Neurosci. Bull. June, 2019, 35(3):522–526
https://doi.org/10.1007/s12264-019-00359-8

www.neurosci.cn
www.springer.com/12264

LETTER TO THE EDITOR

Abnormal Brain Structure and Function in First-Episode Childhood- and Adolescence-Onset Schizophrenia: Association with Clinical Symptoms

Yanhong Xia[1] · Dan Lv[2] · Yinghui Liang[1] · Haisan Zhang[3] · Keyang Pei[4] · Rongrong Shao[1] · Yali Li[1] · Yan Zhang[1] · Yuling Li[1] · Jinghua Guo[1] · Luxian Lv[1] · Suqin Guo[1]

Received: 9 August 2018 / Accepted: 28 November 2018 / Published online: 9 March 2019

Dear Editor,

Schizophrenia is one of the most complicated and serious psychiatric disorders, and patients often show markedly disrupted structural and functional abnormalities during resting-state imaging scans of the brain. Patients with first-episode childhood- and adolescence-onset schizophrenia (CAOS) refers to individuals under the age of 18 years whose first episode of illness had occurred before they were 13 years old [1]. The symptoms are similar to adult-onset schizophrenia-auditory hallucinations or language deficits and abnormal cognition. However, CAOS patients often present with more severe psychotic symptoms and have a worse prognosis and treatment effect [2]. The pathogenesis of CAOS, however, remains unclear. In recent years, magnetic resonance imaging (MRI) has advanced research on schizophrenia, and studies have suggested that neurobiological processes play a central role in the structural abnormalities underlying its pathophysiology [3]. Further MRI evidence has shown a disordered neuronal architecture and white-matter abnormalities that constitute the basis of the neurobehavioral symptoms [4]. However, to our knowledge, very few studies have investigated the abnormalities of brain structure and function in CAOS. The structural and functional abnormalities in CAOS may be potential biomarkers for its diagnosis and treatment. In this study, we used voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and regional homogeneity (ReHo) to analyze the white-matter volume, white-matter microstructure, and resting-state brain function in patients with CAOS, and related them to the psychotic symptoms.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical College. All participants and legal guardians were given detailed information on the purposes and procedures of the study, gave consent to participate in the study, and signed written informed consent. A total of 40 CAOS patients were recruited from the Second Affiliated Hospital of Xinxiang Medical University. The diagnosis of schizophrenia was confirmed by two experienced psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. The CAOS participants met the following criteria: Han Chinese ethnicity, aged 10–16 years, total PANSS (positive and negative syndrome scale) score $\geq$ 60, first-episode and duration of illness no more than 12 months, and no antipsychotic medication taken before the fMRI scan. All patients had normal intelligence quotient (IQ; Wechsler Intelligence score $>$ 70). The exclusion criteria were: extensive developmental disorders, attention deficit hyperactivity disorder, tic disorder, and MRI scan contraindications. One patient was excluded from the white-matter volume (WMV) date pretreatment duo to the poor image quality, thus 39 patients were

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12264-019-00359-8) contains supplementary material, which is available to authorized users.

✉ Suqin Guo
13603931864@139.com

1 Department of Child and Adolescent Psychiatry, Henan Mental Hospital, The Second Affiliated Hospital of Xinxaing Medical University, Xinxiang 453002, China

2 Institute of Mental health, School of Psychiatry, Qiqihaer Medical University, Qiqihar 161006, China

3 Department of Radiology, Henan Mental Hospital, The Second Affiliated Hospital of Xinxaing Medical University, Xinxiang 453002, China

4 Department of Neurology, The Third Affiliated Hospital of Xinxaing Medical University, Xinxiang 453002, China

enrolled in the WMV patient group. The DTI patient data group included 35 patients, as 5 were excluded due to incomplete data. In the ReHo data pretreatment, 8 patients with incomplete data were excluded, leaving a total of 32 enrolled in this group. Detailed participant information is given in Table S1.

