis revealed a decreased rs-FC pattern between the left MFG and left MSFG associated with cognitive impairments.

Acknowledgements We thank the volunteers for their participation and cooperation.

Author contributions Study design (Chen Zhang and Xing Tian), data collection (Lingfang Yu, Xinyu Fang, Fuyin Yang and Yan Chen), statistical analysis (Lingfang Yu and Lei Guo), drafting the manuscript work or revising it critically for intellectual content (Lingfang Yu, Yewei Wang, Dandan Wang, Zenan Wu, Ruimei Liu and Chen Zhang) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (Lingfang Yu, Lei Guo, Xinyu Fang, Fuyin Yang, Yan Chen, Yewei Wang, Dandan Wang, Zenan Wu, Ruimei Liu, Xing Tian, Chen Zhang).

Funding This work was supported by National Key Research and Development Program of China (Grant Number 2018YFC1314302), National Natural Science Foundation of China (Grant Numbers 81471358 and 81771450), Western Medicine Guide Project of Shanghai Municipal Commission of Science and Technology (Grant Number 14411969000), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (Grant Number 20152530).

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study was reviewed and approved by the Review Boards of the Shanghai Mental Health Center. Informed consent was obtained from all participants included in the study.

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