ORIGINAL INVESTIGATION

Abnormal intrinsic cerebro-cerebellar functional connectivity in un-medicated patients with bipolar disorder and major depressive disorder

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Abstract

Objective The cerebellum plays an important role in depression. Cerebro-cerebellar circuits have been found to show aberrance in bipolar disorder (BD) and major depressive disorder (MDD). However, whether the cerebro-cerebellar connectivity contributes equally to the pathologic mechanisms of BD and MDD remains unknown.

Methods We recruited 33 patients with MDD, 32 patients with BD, and 43 healthy controls (HC). We selected six seed regions (three per hemisphere) in the cerebrum, corresponding to the affective, cognitive control, and default mode networks, to establish cerebro-cerebellar functional connectivity maps.

Results Relative to the HC, both the BD and MDD patients exhibited weaker negative connectivity between the right subgenual anterior cingulate cortex and the cerebellar vermis IV_V ($p_{BD} = 0.03$, $p_{MDD} = 0.001$) and weaker positive connectivity between the left precuneus and the left cerebellar lobule IX ($p_{BD} = 0.043$, $p_{MDD} = 0.000$). Moreover, the MDD patients showed weaker positive connectivity in the left precuneus—left cerebellar lobule IX circuit than the BD patients ($p = 0.049$). In addition, the BD patients showed weaker positive connectivity in the right dorsolateral prefrontal cortex—left cerebellar lobule Crus I circuit compared to the HC ($p = 0.002$) or the MDD patients ($p = 0.013$). Receiver operating characteristic curves analyses showed that the altered cerebro-cerebellar connectivities could be used to distinguish the patients from the HC with relatively high accuracy.

Conclusions Our findings suggested that differences in connectivity of cerebro-cerebellar circuits, which are involved in affective or cognitive functioning, significantly contributed to BD and MDD.

Keywords Mood disorders · Functional MRI · Neuropsychiatry

Yuan He and Ying Wang contributed equally to this work.

Highlights
- The BD patients showed weaker cerebro-cerebellar positive connectivity between the right dorsolateral prefrontal cortex (DLPFC) and the left cerebellar lobule Crus I compared to the HC and MDD groups;
- Cerebro-cerebellar negative connectivity between the right subgenual anterior cingulate cortex (sACC) and the cerebellar vermis IV_V was weaker in both the BD and MDD patients;
- Both the MDD and BD patients showed a weaker positive connectivity between the left precuneus and the left cerebellar lobule IX; in addition, the MDD patients showed a weaker RSFC in that coupling than the BD patients.

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Abbreviations

BD	Bipolar disorder
MDD	Major depressive disorder
HC	Healthy controls
DLPFC	Dorsolateral prefrontal cortex
SCID-IV	Structured Clinical Interview for DSM-IV
HDRS	Hamilton Depression Rating Scale
YMRS	Young Mania Rating Scale
TR	Repetition time
TE	Echo time
FOV	Field of view
FD-J	Frame-wise displacement Jenkinson
ROI	Region of interest
sACC	Subgenual anterior cingulate cortex
PREC	Precuneus
M1	Postcentral gyri
FDR	False discovery rate
ANCOVA	One-way analysis of covariance
LSD	Least significant difference test
ROC	Receiver operating characteristic

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are the most debilitating mood disorders worldwide (Clark et al. 2008) with a prevalence of at least 15% and 1%, respectively, and result in psychosocial, emotional, and cognitive dysfunction in affected individuals (Manelis et al. 2016). MDD is characterized by depressive episodes, whereas BD is characterized by alternating episodes of depression and mania or hypomania (Merikangas et al. 2011). However, the majority of BD patients suffer more frequently from depressive symptoms than from manic or hypomanic symptoms during the course of BD (Judd et al. 2012), causing BD patients to be difficult to distinguish from MDD patients (Hirschfeld et al. 2003). In fact, around 60% of patients with BD are initially misdiagnosed as MDD (Hirschfeld et al. 2003). Therefore, it is imperative to identify the objective biomarkers of BD and MDD to advance our understanding of the pathological mechanisms underlying the two mood disorders.

Recent advances in understanding large-scale brain functional networks have provided useful information that can be used to detect aberrant cognitive and affective function in psychiatric and neurological disorders (Menon 2011). Resting-state functional connectivity examines inter-regional temporal correlations in slow (< 0.1 Hz) spontaneous fluctuations in the BOLD signal (Fox and Raichle 2007). A high correlation, also regarded as synchrony and coherence, may serve a role in integrating neuronal processes for similar goals or cooperating representations. But a negative correlation, also regarded as anticorrelation, may serve a role in segregating neuronal processes for opposing goals or competing representations (Fox