A total of 35 right-handed healthy controls were matched with the CAOS group for age, gender, years of education, and IQ. All the controls met the following criteria: no personal or family history of psychotic disorder, no history of serious physical disease or other neurological illness, and no history of alcohol/substance abuse. In the WMV data pretreatment, 30 participants were enrolled in the control group; 5 were excluded due to poor image quality. In the DTI data pretreatment, 1 participant with incomplete data was excluded, leaving 34 in the control group. In the ReHo data pretreatment, 2 participants with incomplete data were excluded, leaving 33 in the control group. The CAOS and control groups did not differ in sex, age, and years of education (Table S1). Detailed methods of data acquisition, preprocessing, and analysis are provided in the Supplementary Materials. The VBM analysis showed significantly lower volumes of certain brain regions in CAOS patients than in controls; these regions were distributed over the left frontal lobe, right limbic lobe, and left cingulate gyrus (AlphaSim corrected, $P < 0.05$, Fig. 1, Table S2). These findings are consistent with previous findings in early-onset and adult-onset schizophrenia [5, 6], suggesting that this pattern of volumetric changes are an inherent feature of the disease. Similar results have been reported by Hao *et al.* [7], who used DTI to examine the white matter in first-episode schizophrenia and found a reduced fractional anisotropy (FA) in the frontal regions, hippocampal gyrus, and right anterior cingulum bundle. Furthermore, other studies using VBM have also shown that first-episode schizophrenia patients exhibit decreases in the superior frontal gyrus, temporal lobes, and bilateral posterior limb of the internal capsule [8, 9]. A review of neuroimaging literature reported global deficits in cerebral volume in childhood schizophrenia [10]. Here, we also found that the WMV of the left frontal lobe was negatively correlated with the total PANSS score ($r = -0.334$, $P = 0.038$), and that of the left cingulate gyrus was negatively correlated with the positive ($r = -0.326$, $P = 0.043$) and total ($r = -0.348$, $P = 0.030$) PANSS scores. These results indicated that these regions are involved in the formation of psychiatric symptom in CAOS. These findings also provide further insights into the nature of the disease and the optimal path for early therapeutic intervention, as well as improving our understanding of the neuropathology associated with white-matter abnormalities in schizophrenia.

In the DTI analysis, compared with healthy controls, significantly decreased FA values in CAOS patients were dominant in the body, genu, and splenium of the corpus callosum, cingulum bundle, right upper corona radiata, and upper left corona radiata (AlphaSim corrected, $P < 0.05$; Fig. 2, Table S3). DTI is a non-invasive MRI technique that can quantify the fiber orientation and has been widely used in studies of structural connections in schizophrenia. The white-matter integrity *in vivo* is typically assessed by FA. A decreased FA value of regional white matter in patients suggests damage to its microstructure. So, our DTI findings suggest that abnormalities of white matter microstructure are present even at the early stage of first-episode CAOS, and support the disconnection hypothesis of schizophrenia [11]. The FA reduction in CAOS patients compared with controls is in line with a study evaluating FA in patients with first-episode adult-onset schizophrenia [12], as well as in those with first-episode early-onset

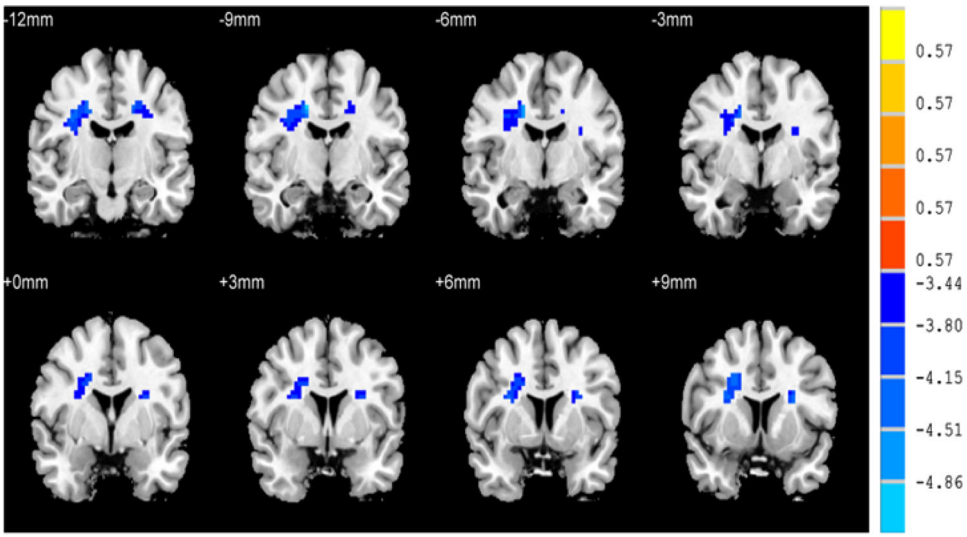

Fig. 1 Blue regions indicate lower white-matter volume in patients with first-episode childhood- and adolescence-onset schizophrenia than in controls. For x/y/z coordinates see Table S2 (AlphaSim corrected $P < 0.05$).

