Schizophrenia Research 160 (2014) 67–72

Contents lists available at ScienceDirect

Schizophrenia Research

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

Disruptive changes of cerebellar functional connectivity with the default mode network in schizophrenia

Lubin Wang [a,b,1], Feng Zou [a,b,1], Yongcong Shao [a,b], Enmao Ye [a,b], Xiao Jin [a,b], Shuwen Tan [a,b], Dewen Hu [c,*], Zheng Yang [a,b,**]

[a] Beijing Institute of Basic Medical Sciences, Beijing, PR China
[b] Cognitive and Mental Health Research Center, Beijing, PR China
[c] College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan, PR China

ARTICLE INFO

Article history:
Received 1 January 2014
Received in revised form 31 August 2014
Accepted 16 September 2014
Available online 30 October 2014

Keywords:
Schizophrenia
Cerebellum
Default mode network
Functional connectivity

ABSTRACT

The default mode network (DMN) plays an important role in the physiopathology of schizophrenia. Previous studies have suggested that the cerebellum participates in higher-order cognitive networks such as the DMN. However, the specific contribution of the cerebellum to the DMN abnormalities in schizophrenia has yet to be established. In this study, we investigated cerebellar functional connectivity differences between 60 patients with schizophrenia and 60 healthy controls from a public resting-state fMRI database. Seed-based correlation analysis was performed by using seeds from the left Crus I, right Crus I and Lobule IX, which have previously been identified as being involved in the DMN. Our results revealed that, compared with the healthy controls, the patients showed significantly reduced cerebellar functional connectivity with the thalamus and several frontal regions including the middle frontal gyrus, anterior cingulate cortex, and supplementary motor area. Moreover, the positive correlations between the strength of frontocerebellar and thalamocerebellar functional connectivity observed in the healthy subjects were diminished in the patients. Our findings implicate disruptive changes of the fronto-thalamo-cerebellar circuit in schizophrenia, which may provide further evidence for the "cognitive dysmetria" concept of schizophrenia.

1. Introduction

Schizophrenia is a complex mental disorder characterized by a diverse range of symptoms, including hallucination, delusions, reduction in affect and behavior, and disorganization of thought and language (Liddle, 1987). Although the causes and neural mechanisms underlying schizophrenia are far from clear, a "disconnection" hypothesis has been proposed for the physiological explanation of the behavioral syndromes of this mental disorder (Friston and Frith, 1995). This hypothesis proposes that schizophrenia arises from dysfunctional integration of distributed brain regions or disruptive changes of neural circuitry, which may lead to an impairment in the fluid coordination of mental processes, sometimes referred to as "cognitive dysmetria" (Andreasen et al., 1998, 1999).

Previous neuroimaging studies have consistently found dysfunctions of the default mode network (DMN) in schizophrenia. The DMN is a distributed network of brain regions more active during rest than during performance of attention-demanding tasks, which subserves cognitive operations involving episodic memory retrieval, self-referential thought, and stream-of-consciousness processing (Gusnard and Raichle, 2001; Raichle et al., 2001; Buckner and Carroll, 2007). Task-related fMRI studies have revealed atypical patterns of brain activity in the DMN in patients with schizophrenia during a broad range of cognitive tasks (Garrity et al., 2007; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Schneider et al., 2011). Recent resting-state fMRI and diffusion tensor imaging studies have also shown aberrant DMN connectivity in schizophrenia, further supporting the "disconnection" hypothesis of the disease (Bluhm et al., 2007; Skudlarski et al., 2010; Camchong et al., 2011; Mingoia et al., 2012). Additionally, the DMN abnormalities were found to be associated with clinical symptoms as well as cognitive ability deficits in patients with schizophrenia (Park et al., 2009; Skudlarski et al., 2010; Camchong et al., 2011). These findings suggest that the DMN plays an important role in the physiopathology of schizophrenia.

Recently, there is an increased recognition of the higher-order functions of the cerebellum. A meta-analysis of task-related neuroimaging studies of the cerebellum has documented its role in various cognitive

* Correspondence to: D. Hu, College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan 410073, PR China. Tel./fax: +86 731 8457 4992.
** Correspondence to: Z. Yang, Beijing Institute of Basic Medical Sciences, Cognitive and Mental Health Research Center, 27 Taiping Road, Beijing 100850, PR China. Tel./fax: +86 10 68213284.
E-mail addresses: dwhu@nudt.edu.cn (D. Hu), yangzhengchina@aliyun.com (Z. Yang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.schres.2014.09.034
0920-9964/

and emotional processing (Stoodley and Schmahmann, 2009). A number of resting-state functional connectivity studies have also demonstrated that the cerebellum participates in higher-order networks such as the DMN (Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010; Buckner et al., 2011; Bernard et al., 2012). The role of the cerebellum in schizophrenia has been highlighted by Andreasen's hypothesis of "cognitive dysmetria", which suggests that dysfunctions in the cortico-cerebellar-thalamo-cortical circuit (CCTCC) could explain a variety of behavioral symptoms of this disease (Andreasen et al., 1998, 1999). Up to now, cerebellar abnormalities in schizophrenia have been supported by many clinical, cognitive, behavioral, and neuroimaging studies (Picard et al., 2008; Lungu et al., 2013). Notably, some researchers have begun to pay attention to abnormal functional connectivity associated with the cerebellum in schizophrenia (Shen et al., 2010; Collin et al., 2011). However, the potential contribution of the cerebellum to the DMN abnormalities in schizophrenia has yet to be established.

