Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Abnormal regional homogeneity as a potential imaging biomarker for adolescent-onset schizophrenia: A resting-state fMRI study and support vector machine analysis

Shuai Wang [a,b,c,d,e], Yan Zhang [f], Luxian Lv [f], Renrong Wu [a,b,c,d,e], Xiaoduo Fan [g], Jingping Zhao [a,b,c,d,e,f,*], Wenbin Guo [a,b,c,d,e,*]

[a] Department of Psychiatry, the Second Xiangya Hospital, Central South University, Changsha, China
[b] Mental Health Institute of the Second Xiangya Hospital, Central South University, Changsha, China
[c] National Clinical Research Center on Mental Disorders, Changsha, China
[d] National Technology Institute on Mental Disorders, Changsha, China
[e] Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, China
[f] Henan Key Laboratory of Biological Psychiatry, Henan Mental Hospital, Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, China
[g] UMass Memorial Medical Center, UMass Medical School, Worcester, USA

ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 4 May 2017
Accepted 30 May 2017
Available online xxxx

Keywords:
Adolescent-onset schizophrenia
Regional homogeneity
Resting-state functional magnetic resonance
Support vector machine
Biomarker

ABSTRACT

Objective: Structural and functional abnormalities have been reported in the brain of patients with adolescent-onset schizophrenia (AOS). The brain regional functional synchronization in patients with AOS remains unclear.
Methods: We analyzed resting-state functional magnetic resonance scans in 48 drug-naive patients with AOS and 31 healthy controls by using regional homogeneity (ReHo), a measurement that reflects brain local functional connectivity or synchronization and indicates regional integration of information processing. Then, receiver operating characteristic curves and support vector machines were used to evaluate the effect of abnormal regional homogeneity in differentiating patients from controls.
Results: Patients with AOS showed significantly increased ReHo values in the bilateral superior medial prefrontal cortex (MPFC) and significantly decreased ReHo values in the left superior temporal gyrus (STG), right precentral lobule, right inferior parietal lobule (IPL), and left paracentral lobule when compared with controls. A combination of the ReHo values in bilateral superior MPFC, left STG, and right IPL was able to discriminate patients from controls with the sensitivity of 88.24%, specificity of 91.89%, and accuracy of 90.14%.
Conclusion: The brain regional functional synchronization abnormalities exist in drug-naive patients with AOS. A combination of ReHo values in these abnormal regions might serve as potential imaging biomarker to identify patients with AOS.

1. Introduction

Adolescent-onset schizophrenia (AOS), which belongs to early-onset schizophrenia (EOS), refers to those patients who have the first episode schizophrenia between 13 and 18 years old (Kumra et al., 2008). It is estimated that 12–33% schizophrenia patients are AOS (Kumra et al., 2008). Compared with adult, patients with AOS have less exposure to life events or psychotropic medications, which are important confounding factors. In addition, adolescence represents a critical time period for brain development including myelination and synaptic pruning (Paus et al., 2008). Therefore studying AOS may provide valuable evidence for us to understand the neurodevelopmental abnormalities and etiology of schizophrenia.

The voxel-based structural neuroimaging studies have suggested decreased gray matter (GM) in several brain regions in patients with EOS, such as the parietal cortex, left middle and superior temporal gyrus (Honea et al., 2008; Kyriakopoulos et al., 2008; Zhang et al., 2015). Functional magnetic resonance imaging (fMRI) studies in patients with AOS have shown abnormal activity and connectivity in the dorsolateral prefrontal cortex, which is associated with working memory impairment (Kyriakopoulos et al., 2012). Recent studies using diffusion tensor imaging and fMRI have found white matter abnormalities in the bilateral parietal association cortex and left middle cerebellar peduncle (Kyriakopoulos et al., 2008) and connectivity abnormalities between the left posterior hippocampus and the prefrontal cortex in patients with EOS (White et al., 2007).

* Corresponding authors at: Department of Psychiatry, the Second Xiangya Hospital, Central South University, No. 139, Middle Renming Road, Changsha 410011, China.
E-mail addresses: zhaojingpingcsu@163.com (J. Zhao), guowenbin76@163.com (W. Guo).

http://dx.doi.org/10.1016/j.schres.2017.05.038
0920-9964/

Regional homogeneity (ReHo) is a method for analyzing the blood oxygen level dependent signal in the brain during resting state fMRI (rs-fMRI) with the assumption that a given voxel is temporally similar to those of its neighbors. Kendall's coefficient concordance (KCC) is used to measure the similarity or synchronization of the time series of a given voxel to those of its nearest neighbors in a voxel-wise way (Zang et al., 2004), and thus, reflecting a regional functional connectivity or synchronization and indicating the regional integration of information processing (Jiang et al., 2015). ReHo analysis has been successfully used to detect the abnormalities of regional functional synchronization in individuals with psychosis risk syndrome (Wang et al., 2016b) and various psychiatric disorders, including schizophrenia (Liao et al., 2012; Liu et al., 2006; Yu et al., 2013), depression (Guo et al., 2011), and attention deficit hyperactivity disorder (Cao et al., 2007).

Patients with AOS have multiple abnormalities in brain structural and functional connectivity (Kyriakopoulos et al., 2012; Zhang et al., 2015). However, whether or not these patients have abnormal brain regional functional synchronization during resting state remains unclear. The present study was the first to examine regional functional synchronization in patients with AOS by using the ReHo analysis of the rs-fMRI. Further we would like to examine whether abnormal regional functional synchronization in the brain can be served as a potential imaging biomarker to identify AOS.

