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Research paper

Abnormal cerebellum-DMN regions connectivity in unmedicated bipolar II disorder

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ABSTRACT

Objective: Bipolar disorder (BD) is a common psychiatric disease. Previous studies have found abnormalities in structural and functional brain connectivity in BD patients. However, few studies have focused on the functional connectivity (FC) of the cerebellum and its sub-regions in patients with BD. The present study aimed to examine the FC of cerebellum-default mode network (DMN) regions in patients with BD II.

Method: Ninety patients with unmedicated BD II depression and 100 healthy controls (HCs) underwent resting-state functional magnetic resonance imaging. We selected three pairs of subregions of the cerebellum that are DMN-related (the bilateral Crus I, Crus II, and lobule IX) as seed regions and calculated the whole brain FC for each subregion.

Results: Compared with the HCs, the patients with BD II depression showed increased connectivity between the right Crus I and bilateral precuneus and decreased connectivity between the left Crus II and bilateral medial prefrontal cortex (mPFC) and between the left Crus II and right medial frontal gyrus (MFG). There was no significant difference in the whole FC of the left Crus I and bilateral lobule IX between the BD II depression group and the HCs group.

Limitations: This study was cross-sectional and did not examine data from euthymic BD patients.

Conclusions: The findings showed impaired FC of cerebellum-DMN regions in BD; partial FC between the Crus I and precuneus and the Crus II and prefrontal cortex suggests the importance of abnormal cerebellum-DMN regions FC in the pathophysiology of BD.

1. Introduction

Bipolar disorder (BD), a severe, chronic psychiatric disease, is a leading cause of disability, morbidity, and mortality from suicide, and is associated with several medical conditions, such as cardiovascular disease, diabetes mellitus, and neurovascular disease (Merikangas et al., 2007; Prieto et al., 2014). It is characterized by episodes of depression, mania (BD I), and hypomania (BD II) that seriously affect the social functioning and quality of life of patients (Dean et al., 2004; Merikangas et al., 2007). Neuroimaging studies showed that BD can be interpreted as a disruptive integration of the coordination of the prefrontal-limbic circuits (Liu et al., 2012a; Teng et al., 2014). Recently, there have been also several studies that found abnormal gray matter volume (Sani et al., 2016), white matter integrity (Ambrosi et al., 2016), and regional function (Yu et al., 2017b) of the cerebellum in BD patients. However, the role of the cerebellum in the brain circuits in BD remains unclear.

The cerebellum is divided into the anterior cerebellar hemisphere (I–V), posterior lobe (VI, Crus I, Crus II, VII–IX) and posterior vermis. The anterior hemisphere of the cerebellum is regarded as being primarily related to motor learning and coordination while the posterior lobe is involved in emotion, awareness, and cognitive processing of higher-order functions in humans (Laricchiuta et al., 2015; Olivito et al., 2018; Stoodley and Schmahmann, 2009). Structural MRI studies

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found reduced gray matter density of the posterior cerebellar regions in BD patients (Kim et al., 2013; Moorhead et al., 2007). Moreover, a diffusional kurtosis imaging study exhibited microstructural changes in the cerebellum in BD, such as decreased fractional anisotropy, axial diffusivity, and radial kurtosis (Zhao et al., 2016). Several previous resting-state functional magnetic resonance imaging (rs-fMRI) studies found decreased functional activity (i.e., fractional amplitude of low-frequency fluctuations) (Yu et al., 2017a), functional homotopy (voxel-mirrored homotopic connectivity) (Wang et al., 2015b), and functional connectivity strength (FCS, a data-driven graph theory approach that measures the numbers of functional connections between a given voxel and other voxels (Tomasi and Volkow, 2010)) (Wang et al., 2016c, 2017) in the anterior and posterior lobe of the cerebellum in patients with BD.

The default mode network (DMN) is a large-scale brain network of core regions including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/ precuneus, inferior parietal lobule, and lateral temporal cortex and is more active during rest than during the initiation of task-related activity (Andrews-Hanna et al., 2010; Buckner et al., 2008; Ralchle and Snyder, 2007). Previous studies indicated that activity in the anterior DMN (i.e., the mPFC) is related to self-referential thought and reviewing past knowledge for preparing future action, while the posterior DMN (i.e., the PCC/precuneus) is responsible for episodic memory, consciousness, and awareness (Andrews-Hanna et al., 2014; Sheline et al., 2009). Several fMRI studies found abnormal function of the DMN in BD at rest (Gong et al., 2018; Ongur et al., 2010; Wang et al., 2015a). For example, Wang et al. (2015a) identified decreased FCS in the DMN regions, including the mPFC, precuneus, and PCC in patients with BD II depression when compared with healthy controls (HCs). Brady et al. (2017) found increased functional connectivity (FC) between the mPFC and the precuneus of the DMN in bipolar mania compared with bipolar euthymic subjects using a seed-based FC approach. Recently, dynamic functional network connectivity captured by sliding time window analysis revealed significantly abnormal connectivity in the DMN (parietal components, temporal components) in bipolar patients compared with HCs (Rashid et al., 2014). These findings indicate that the DMN plays an important role in the neurobiology of BD.