Taking advantage of a large public resting-state fMRI dataset, this study investigated the potential contribution of the cerebellum to the abnormal functional connectivity of the DMN in schizophrenia. Using a seed-based correlation method, we first reconstructed the intrinsic connectivity of the left Crus I, right Crus I and Louble IX in the control group and patient group, respectively. These cerebellar regions have been found to be involved in the DMN by previous studies (Habas et al., 2009; Krienen and Buckner, 2009; Bernard et al., 2012). Then, we examined the differences in the cerebellar functional connectivity between the two groups. Based on previous studies, we hypothesized that patients with schizophrenia would have decreased cerebellar functional connectivity with brain regions in the CCTCC circuit compared with healthy individuals.

2. Materials and methods

2.1. Subjects and imaging protocols

Data analyzed in this study came from an open access resting-state fMRI dataset comprising 72 patients with schizophrenia and 74 healthy controls. This publicly available dataset is contributed by the Center for Biomedical Research Excellence (COBRE, http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html), and has been previously studied by Anderson and Cohen (2013), Sui et al. (2013). All the subjects in the COBRE were screened and excluded if they had history of neurological disorder, history of mental retardation, history of severe head trauma with more than 5 minute loss of consciousness, history of substance abuse or dependence within the last 12 months. The patients were treated with atypical antipsychotic medications and were retrospective and prospective clinical stability. Diagnostic information was collected using the Structured Clinical Interview used for DSM Disorders.

The subjects underwent resting-state scans on a 3-T SIEMENS MRI scanner with the following parameters: 33 axial slices, repetition time = 2000 ms, echo time = 29 ms, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, acquisition matrix = 64 × 64, field of view = 240 mm. A total of 150 volumes of functional images were obtained for all the subjects except one (this subject was excluded from the present study). Another 15 subjects were excluded because of serious head motion (more than 2 mm translation or 2° of rotation) or partial cerebellum coverage of their fMRI scans. To match subjects across the two groups for age and sex, 10 healthy controls were further excluded from this study. Finally, 60 patients with schizophrenia and 60 healthy controls were included in the present analyses. Characteristics of the patient group and control group are shown in Table 1.

Table 1
Characteristics of the patient and control groups in this study.

Variable	Patient	Control	*p*-Value
Sample size	60	60	
Age (years)	38.0 ± 13.9	37.6 ± 11.6	0.86
Gender (M/F)	48/12	47/13	0.82[a]
Handedness (L/R)[b]	9/49	1/57	0.008[a]
Diagnosis score	295.4 ± 0.7		

[a] Pearson Chi-square test.
[b] Two subjects are ambidextrous in both the patient and control groups.

2.2. Data preprocessing

Functional scans were preprocessed using the SPM8 software (Wellcome Department of Imaging Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). Prior to preprocessing, the first 5 volumes of each scan were discarded for magnetic saturation. The remaining 145 volumes were corrected by registering to the first volume to account for head motion. All subjects in this study had less than 2 mm translation and 2° of rotation in any of the x, y, and z axes. Then, the volumes were normalized to the standard EPI template in the Montreal Neurological Institute (MNI) space and resliced to 3 × 3 × 3 mm^3. The resulting images were spatially smoothed with a Gaussian filter of 8 mm full-width half-maximum kernel. To avoid the blurring of fMRI signal across the cerebellar–cerebral boundary during spatial smoothing, the functional data in the cerebellum and cerebrum were extracted from the whole brain and smoothed separately. Subsequently, the data were temporally filtered with a band-pass filter (0.01–0.1 Hz), followed by linear detrending to remove any residual drift. Nine nuisance signals were further removed from the data via multiple regression, including the signals averaged from the white matter, the cerebrospinal fluid and the whole brain, and six parameters obtained by head motion correction. This regression procedure was utilized to reduce spurious variance unlikely to reflect neuronal activity.

2.3. Functional connectivity analysis

A seed-based correlation method was used to identify the resting cerebellar functional connectivity patterns in the patients with schizophrenia and in the healthy controls. Seed regions were defined as 6-mm-radius spheres centered on previously published foci. In this study, we selected 3 seed regions centered in the left Crus I (MNI: −33, −76, −34), right Crus I (MNI: 33, −76, −34), and Lobule IX (MNI: 0, −55, −49), which have been found to contribute to the intrinsic connectivity of the DMN in healthy individuals (Habas et al., 2009; Krienen and Buckner, 2009; Bernard et al., 2012). The time series of each seed region were calculated by averaging the fMRI time series over all voxels within the sphere. For each subject, correlation maps were created by calculating the Pearson's correlation coefficients between the time series of the seed regions and that of each voxel in the brain. These correlation maps were converted to z-value maps using Fisher's r-to-z transformation, to improve the normality of the correlation coefficients.

Group analyses were performed for the correlation maps of each seed region. First, correlation maps of the patients with schizophrenia and healthy controls were separately underwent a voxel-wise one-sample *t*-test, to determine the brain regions with significant correlations to the cerebellar seed regions. Then, a voxel-wise two-sample *t*-test was conducted between the correlation maps of the patients and healthy subjects, to identify significant cerebellar functional connectivity changes in schizophrenia. The significance level was set at $p < 0.001$, uncorrected. Multiple comparisons were corrected at the cluster level ($p < 0.05$, false discovery rate).

3. Results

3.1. Functional connectivity of the cerebellar seed regions

Resting-state functional connectivity patterns of the left Crus I, right Crus I and Lobule IX are shown in Fig. 1. For the control group, the