et al. 2005). Coupling resting-state functional connectivity, with the existing knowledge about large-scale brain functional networks has been found to be helpful for identifying neurophysiological abnormalities in BD and MDD patients (Brady Jr. et al. 2017; Goya-Maldonado et al. 2016; Kaiser et al. 2015). Among the most well-established brain networks, the cognitive control network, affective network, and default mode network are the three core networks that appear to be particularly important for understanding dysfunction in the pathophysiology of depression (Fischer et al. 2016; Li et al. 2017; Menon 2011). The cognitive control network is comprised of the dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area, inferior frontal junction, dorsal pre-motor cortex, anterior insular cortex, and posterior parietal cortex (Cole and Schneider 2007). It is responsible for high level cognitive functions, such as decision-making, planning, and attention (Menon 2011). The affective network contains the anterior cingulate cortex (Bush et al. 2000), amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex (Ongur et al. 2003) and is believed to be involved in emotional regulation and monitoring for the salience of motivational stimuli (Sheline et al. 2010). The default mode network contains the posterior cingulate cortex, precuneus, and medial prefrontal cortex (Raichle et al. 2001). It has been suggested to be in charge of self-referential mental processes (Menon 2011), including evaluating the salience of internal and external cues, remembering the past, and planning the future (Sheline et al. 2010). These three networks constitute the core components of self-regulation and control of cognitive and affective functioning; thus aberrant resting-state functional connectivity in these three core networks may contribute to clinical symptoms for depression (Kaiser et al. 2015; Menon 2011). Deficits in engagement and disengagement of these three core networks have therefore been suggested as being associated with many psychiatric and neurological disorders, especially depression (Menon 2011).

Although several studies have suggested the role of the cerebral networks in depression (Goya-Maldonado et al. 2016; He et al. 2017; Kaiser et al. 2015; Menon 2011), a growing body of evidence has suggested that the cerebellum contributes to the dysfunctional brain circuits in depressive disorder (Minichino et al. 2014; Phillips et al. 2015; Wise et al. 2017; Zhao et al. 2016). The cerebellum is a highly heterogeneous structure, which can be anatomically divided into lobules designated I-X (Schmahmann et al. 1999). The unique afferent and efferent connectivity of each individual cerebellar lobule highly reflects the functional and structural diversity (Diedrichsen et al. 2009). The anterior lobe (lobules I-V) and lobule VIII are linked to sensorimotor areas, while the posterior lobe (especially lobules VI-VII) is connected to the prefrontal and parietal cortices, which receive non-motor inputs (Buckner et al. 2011; Stoodley and Schmahmann 2010; Strick et al. 2009). In addition, the cerebellar vermis is connected with limbic-related structures (Buckner et al. 2011; Stoodley and Schmahmann 2010).

Based on their functional properties, the cerebellum can be parceled into several subdivisions, some of them coupled with a specific cortical network, including the sensorimotor, default mode, frontoparietal, and limbic networks (Buckner et al. 2011; Habas et al. 2009; O'Reilly et al. 2010). By forming structurally and functionally closed-loop circuits with cognitive and affective regions of cortical and subcortical structures, the cerebellum is likely playing a role in cognitive function and emotion.

Evidence has suggested that the cerebellum is not only involved in motor control but also supports multiple higher-level functions, including emotion regulation, cognitive processing, learning, and memory (Habas et al. 2009; Krienen and Buckner 2009; Moulton et al. 2011; O'Reilly et al. 2010; Oertel-Knöchel et al. 2015; Schmahmann and Sherman 1998). Damage to the posterior cerebellar lobe is often accompanied by the clinical cerebellar cognitive affective syndrome (Schmahmann and Sherman 1998). These findings may explain some of the pathological basis of cerebellar abnormalities contributing to the affective and cognitive dysfunction in psychiatric disorders. Cordova-Palomera et al. (2016) suggested that cerebellar alterations in the resting state constitute a key candidate mechanism for depressive psychopathology. Specifically, abnormal cerebellar gray matter volume or blood flow (DelBello et al. 1999; Depping et al. 2017, 2018; Mills et al. 2005; Shen et al. 2016) were found in BD and MDD. A voxel-based meta-analysis suggested that the volume of some of the cerebellar regions is larger in BD patients than in healthy controls or in MDD patients (Wise et al. 2017). Another meta-analysis suggested that MDD patients showed less cerebellar gray matter compared to healthy subjects (Arnone et al. 2016). Cerebro-cerebellar functional connectivity was also studied in a variety of populations of people with MDD (Alalade et al. 2011; Guo et al. 2013a, b; Liu et al. 2012; Ma et al. 2013; Zeng et al. 2012). For instance, Alalade et al. (2011) found that people with geriatric depression had reduced connectivity between the ventromedial prefrontal cortex and regions of the cerebellum, specifically in the cerebellar executive and affective-limbic networks. Liu et al. (2012) found that adults with MDD showed weaker connectivity between the cerebellum and brain areas in the default mode network and the executive control network. Guo et al. (2013a) reported that patients with first-episode, treatment-naive MDD showed weaker connectivity between the cerebellum and bilateral inferior temporal gyrus as well as the inferior parietal lobule. Both Zeng et al. (2012) and Ma et al. (2013) found that altered connectivity in cerebro-cerebellar circuits can be used to distinguish MDD patients from healthy subjects. Abnormal functional interactions between the cerebrum and cerebellum in BD were also reported in many studies (Mamah et al. 2013; Samudra et al. 2015; Wang et al. 2015). In addition, cerebro-cerebellar connectivity in the salience and frontoparietal networks was weaker in BD in Shinn et al.' s study (2017). Another study (Wang et al.

