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Dysfunctional resting-state connectivities of brain regions with structural deficits in drug-naive first-episode schizophrenia adolescents

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ABSTRACT

Objective: Individuals with adolescent-onset schizophrenia (AOS) are a subgroup of patients who present clinical symptoms between 13 and 18 years of age. Little is known about neurodevelopmental abnormalities in this patient population. The present study was to examine possible resting-state dysfunctional connectivity of brain regions with altered gray matter volume in AOS.

Methods: Gray matter volume was investigated by voxel-based morphometry (VBM) analysis. Resting-state functional connectivity analysis was used to examine the correlations between regions with structural deficits and the remaining regions.

Results: Thirty-seven first-episode schizophrenia adolescents and 30 healthy controls were enrolled. Compared to the controls, the patients showed significantly decreased gray matter volumes in the right superior temporal gyrus (STG) and middle temporal gyrus (MTG) ($ps < 0.05$). With the right STG as seed, significantly reduced connectivities were found within the frontal–temporal networks in the patient group ($ps < 0.05$). With the right MTG as seed, the patient group showed significantly reduced connectivities in the default-mode networks and visual networks ($ps < 0.05$). Compared to significant correlations in the controls ($p = 0.02$), the patients had no observed correlations between functional connectivity of the right STG and gray matter volume of this region. Significant positive correlations were found between functional connectivity of the right STG with the left middle frontal gyrus and the Positive and Negative Syndrome Scale total scores ($p = 0.048$) after controlling the confounding variables.

Conclusions: These findings show dysfunctional resting-state connectivities of the right STG and MTG with decreased gray matter volume in adolescents with AOS, suggesting that neurodevelopmental abnormalities may be present in AOS.

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1. Introduction

Early-onset schizophrenia (EOS) includes childhood-onset schizophrenia (COS) (onset before age 13) and adolescent-onset schizophrenia (AOS) (onset between 13 and 18 years of age) (Frangou, 2013). While COS is rare, AOS is relatively common (Frangou, 2013). Compared to adult-onset schizophrenia, EOS is associated with a higher familial risk (Nicolson et al., 2003), more severe premorbid abnormality (Hollis, 2003), more severe general psychopathology (Frazier et al., 2007), and tends to be more resistant to antipsychotic treatment with poorer prognosis (Hollis, 2000). Although it remains unclear what accounts for the early onset of psychiatric symptoms in this patient group, it has been speculated that neurodevelopmental abnormality may be more predominant in EOS than that in adult-onset schizophrenia. As adolescence represents a critical time period for maturational processes such as synaptic pruning and myelination (Paus et al., 2008), the study of neurodevelopmental abnormality in AOS may shed light on the pathogenesis of the illness.

Structural magnetic resonance imaging (sMRI) has been used to examine brain structural alterations in EOS. Morphometry studies have reported enlargement of the lateral ventricles (Kumra et al., 2000; Sowell et al., 2000), and decreased gray matter volume in the superior temporal gyrus (STG) (Matsumoto et al., 2001; J. Tang et al., 2012), thalamus (James et al., 2004; Kumra et al., 2000), and frontal lobe (James et al., 2004; Moreno et al., 2005) in patients with EOS. Longitudinal MRI studies have demonstrated progressive gray matter

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loss during adolescence in COS (Sporn et al., 2003), particularly in the medial frontal lobe (Arango et al., 2008; Vidal et al., 2006). In addition, functional magnetic resonance imaging (fMRI) studies have indicated an extensive collection of functional deficits in EOS patients. Kyriakopoulos et al. reported reduced dorsolateral prefrontal cortex (DLPFC) connectivity within the working memory network and reduced coupling of the DLPFC with the anterior cingulate cortex (ACC), inferior parietal lobule, and middle occipital gyrus in patients with EOS compared to healthy adolescents (Kyriakopoulos et al., 2012). White et al. also reported three abnormal functional connectivities in networks involving the bilateral ACC, cerebellum, striatum and occipital lobe during a verbal working memory task in children and adolescents with schizophrenia (White et al., 2011).

Although previous studies have provided valuable findings on abnormal gray matter volume and dysconnectivity within or between neural networks, results across different studies of EOS were inconsistent. For example, Tang et al. reported decreased gray matter volumes in the left STG and MTG (J. Tang et al., 2012). Another study reported no change in gray matter volume in the temporal lobe (Repovs et al., 2011). The discrepant findings might be related to confounding factors such as antipsychotic treatment and illness duration. Longitudinal studies have indicated that the exposure to antipsychotic medications may cause both structural (Jacobsen et al., 1998) and functional (Bluhm et al., 2007; Liang et al., 2006; Zhou et al., 2007a) changes in the brain. In addition, several previous studies have shown an inverse correlation between duration of untreated psychosis and reduced gray matter volume in schizophrenia patients (Crespo-Facorro et al., 2007; Guo et al., 2013). Thus, compared to chronic or medicated patients, drug-naive, first-episode schizophrenia patients have a unique value to be used to explore the neuropathological process of illness, and thus minimize the effects of potential confounding factors.