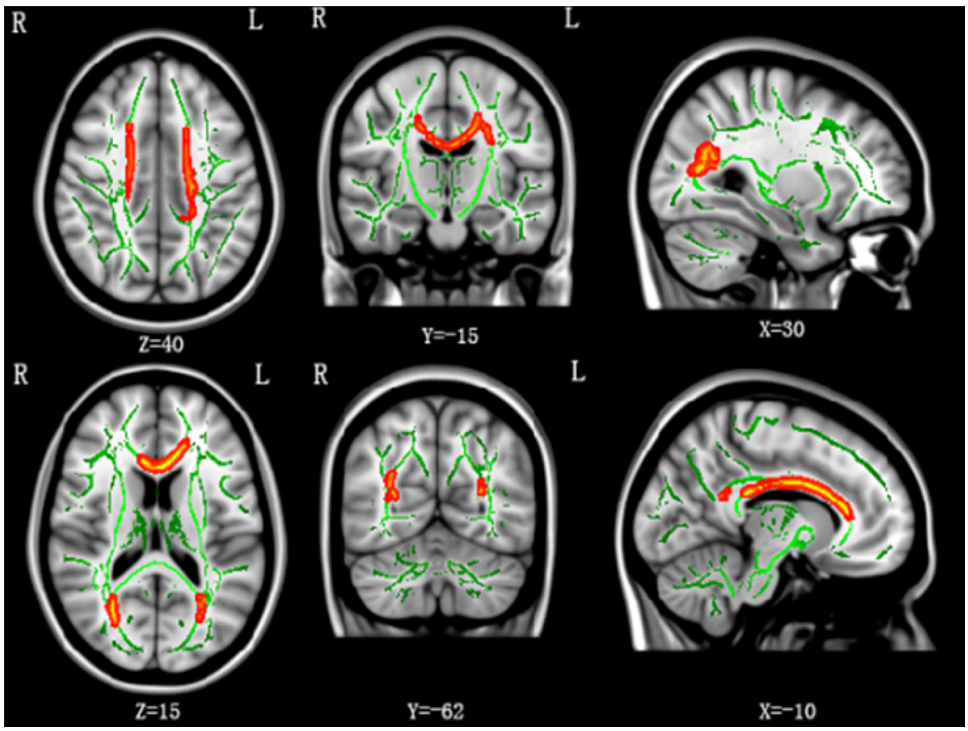

Fig. 2 Green regions indicate the white-matter fiber 'skeleton', Red regions indicate areas of lower fractional anisotropy in patients with first-episode childhood- and adolescence-onset schizophrenia than in controls, for x/y/z coordinates see Table S3 (AlphaSim corrected $P < 0.05$).

schizophrenia [13]. This suggests that the white-matter disruption might be related to the pathological mechanisms of schizophrenia. However, other studies have found increased FA in schizophrenia [14], or even failed to find differences in FA between patients with schizophrenia and healthy controls. The differences in FA analysis, duration of illness, and sampling of patients may be responsible for this inconsistency. In addition, a previous report showed that a lower FA can reflect abnormalities of myelination or alterations in fiber orientation [15], but this needs further investigation. Recently, inconsistencies have been found when evaluating the relationship between FA values and the PANSS scores in schizophrenia. Nakamura [16] showed that the low FA in the anterior corpus callosum is negatively associated with the negative symptoms of schizophrenia. However, Liu *et al.* [17] did not find any significant association between FA and clinical symptoms in patients with chronic schizophrenia. In our study, the DTI data also showed no association with the PANSS score. The difference in the association between FA values and clinical symptoms is unclear, and may be related to the differences in age and characteristics of participants, as well as the anatomical variations among populations of different ethnicity. Therefore, future studies with larger numbers of CAOS patients are needed.