2. Materials and methods

2.1. Participants

In this study, we recruited 49 drug-naive patients with AOS from the Second Affiliated Hospital of Xinxiang Medical University in Henan Province, China, and 32 healthy controls from the local community through advertising. The details of the participants and cognitive battery evaluations were described in our previous report (Wang et al., 2017). In addition, patients were assessed with the Positive and Negative Syndrome Scale (PANSS) to evaluate the severity of schizophrenia.

The Ethics Committee of Henan Mental Hospital approved the study. We conducted the study in accordance with the Helsinki Declaration (Harrison, 2005). All participants and their legal guardians signed the written informed consents.

2.2. Scan acquisition

The rs-fMRI scanning was performed on a 3.0 T scanner (Siemens Medical Systems, Erlangen, Germany) to acquire brain MRI images. The participants were supine in the scanner and remained motionless with eyes closed. Their head were fixed with foam pads. Echo planar imaging (EPI) was used to acquire the functional images in the resting-state. The parameters were set as: repetition time/echo time = 2000/30 ms, 33 axial slices, 64 × 64 matrix, 90° flip angle, 22 cm field of view, 4 mm section thickness, 0.6 mm slice gap, and 240 volumes.

2.3. Data preprocessing

Data Processing Assistant for Resting-State fMRI (DPARSF) were employed for image preprocessing (Chao-Gan and Yu-Feng, 2010). The first 10 images were excluded from analysis because of the instability of the initial MRI signal and for the subjects to adapt the circumstances. The fMRI images were corrected for acquisition delay between slices and for head motion. All participants should have <2 mm of translation in the *x*, *y*, or *z* and 2° of rotation in each axis. Furthermore, two-sample *t*-tests were performed in the mean absolute estimated movement parameters (translation and rotation, respectively) on all three axes to examine between-group differences in the degree of head motion. There were no significant differences in the mean absolute estimated movement parameters between patients and controls. After motion correction, the images were spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template and resampled to $3 \times 3 \times 3\ mm^3$. Finally, the images were linearly detrended and temporally band-pass-filtered (0.01 Hz to 0.08 Hz) to reduce the effect of low-frequency drifts and physiological high-frequency noise (Biswal et al., 1995; Lowe et al., 1998).

2.4. ReHo analysis

The REST software (http://resting-fmri.sourceforge.net) was used for the ReHo analysis (Zang et al., 2004). The details of ReHo analysis were provided in our previous report (Wang et al., 2016b). The generated ReHo maps were spatially smoothed with a 4 mm full width at half maximum (FWHM) Gaussian kernel.

2.5. Statistical analysis

The SPSS 18.0 software (Chicago, IL) was used for statistical analyses. Group comparisons in continuous or categorical variables were conducted by Student's *t*-test or Chi-square (χ^2) test with the significance level $p < 0.05$. General linear model was used for group comparisons in voxel-based ReHo maps of the entire brain with the significance level $p < 0.005$ corrected for multiple comparisons based on the Gaussian random field (GRF) theory (voxel significance $p < 0.001$, cluster significance $p < 0.005$). Age is applied as a covariate in the group comparisons to limit the potential effect of this variable. The correlations between the ReHo values and variables of cognitive scales and symptoms in patients were performed using Pearson's correlation analysis with the significance level $p < 0.05$ and controlling for age, gender, years of education, and disease duration. The Bonferroni correction was applied to minimize type I error in the multiple tests. For brain regions with significant difference in ReHo values between patients and healthy controls, the receiver operating characteristic curve (ROC) analysis was used to evaluate the effect of these clusters for differentiating patients from controls.

2.6. Classification analysis using SVM

SVM using the LIBSVM software package (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) (Chang and Lin, 2011) in Matlab was used to examine the possibility of a combination of these clusters to differentiate

Table 1
Demographic data and clinical baselines of the participants.

Characteristics	AOS (mean ± SD)	HC (mean ± SD)	t/χ^2	*p*
Sample size	48	31		
Age (years)	15.79 ± 1.64	15.42 ± 1.52	1.014	0.314
Gender (male/female)	21/27	14/17	0.015	0.902
Years of education (years)	8.88 ± 1.95	8.44 ± 1.56	1.056	0.294
TMT-A	59.52 ± 38.63	40.94 ± 14.48	3.021	0.004
BACS-SC	39.44 ± 12.17	55.81 ± 9.84	−6.276	<0.001
HVLT-R	19.79 ± 6.05	26.13 ± 4.79	−4.919	<0.001
BVMT-R	18.65 ± 8.37	28.94 ± 5.25	−6.716	<0.001
NAB-M	10.31 ± 6.53	15.29 ± 6.40	−3.333	0.001
CF	15.54 ± 4.61	18.32 ± 4.81	−2.576	0.012
Stroop color	70.54 ± 20.96	90.58 ± 14.34	−4.660	<0.001
Stroop word	43.10 ± 18.10	62.77 ± 14.00	−5.136	<0.001
Stroop color-word	24.08 ± 12.05	34.42 ± 7.11	−4.309	<0.001
PANSS				
Positive	21.50 ± 5.01			
Negative	17.92 ± 6.95			
General	34.25 ± 5.89			
Total	75.10 ± 9.88			
Disease duration (months)	5.35 ± 6.12			

AOS, adolescent-onset schizophrenia; HC, healthy control; TMT-A, trail making test part A; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; HVLT-R, Hopkins verbal learning test-revised; BVMT-R, brief visuospatial memory test-revised; NAB-M, neuropsychological assessment battery-mazes; CF, category fluency; PANSS, positive and negative syndrome scale.

Please cite this article as: Wang, S., et al., Abnormal regional homogeneity as a potential imaging biomarker for adolescent-onset schizophrenia: A resting-state fMRI study and ..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.05.038