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Abnormal neural activity as a potential biomarker for drug-naive first-episode adolescent-onset schizophrenia with coherence regional homogeneity and support vector machine analyses

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ABSTRACT

Background: Patients with adolescent-onset schizophrenia (AOS) hold the same but severe form of symptoms with adult-onset schizophrenia, and with worse outcome and poor treatment response to antipsychotics. Several dominant brain regions of schizophrenia patients show significantly abnormal structural and functional connectivity during resting-state scans. However, coherence regional homogeneity (Cohe-ReHo) in drug-naive first-episode patients with AOS remains unclear.

Method: A total of 48 drug-naive first-episode AOS outpatients and 31 healthy controls underwent resting-state functional magnetic resonance scans. Cohe-ReHo and support vector machine analyses were used to analyze the data.

Results: Compared with the healthy controls, the AOS group showed significantly decreased Cohe-ReHo values distributed over brain regions, including the left postcentral gyrus, left superior temporal gyrus, left paracentral lobule, right precentral gyrus, right inferior parietal lobule (IPL), right middle frontal gyrus, and bilateral precuneus. No region with increased Cohe-ReHo values was observed in the AOS group compared with healthy controls. In addition, the right IPL was correlated with fluency ($r = -0.324$, $p = 0.030$). However, the correlation was not significant after the Bonferroni correction at $p < 0.0083$ (0.05/6). A combination of the Cohe-ReHo values in the bilateral precuneus and right IPL discriminated the patients from controls with the sensitivity, specificity, and accuracy of 91.67%, 87.10%, and 89.87%, respectively.

Conclusion: Our findings suggested that the AOS patients exhibited diminished Cohe-ReHo values in some regions within the DMN network and sensorimotor network. The abnormalities in particular brain regions (bilateral precuneus and right IPL) may serve as potential biomarkers for AOS.

1. Introduction

Early-onset schizophrenia is defined as schizophrenia of illness onset before age 18 years (Frazier et al., 2007). It includes childhood-onset schizophrenia, with age of onset before 13 years, and adolescent-onset schizophrenia (AOS), with age of onset between 13 and 18 years (Fraguas et al., 2016). Similar to adult-onset schizophrenia, Early-onset schizophrenia is a disabling condition characterized by psychotic symptoms, neurocognitive impairment, and abnormal social behavior, sharing the same diagnostic criteria with those of adult-onset schizophrenia (Hollis, 2000). However, early-onset schizophrenia is believed to represent a rarer and more clinically neurobiologically severe form of schizophrenia (Douaud et al., 2009) with higher genetic vulnerability (Nicolson and Rapoport, 1999). Long-term follow-up studies have provided strong evidence suggesting similar cognitive, genetic, and neuroimaging continuity and correlations between early-onset schizophrenia and adult-onset schizophrenia, but with poor outcome and disappointing treatment response to antipsychotics (Hollis, 2000). Schizophrenia is well known as a severe neurodevelopment disorder; with brain changes evolve along a dynamic trajectory emerging before disease onset and progressing with illness (Schmidt et al., 2014). A stronger linkage between early-onset schizophrenia and adult-onset schizophrenia has been found; hence, exploring early-onset schizophrenia is of great

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importance for the understanding of the biological mechanism of schizophrenia. However, childhood-onset schizophrenia is rarer (Nicolson and Rapoport, 1999) and more difficult to study for complicated reasons. Thus, in this article, we chose AOS for research. We expect the study to provide novel perspectives on the neuroimaging pathogenesis mechanism or biomarkers of schizophrenia.

From the first functional magnetic resonance imaging (fMRI) study in 1995 by Biswal et al., researchers have found that low-frequency fluctuations in the blood oxygenation level dependent signal are highly synchronous throughout the sensorimotor cortex during rest (Biswal et al., 1995). Since then, resting-state fMRI has been viewed as a new and unique method for evaluating brain regional structures and function in vivo for brain disorders. Numerous resting-state fMRI studies that aimed to detect the pathophysiology of schizophrenia have been conducted over the last decades. The majority of these studies have offered overwhelming evidence about brain structural deficits and abnormal brain functional connectivity in schizophrenia (Shenton et al., 2001). These abnormal brain activities and functional connectivity occurred primarily in four brain networks, namely, the default mode network (DMN), dorsal attention network, executive control network, and salience network (Guo et al., 2015a; Woodward et al., 2011). Brain structural magnetic resonance imaging (sMRI) studies also demonstrated a distinct decrease in gray matter volume in the four brain networks, i.e., dominant decreases in volume in the dorsal prefrontal lobe, thalamus, and superior temporal lobe (Gong et al., 2016). Furthermore, brain fMRI revealed a similar decreased connectivity along with aberrant regional neural activities in the four brain networks (Chan et al., 2011; Gong et al., 2016). Schizophrenia patients are regarded by many scholars to present with gray matter reduction and abnormal regional activity in the DMN. This notion suggests that the analysis of specific neural activity in brain networks is of great importance in detecting the pathogenesis of schizophrenia via the local features of spontaneous brain activity.