Regional homogeneity (ReHo) is a measure of "local" synchronization, and reflects the similarity of the time series of a given voxel to its nearest neighbours within a single region [18]. An abnormal ReHo indicates abnormal spontaneous neural activity in a specific region. Therefore, using these methods, abnormal spontaneous neuronal activities in schizophrenia can be identified [19]. A recent study using ReHo has found abnormal functional activity in the bilateral precentral lobule and left superior temporal gyrus in drug-naive patients with adolescent-onset schizophrenia [20]. In the ReHo analysis of fMRI to explore the brain activity in CAOS patients, we also found that, compared with controls, the patients exhibited significantly decreased ReHo values in the left medial frontal gyrus, left superior temporal gyrus, and left precentral gyrus, and significantly increased ReHo values in the right inferior occipital gyrus, body of the caudate, left inferior frontal gyrus, right posterior cingulate gyrus/precuneus, and bilateral superior frontal gyrus (AlphaSim corrected, $P < 0.05$; Fig. S1, Table S4). These findings agree with previously-reported dysfunctional connectivity and ReHo abnormalities in patients with first-episode adolescent-onset [21, 22] and those with adult-onset schizophrenia [23]. Our findings suggest that patients with CAOS may have extensive brain dysfunction in the resting state and have patterns of resting-state dysfunction similar to those with adult-onset schizophrenia. Interestingly, the ReHo value of the left medial frontal gyrus was negatively correlated with positive PANSS scores ($r = -0.358$, $P = 0.044$), which is inconsistent with adult-onset schizophrenia. This may be related to the age of the participants studied, the immaturity of brain development, and the different reference index. Therefore, future studies

with larger sample sizes are needed to validate/refute these findings. Also, the left superior temporal gyrus was negatively correlated with the general scores ($r = -0.379$, $P = 0.032$), consistent with a previous rs-fMRI study on ReHo [24]. Therefore, the current findings suggest that the abnormal functional activity in some regions is evident in patients with CAOS, and the abnormal functional activity of different regions may be associated with its different psychiatric symptoms. These results will be helpful to better understand the pathological and neurobiological mechanisms of schizophrenia.

From the above study, interestingly, we found that the frontal lobe has both structural and functional abnormities. The frontal lobe is the "highest" part of the brain, and is associated with memory, attention, and writing. Frontal lobe dysfunction is correlated with cognitive deficits and psychiatric symptoms in schizophrenia. In this study, we also found that abnormal structure and function of the frontal region were associated with the psychiatric symptoms of CAOS. From this, we can conclude that there are structural and functional abnormalities in the frontal lobe in CAOS, and the structural abnormality may be the basis of abnormal function.

In summary, first, we used VBM analysis to evaluate the differences in WMV between CAOS patients and controls. The results showed significantly lower volume of three brain regions in patients than in controls. Furthermore, these localized reductions in WMV were correlated with psychotic symptoms. These findings suggest that the number of white-matter fibers connecting regions is decreased in CAOS patients, and the abnormal WMV is associated with the clinical symptoms of schizophrenia. Our findings also showed that patients with first-episode childhood schizophrenia have lower FA values in five brain regions; this implies that the white-matter microstructure in these specific areas is not fully functional. Finally, through ReHo analysis, we found that CAOS patients had abnormal function in different regions in the resting state, and these regions were related to the psychiatric symptoms of CAOS. These results may aid in our understanding of the neurodevelopment and pathological mechanisms of schizophrenia, and the application of MRI may be helpful for further diagnosis of schizophrenia, Understanding the abnormal structure and functional activity in various regions may help distinguish schizophrenia patients from healthy controls.

Finally, our results have to be interpreted in the light of some limitations. First, our sample size was relatively small. Second, this study was a cross-sectional, and longitudinal studies are needed to analyze the development of white matter and whether ReHo abnormalities change with antipsychotic treatment and through the entire course of schizophrenia.

Acknowledgements This work was supported by the National Program for Science and Technology Development of Henan (182102310155), and the National Natural Science Foundation of China (81671330). We thank the Department of Child and Adolescent Psychiatry, Henan Mental Hospital, the Second Affiliated Hospital of Xinxiang Medical University. We also thank all the participants in this study.

Conflict of interest The authors disclosed that there is no conflict of interest.