Previous researches showed that the bilateral Crus I, Crus II, and lobule IX subregions of the cerebellum strongly connect to the DMN in humans (Buckner et al., 2011; Diedrichsen et al., 2009; Habas et al., 2009; Halko et al., 2014). Previous seed-based FC studies found an abnormal FC of the cerebellum-DMN regions, including the PCC and mPFC, in major depressive disorder (Guo et al., 2015b) and schizophrenia (Guo et al., 2015c). Recently, a seed-based FC rs-fMRI study by our group revealed abnormal FC between the posterior cerebellum and the DMN region PCC/precuneus in patients with remitted BD II (Wang et al., 2017) while Shinn et al. (2017) found no significant connectivity difference in the cerebro-cerebellar DMN but identified several cerebellar regions of with great differences in the cerebro-cerebellar somatomotor network, ventral attention network, salience network, and execution control network in psychotic bipolar patients with mania or mixed episodes when compared with HCs. The following may account for the inconsistent results: small sample sizes, psychotropic medication use (i.e., lithium, mood stabilizer, antipsychotics), different BD subtypes (i.e., BD I or BD II), the state of BD (i.e., depressed, manic, mixed, or euthymic phase), and different methodologies (i.e., the scanning parameters, the regression approaches for removing motion parameters during pre-processing, and whether the impact of the standardization effect of global signal regression in pre-processing was evaluated). Because of these differences in the findings, the potential contribution of the cerebellum to the DMN abnormalities in patients with BD, especially differences in the intrinsic patterns of cerebellar subregion connectivity, remains unclear.

However, several studies focused on BD I patients or on patients with BD I, BD II, and BD not-otherwise-specified (Abe et al., 2016; Cerullo et al., 2009). The type of BD is a confounding variable in studies because the differences in the two disorders in symptoms and severity suggest partly different pathophysiology and the neurobiological mechanisms (Abe et al., 2016). In addition, neuroimaging studies showed the differences in structure (Abe et al., 2016; Ha et al., 2009; Maller et al., 2014) and task-based function (Caseras et al., 2015; Dell'Osso et al., 2015) between BD I and BD II. However, few studies have investigated the patients with BD II depression.

Here, we collected a large resting-state fMRI dataset (90 patients &100 HCs) to investigate intrinsic FC patterns of cerebellum-DMN regions in unmedicated BD II depression patients and HCs using a seed-based approach. We hypothesized that patients with BD II would show a disrupted FC of the cerebellum-DMN regions.

2. Methods and materials

2.1. Subjects

A total of 93 currently depressed adults diagnosed with BD II were recruited from the psychiatry department, First Affiliated Hospital of Jinan University, Guangzhou, China. The patients were aged from 18 to 55 years. All the patients met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (known as DSM-V) criteria for BD II according to a diagnostic assessment by the Structured Clinical Interview for DSM-V Patient Edition (SCID-P). The clinical state was assessed by using the 24-item Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) during the 3-day period prior to the imaging session. All the patients with BD were suffering from depression (YMRS score < 7 and HDRS-24 score > 21). The diagnosis of BD II was determined by two experienced clinical psychiatrists (Y.J. and S.Z., with 20 and 5 years of experience in clinical psychiatry, respectively). The exclusion criteria were patients with other Axis-I psychiatric disorders (except for BD and anxiety disorders), a history of electroconvulsive therapy, neurological disorders, any history of organic brain disorder, mental retardation (a developmental disability characterized by subaverage intelligence and impairments in adaptive daily life skills (Bisconer and Suttie, 1998)), pregnancy, alcohol/substance abuse, cardiovascular diseases, or any presence of a concurrent and major physical illness. At the time of testing, all the patients were either medication-naïve or had not been medicated for at least 6 months. In addition, 103 HCs were recruited via local advertisements. They were carefully screened through a diagnostic interview, the Structured Clinical Interview for DSM-V Nonpatient Edition (SCID-NP), to exclude the presence of current or past history of any psychiatric illness, including alcohol/substance abuse. Further exclusion criteria for HCs were any history of psychiatric illness in first-degree relatives or current or past significant medical or neurological illness.

This study was approved by the Ethics Committee of First Affiliated Hospital of Jinan University, Guangzhou, China. All the subjects were right-handed. They volunteered to participate in the study without coercion and signed a written informed consent form after a full written and verbal explanation of the study. Two senior clinical psychiatrists (Y.J. and S.Z., with 20 and 5 years of experienced in clinical psychiatry, respectively) confirmed that all the subjects had the ability to consent to participate in the examination.

2.2. MRI data acquisition

All the MRI data were obtained on a GE Discovery MR750 3.0T System with an 8-channel phased array head coil. The subjects were scanned in a supine, head-first position with symmetrically placed cushions on both sides of the head to decrease motion. Before the scanning, the participants were instructed to relax with their eyes closed without falling asleep repeatedly; after the experiment, only participants who confirmed that they had not fallen asleep were included; otherwise he/she was excluded.