Regional homogeneity (ReHo), a data-driven method proposed by Zang et al. (2004), is considered an ideal complementary analysis to functional connectivity approaches. The analysis is conducted by calculating Kendall's coefficient of concordance (KCC) of the time series of a given voxel in relation to those of its nearest neighbors (26 voxels) in a voxel-wise analysis. A large ReHo value indicates high regional synchronization. Unlike traditional functional connectivity analyses, the ReHo method is insensitive to phase variability across measured time series and phase differences across brain regions. Thus, ReHo plays a preponderant role in localization of brain regions with significant differences (Chao-Gan and Yu-Feng, 2010; Jiang and Zuo, 2016). The ReHo method can detect local abnormalities in many psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) (Cao et al., 2006), major depressive disorder (Guo et al., 2012), autism spectrum disorder (Maximo et al., 2013; Paakki et al., 2010; Shukla et al., 2010), and schizophrenia (Liu et al., 2006). This method also includes KCC-ReHo and Cohe-ReHo (coherence regional homogeneity). KCC-ReHo adopts KCC to measure similarity among time series of voxels. KCC-ReHo is based on temporal information of time series, and it decreases in the presence of lags in time series. Cohe-ReHo measures synchronization in frequency domains that exhibit low susceptibility to phase variability across measured time series; it is superior to KCC-ReHo in measuring local synchronization of resting-state fMRI signals and is deemed suitable when phase differences vary largely across brain regions (Miezin et al., 2000; Sun et al., 2004). Previous research indicated that compared with KCC-ReHo, Cohe-ReHo is more sensitive to differences in spontaneous activities of ADHD and healthy controls (Liu et al., 2010).

The present study examined local synchronization of resting-state fMRI signals in patients with AOS using Cohe-ReHo. Compared with ReHo, Cohe-ReHo is more sensitive to differences in spontaneous activity and exhibits lower susceptibility to phase variability across measured time series. Previous studies reported abnormal ReHo values in brain regions of patients with adult-onset schizophrenia (Liu et al., 2006; Malaspina et al., 2004; Pascual-Marqui et al., 1999). Therefore, we hypothesized that patients with AOS would show similar Cohe-ReHo changes as those in patients with adult-onset schizophrenia. Considering that patients with AOS and patients with adult-onset schizophrenia share the same diagnostic criteria and clinical features, we also hypothesized that abnormal Cohe-ReHo observed in patients with AOS may be candidate endophenotypes for schizophrenia and can be used to differentiate patients from controls. We also examined correlations between abnormal Cohe-ReHo and symptom severity or cognitive function in patients.

Support vector machine (SVM) is a supervised learning algorithm popular for its four primary factors, namely, strong theoretical foundation, suitable scaling to large datasets, flexibility, and most importantly, accuracy. SVM has been applied in numerous domains, including text categorization, hand-written digital recognition (Schölkop, 2003), and bioinformatics (Ding and Dubchak, 2001; Zien et al., 2000). The algorithm performs discriminative classification and learns by example to predict the classifications of previously unseen data, as well as recognize subtle patterns in complex datasets. SVM is a classification method successfully applied to diagnosis and prognosis problems (Pavlidis et al., 2004).

2. Methods

2.1. Subjects

In the current study, 48 right-handed outpatients with AOS were recruited from the Second Affiliated Hospital of Xinxiang Medical University. All participants were drug-naive adolescent outpatients with first-episode schizophrenia. The AOS participants met the following inclusion criteria: (1) aged 13–18 years, (2) received formal education of >6 years, (3) possessed an IQ of >70, (4) met the DSM-IV-TR criteria for schizophrenia, (5) without co-morbid Axis I disease, (6) suffered illness for no >2 years, and (7) Did not receive antipsychotic medications or other psychotropic medications. The diagnosis of schizophrenia was confirmed by experienced psychiatrists based on the Structured Clinical Interview for the DSM-IV-TR, Patient Version (SCID-I/P). Symptom severity was assessed using the positive and negative syndrome scale (PANSS). The duration of illness of each participant was recorded.

Thirty-one right-handed healthy adolescents were recruited from the local community through advertisements. We used the SCID to screen the healthy controls, who were subsequently found with no neuropsychotic condition or serious medical illness. The healthy controls also denied any major psychiatric or neurological illness in their first-degree relatives. All the participants met the following criteria: (1) age, educational years, and IQ matched with the AOS group; (2) no diagnosis of past or current neurological disorders, claustrophobia, or family history of hereditary neurological disorders; (3) no history of head injury resulting in loss of consciousness; (4) no experience of alcohol or substance abuse; and (5) without incompatible implants. The two groups showed no differences in age, sex, and years of education.

The entire cognitive battery was employed to assess cognition achievement of the two groups. The tests included the Trail Making Test, Brief Assessment of Cognition in Schizophrenia: Symbol Coding; HOPKINS Verbal Learning Test-Revised™; Wechsler Memory Scale-III: Spatial Span; Neuropsychological Assessment Battery: Mazes, Brief Visuospatial Memory Test-Revised™; Category Fluency: Animal Naming (Fluency); Continuous Performance Test–Identical Pairs; Stroop; and the Mayer–Salovey–Caruso Emotional Intelligence Test, Managing Emotions branch (Brannick et al., 2011; Eack et al., 2010).

Thorough information of the study procedures was provided to all the participants. Written informed consent was obtained from every participant and their parents or legal guardians. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University.

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