Reference

1. Fraguas D, Díaz-Caneja CM, Pina-Camacho L, Janssen J, Arango C. Progressive brain changes in children and adolescents with early-onset psychosis: a meta-analysis of longitudinal MRI studies. Schizophrenia Res 2016, 173: 132–139.
2. Driver DI, Gogtay N. Childhood onset schizophrenia and early onset schizophrenia spectrum disorders. Child Adolesc Psychiatr Clin N Am 2013, 22: 539–555.
3. Brent BK, Thermenos HW, Keshavan MS, Seidman LJ. Gray matter alterations in schizophrenia high-risk youth and early-onset schizophrenia: a review of structural MRI findings. Child Adolesc Psychiatr Clin N Am 2013, 22: 689–714.
4. Owen MJ, O'Donovan MC, Thapar A. Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 2011, 198: 173–175.
5. Yoshihara Y, Sugihara G, Matsumoto H, Suckling J, Nishimura K, Toyoda T, *et al.* Voxel-based structural magnetic resonance imaging (MRI) study of patients with early onset schizophrenia. Ann Gen Psychiatry 2008, 7: 25.
6. Kim GW. White matter volume change and its correlation with symptom severity in patients with schizophrenia: a VBM-DARTEL study. Neuroreport 2015, 26: 1095–1100.
7. Hao Y, Liu Z, Jiang T, Gong G, Liu H, Tan L, *et al.* White matter integrity of the whole brain is disrupted in first-episode schizophrenia. Neuroreport 2006, 17: 23–26.
8. Yao L, Lui S, Deng W, Wu M, Chen L, Xiao Y, *et al.* Association of white matter deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized VBM study using 3T. MAGMA 2014, 27: 283–290.
9. Kim GW, Kim YH. Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: a DARTEL-based VBM study. PLoS One 2017, 12: e0177251.
10. Baribeau DA. A comparison of neuroimaging findings in childhood onset schizophrenia and autism spectrum disorder: a review of the literature. Front Psychiatry 2013, 4: 175.
11. Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009, 35: 509–527.
12. Asami T, Hyuk Lee S, Bouix S, Rathi Y, Whitford TJ, Niznikiewicz M, *et al.* Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. Psychiatry Res 2014, 222: 52–59.
13. Kumra S, Ashtari M, Cervellione KL, Henderson I, Kester H, Roofeh D, *et al.* White matter abnormalities in early-onset schizophrenia: a voxel-based diffusion tensor imaging study. J Am Acad Child Psychiatry 2005, 44: 934–941.
14. Federspiel A, Begre S, Kiefer C, Schroth G, Strik WK, Dierks T, *et al.* Alterations of white matter connectivity infirst episode schizophrenia. Neurobiol Dis 2006, 22: 702–709.
15. White T, Magnotta VA, Bockholt HJ, Williams S, Wallace S, Ehrlich S, *et al.* Global white matter abnormalities in

schizophrenia: a multisite diffusion tensor imaging study. Schizophr Bull 2011, 37: 222–232.
16. Nakamura K, Kawasaki Y, Takahashi T, Furuichi A, Noguchi K, Seto H, *et al.* Reduced white matter fractional anisotropy and clinical symptoms in schizophrenia: a voxel-based diffusion tensor imaging study. Psychiatry Res 2012, 202: 233–238.
17. Liu X, Lai Y, Wang X, Hao C, Chen L, Zhou Z, *et al.* Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: a diffusion tensor study using TBSS. Behav Brain Res 2013, 252: 157–163.
18. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage 2004, 22: 394–400.
19. Liu C, Xue Z, Palaniyappan L, Zhou L, Liu H, Qi C, *et al.* Abnormally increased and incoherent resting-state activity is shared between patients with schizophrenia and their unaffected siblings. Schizophrenia Res 2016, 171: 158–165.
20. Wang S, Zhang Y, Lv L, Wu R, Fan X, Zhao J, *et al.* Abnormal regional homogeneity as a potential imaging biomarker for adolescent-onset schizophrenia: a resting-state fMRI study and support vector machine analysis. Schizophrenia Res 2018, 192: 179–184.
21. Liu Y, Zhang Y, Lv L. Abnormal neural activity as a potential biomarker for drug-naive first-episode adolescent-onset schizophrenia with coherence regional homogeneity and support vector machine analyses. Schizophrenia Res 2018, 192: 408–415.
22. Wang S, Zhan Y, Zhang Y, Lyu L, Lyu H, Wang G, *et al.* Abnormal long- and short-range functional connectivity in adolescent-onset schizophrenia patients: a resting-state fMRI study. Prog Neuropsychopharmacol Biol Psychiatry 2018, 81: 445–451.
23. Liu C, Xue Z, Palaniyappan L, Zhou L, Liu H, Qi C, *et al.* Abnormally increased and incoherent resting-state activity is shared between patients with schizophrenia and their unaffected siblings. Schizophr Res 2016, 171: 158–165.
24. Liu H, Liu Z, Liang M. Decreased regional homogeneity in schizophrenia: a resting state functional magnetic resonance imaging study. Neuroreport 2006, 17: 19–22.