Schizophrenia Research 208 (2019) 308–316

Contents lists available at ScienceDirect

Schizophrenia Research

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

Altered dynamic global signal topography in antipsychotic-naive adolescents with early-onset schizophrenia

Xiao Wang [a,b], Wei Liao [a,b], Shaoqiang Han [a,b], Jiao Li [a,b], Yan Zhang [c], Jingping Zhao [d,**], Huafu Chen [a,b,*]

[a] The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China, Chengdu 610054, China
[b] School of Life Science and Technology, Center for Information in BioMedicine, University of Electronic Science and Technology of China, Chengdu 610054, China
[c] Mental Health Institute, the Second Xiangya Hospital of Central South University, Key Laboratory for Mental Health of Hunan Province, Changsha, China
[d] Mental Health Institute, the Second Xiangya Hospital of Central South University, 139, Middle Renmin Road, Changsha, Hunan 410011, China

ARTICLE INFO

Article history:
Received 25 June 2018
Received in revised form 14 January 2019
Accepted 26 January 2019
Available online 14 February 2019

Keywords:
fMRI
early-onset schizophrenia
dynamic functional connectivity
BOLD
topography

ABSTRACT

Schizophrenia (SCZ) is a severe neuropsychiatric disease associated with dysfunction of brain regions and networks. Recent, functional magnetic resonance imaging (fMRI) studies have determined that the global signal (GS) is an important source of the local neuronal activity. However, the dynamics of this effect in SCZ remains unknown. To address this issue, 39 drug-naive patients with early-onset schizophrenia (EOS) and 31 age-, gender- and education-matched healthy controls underwent resting-state fMRI scans. Dynamic functional connectivity (DFC) was employed to assess the dynamic patterns of the GS in EOS. Dynamic analysis demonstrated that the topography of the GS in EOS can be divided into five different states. In the state1, the GS mainly affected the sensory regions. In the state2, the GS mainly affected the default mode network (DMN). In the state3, the GS mainly affected the frontoparietal network and the cingulate-opercular network. In the state4, the GS mainly affected the sensory and subcortical regions. In the state5, the GS mainly affected the sensory regions and DMN. In particular, the changes in the cerebellum, putamen and supramarginal gyrus was inversely proportional to the clinical symptoms. Our findings demonstrate that the influence of the GS on brain networks is dynamic and changes of this relationship may associate with clinical behavior in SCZ.

1. Introduction

Schizophrenia (SCZ) is a devastating and chronically debilitating brain disorder characterized by abnormal activity in local regions and networks (Heuvel and Fornito, 2014; Lancaster and Hall, 2016; Liao et al., 2018a; Mp et al., 2013). However, these abnormalities are often affected by multiple factors including environment, age and drugs in the pathological process (Erp et al., 2018; Liao et al., 2018a). Early-onset schizophrenia (EOS) provides an exceptional opportunity to explore the neuropathology of schizophrenia free from the potential confounds of prolonged periods of medication and disease interactions with age-related neurodegeneration (Epstein et al., 2014; Tonya et al., 2008; Wang et al., 2017; Zheng et al., 2017). Many studies have focused on exploration of the blood oxygen level-dependent (BOLD) signals in SCZ patients via functional magnetic resonance imaging (fMRI).

fMRI studies have captured differences in the BOLD signals between SCZ patients and healthy controls (HCs) in both task and resting states (Lowe, 2012). For example, by analyzing the variability of the BOLD signal in SCZ, Yang et al. found that the BOLD signal fluctuations in gray matter are more temporally variable in comparison with HCs, especially in the association regions (Yang et al., 2014b). Spatially specific changes in cortical BOLD patterns may represent a disruption in basic brain functions in SCZ and suggest that altered BOLD variability may impact functional connectivity estimates (Yang et al., 2014b). However, this conjecture is complicated by the use of global signal (GS) regression for resting-state fMRI (rs-fMRI) data (Fox et al., 2009b).

The GS is defined as the spatial average of time-varying BOLD signals across the brain. This signal is believed to reflect non-neuronal noise in many fMRI studies (Power et al., 2014; Power et al., 2016). Recently, however, controversy in the application of the GS to rs-fMRI analyses has been raised (Fox et al., 2009a; Murphy and Fox, 2016; Yang et al., 2016; Yang et al., 2014a) because the GS has also been showed to reflect important neurobiological information. For example, Wong et al. found that caffeine can lead to reductions in global amplitude and that this changed global signal amplitude is related to electroencephalographic vigilance in HCs (Chi et al., 2016; Wong et al., 2013). Yang et al. also found that the variability of the GS in patients with schizophrenia are

* Correspondence to: H. Chen, Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China.
** Corresponding author.
E-mail addresses: zhaojingpingcsu@163.com (J. Zhao), chenhf@uestc.edu.cn (H. Chen).

https://doi.org/10.1016/j.schres.2019.01.035
0920-9964/

Table 1
Demographic and clinical characteristics.