Voxel-based morphometry (VBM) is a useful automatic technique to investigate structural brain alterations (Janssen et al., 2008; Kumra et al., 2000; Lyu et al., 2015; J. Tang et al., 2012). Relative to region of interest (ROI), VBM entails a voxel-wise comparison of whole-brain gray matter volume in the absence of a prior hypothesis (Ashburner and Friston, 2000). Resting-state functional connectivity is a means to evaluate intrinsic brain connectivity or functional networks without external stimuli (Beckmann et al., 2005; De Luca et al., 2006). Compared to task-related imaging, rest-based functional scans may be a more natural measure of brain function (Raichle and Gusnard, 2005), and can reflect intrinsic relationships between brain areas (van de Ven et al., 2004). In addition, the rest procedure is easy to administer to patients. The combination of VBM and resting-state connectivity has been used to investigate structural and functional abnormalities in various psychiatric disorders including schizophrenia (Guo et al., 2015). In the present study, we used the combined approaches to examine possible resting-state functional connectivity abnormalities of brain regions with altered gray matter volume in drug-naive, first-episode schizophrenia adolescents. We hypothesized that there would be an effect of brain structural size on the corresponding connectivity relevant to that structure in patients with AOS.

2. Method

2.1. Study sample

In this study, all participants were right-handed, Han Chinese ethnicity, aged 13 to 18 years old, and had more than 6 years of formal education and IQ more than 70. Thirty-nine drug-naive adolescent inpatients with first-episode schizophrenia were recruited from The Second Affiliated Hospital of Xinxiang Medical University. They met the following inclusion criteria: (1) the DSM-IV-TR criteria for schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, American Psychiatric Association, 2000); (2) no co-morbid Axis I diagnosis; (3) duration of illness less than 2 years and (4) antipsychotic-naive. Schizophrenia was independently diagnosed by the research psychiatrists based on the Structured Clinical Interview for DSM-IV-TR, Patient Version (SCID-I/P). Psychopathology was assessed in patients using the Positive and Negative Syndrome Scale (PANSS). Thirty-one age-, gender-, education- and IQ-matched healthy adolescents were included in this study. The controls were recruited from the local community through advertisements. Psychiatric conditions were ruled out in healthy controls using the SCID; in addition, a thorough physical exam was completed by the same research psychiatrists to rule out any medical conditions. The exclusion criteria for all participants included: (1) any past or current neurological disorders, or family history of hereditary neurological disorders; (2) a history of head injury resulting in loss of consciousness; (3) alcohol or substance abuse; (4) claustrophobia and (5) incompatible implants (exclusion criterion for magnetic resonance imaging (MRI)).

A complete description of the study was provided to, and written consent was obtained from all study subjects and their parents or legal guardians. The study was approved by the Ethics Committee of The Second Affiliated Hospital of Xinxiang Medical University. The study was conducted between February 2012 and January 2013.

2.2. Data acquisition

All subjects were instructed to relax, hold still, and keep their eyes closed during the resting-state fMRI examination. Both sMRI and fMRI data were collected using a Siemens 3 T Trio scanner (Siemens Medical Systems, Erlangen, Germany) with an eight-channel phased array head coil at The Second Affiliated Hospital of Xinxiang Medical University. Imaging was performed on the same day of clinical assessment. The following parameters were used for high-resolution T1-weighted volumetric 3D images axially: repetition time/echo time (TR/TE) = 2530/2.43 ms, 256 × 256 matrix, 7° flip angle, voxel size = 1 × 1 × 1 mm^3 and 158 slices without inter-slice gap. At the same locations as those of the anatomical slices, functional images were acquired by using an echo-planar imaging sequence with the following parameters: TR/TE = 2000/30 ms, 33 slices, 64 × 64 matrix, 90° flip angle, field of view = 220 × 220 mm^2, inter-slice gap = 0.6 mm and voxel size = 3.44 × 3.44 × 4 mm^3. For each subject, the fMRI scan lasted for 480 s, and 240 volumes were obtained.

2.3. Voxel-based morphometry analysis

All structural data were processed using the VBM toolbox (VBM8) (http://dbm.neuro.uni-jena.de/vbm) with the Statistical Parametric Mapping 8 software package (http://www.fil.ion.ucl.ac.uk/spm). The three-dimensional MRI images were normalized to the same standard stereotactic space. This was obtained by registering each of the images to the same template image by estimating the 12-parameter affine transformation. Normalized images were then segmented for signal intensity and prior probability information. Segmented images were spatially normalized to the customized template. Intensity modulation was performed on the optimally normalized segmented gray matter MRI scans by increasing or reducing voxel intensity, depending on whether the surrounding voxels were compressed or expanded in the normalization process. Then an 8 mm FWHM Gaussian kernel was used to smooth the gray matter images, and to reduce the individual difference of brain anatomy and to increase the signal to noise ratio. Then, voxel-wise two sample *t*-test was performed to compare regional gray matter volume differences between the two groups. The two sample *t*-test was carried out in SPM8 with age and gender as covariates. The significance level was set as $p < 0.05$ using the AlphaSim correction (combined height threshold of $p < 0.005$ and a minimum cluster size of 1115 voxels) (Ren et al., 2013). This correction was conducted using the AlphaSim program embedded into the REST Software (http://www.restfmri.net/forum/REST_V1.8), which applied Monte Carlo simulation to calculate the probability of false positive detection

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