Demographics, mean (SD)	EOS $N = 35$	Control $N = 30$	P value
Age (year)	15.5 (1.8)	15.3 (1.6)	0.57[a]
Gender (male/female)	20/15	13/17	0.27[b]
Education (years)	8.5 (1.48)	8.7 (1.42)	0.605[a]
Duration of psychosis (months)	16.0 (14.4)	–	–
Handedness (right/left)	35/0	30/0	–
PANSS positive symptoms	20.42 (5.72)	–	–
PANSS negative symptoms	20.91 (8.41)	–	–
PANSS general symptoms	33.28 (6.69)	–	–
PANSS total symptoms	74.62 (10.61)	–	–

P^a-value was obtained by two-sample t-test.
P^b-value was obtained by χ^2 two-tailed test.

related to schizophrenia symptoms (Yang et al., 2017; Yang et al., 2014b). Similar results have been obtained in studies on the autism spectrum (Gotts et al., 2012) and major depressive disorder (Zhu et al., 2018). These studies suggest that the GS is not merely nonneuronal physiological noise but also an important source of the neuronal activity itself, thus may contain important clinical information on psychiatric disorders. Moreover, the spatial topography of the GS, the representation of the GS in specific regions, has also been examined (Wen and Liu, 2016; Yang et al., 2016) and proposed a hypothesis that the clinical behavior are affected by this Spatiotemporal Psychopathology (Zhang et al., 2018). However, studies about the dynamic characteristics of this hypothesis is still lacking. Using a dynamic method to explore the spatiotemporal properties of the GS in EOS may provide a new way to understand the psychopathology in SCZ.

The current study aimed to assess the dynamic topography of the GS in EOS. The dynamic functional connectivity (DFC) method was employed to investigate the dynamic properties of the GS topography and two-sample t-tests were used for statistical analyses. The relationship between the aberrance and clinical symptoms was then investigated to test the contributions of pattern-specific alterations in coordination to the clinicopathology of EOS.

2. Materials and methods

2.1. Participants

A total of 39 patients with EOS and 31 age-, gender-, education-, and IQ-matched healthy adolescents were enrolled from the Second Affiliated Hospital of Xinxiang Medical University. All participants aged between 12 and 18 years, right-handed Han Chinese and had received >6 years of formal education. Exclusion criteria for all participants consisted of: (1) any past or current neurological disorders or family history of hereditary neurological disorders; (2) history of head injury with loss of consciousness; (3) alcohol or substance abuse; (4) claustrophobia; (5) MRI contraindications. Patients had to fulfill the following inclusion criteria: (1) diagnosis of schizophrenia according to DSM criteria (DSM-VI-TR); (2) no co-morbid Axis I diagnosis; (3) duration of illness <2 years; (4) no current or previous antipsychotic medication. Clinical symptoms were independently assessed by 2 experienced psychiatrists using DSM-VI based structured interviews (SCID-I/Patient version). To validate the initial diagnosis, all patients were re-assessed 6 months after the initial diagnostic interview (Li et al., 2018b; Wang et al., 2017). Clinical symptomatology was further evaluated using the Positive and Negative Syndrome Scale (PANSS).

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University, and informed written consents were obtained from all subjects.

2.2. Data acquisition

All subjects were instructed to rest with their eyes closed, not to think of anything in particular, and not to fall asleep during the rs-fMRI scan. fMRI data were acquired using the 3 T MRI scanner (Siemens-Trio, Erlangen, Germany) in the Second Affiliated Hospital of Xinxiang Medical University. Scanning and clinical assessments were performed in one day. Functional images were collected transversely using an echo-planar imaging (EPI) sequence with the following

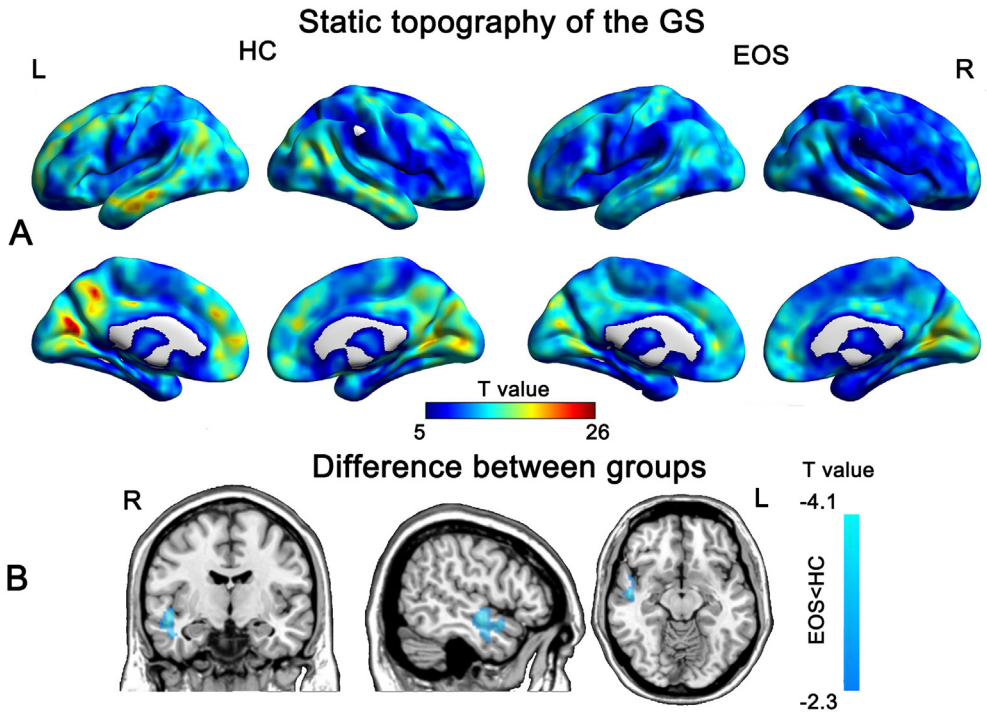

Fig. 1. Static topography of the GS and difference between the EOS and HC groups. (A) Surface visualization of group-level T-map computed across groups, left is the HC group, right is the EOS group. The T-map highlights positive FC values and covers virtually the entire brain. (B) GS representation is spatially altered in EOS. Cool color represents lower FC in the EOS than HC. GS, global signal; EOS, early-onset schizophrenia; HC, healthy control; FC, functional connectivity.