2017) also found weaker functional connectivity between the right posterior cerebellum and the default mode network (i.e., the right posterior cingulate cortex/precuneus and right superior temporal gyrus), bilateral hippocampus, and right putamen as well as between the left posterior cerebellum and the right inferior parietal lobule in patients with remitted BD. All of these studies reported preliminary results indicating that abnormal cerebro-cerebellar circuits contribute to MDD and BD. However, although the pathogenesis of BD and MDD is presumed to be different, no detailed study to detect whether there is a difference in cerebro-cerebellar connectivity between BD and MDD patients has yet been performed.

Our goal was to use a seed-based functional connectivity approach to study the intrinsic cerebro-cerebellar connectivity in patients with BD and MDD. Based on the literature reviewed above, we selected seed regions in the cerebrum that corresponded to the cognitive control network, default mode network, and affective network (Anand et al. 2005; McCarthy et al. 2013; Schmahmann et al. 1998; Sierakowiak et al. 2015). The temporal correlation was calculated between the time series for each given seed and each voxel in the cerebellum to establish cerebro-cerebellar connectivity maps. Since abnormal connectivity between the cerebellar and cerebral regions, specifically in areas of the affective-limbic network, the default mode network, and/or the cognitive control network, has been found in BD and MDD (Alalade et al. 2011; Guo et al. 2013a; Liu et al. 2012; Shinn et al. 2017; Wang et al. 2017), we hypothesized that there would be abnormal and weaker cerebro-cerebellar connectivity involved with cognitive and affective functioning in BD and MDD.

Methods and materials

Subjects

Thirty-three patients with MDD (11 M/22F, age = 30.76 ± 8.57 years old) and 32 patients with BD (18 M/14F, age = 28.25 ± 9.55 years old) were recruited from the Psychiatry Department of the First Affiliated Hospital of Jinan University, Guangzhou, China. Among the 32 BD patients, 3 were diagnosed with BD-I and 29 with BD-II. For each patient, the diagnosis was made according to the Structured Clinical Interview for DSM-IV (SCID-IV) by two experienced psychiatrists (Y.J. and S.Z.). The clinical state for each patient was assessed using the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the Young Mania Rating Scale (YMRS) (Young et al. 1978). Both the BD and MDD patients were experiencing a major depressive episode when they were recruited. The inclusion criteria for the MDD patients was a HDRS score > 21 and for the BD patients was a YMRS score < 7 and a HDRS score > 21. All the patients were either medication-naive or un-medicated for at least 6 months before

the MRI scanning. None of the patients had received electro-convulsive therapy prior to participating in the present study. The exclusion criteria for the patients were as follows: (1) any Axis I disorders other than BD and MDD, (2) any history of organic brain disorders, (3) neurological illness, and (4) mental retardation, cardiovascular diseases, alcohol/substance abuse or any physical illness. In addition, we recruited 43 healthy subjects (18 M/25 F, age = 24.49 ± 9.91 years old) as healthy controls (HC) via local advertisements. The exclusion criteria for the HC were same as for the patients with the addition that they could not have had any history of psychiatric illness, any first-degree relatives with psychiatric illness, nor a significant medical or neurological illness either currently or previously. All the subjects satisfied the criteria for undergoing MRI scanning based on a screening questionnaire.

This study was approved by the Ethics Committee of First Affiliated Hospital of Jinan University, Guangzhou, China. Before the scanning, each subject signed a written informed consent form after a full written and verbal explanation of the study. The demographics for all subjects in this study are listed in Table 1.

Data acquisition

All images were acquired on a GE 3T MR 750 Discovery System with an eight-channel phased-array receiver-only head coil. All of the participants underwent a 7-min R-fMRI scan. The R-fMRI data were acquired using a single-shot gradient-echo EPI sequence with the following parameters: volume repetition time (TR) = 2000 ms, echo time (TE) = 25 ms, flip angle = 90°, field of view (FOV) = 240 mm × 240 mm, data matrix = 64 × 64, thickness = 3.0 mm, inter-slice gap = 1.0 mm, 35 interleaved axial slices covering the whole brain, and 210 volumes. High resolution brain structural images were collected using a T1-weighted 3D Ax FSPGR BRAVO sequence (TR = 8.2 ms, TE = 3.2 ms, flip angle = 12°, data matrix = 256 × 256, FOV = 256 mm × 256 mm, thickness = 1 mm, and 136 axial slices covering the whole brain). In addition, the routine axial T1-weighted fluid attenuation inversion recovery and fast spin-echo T2-weighted MR sequences were applied to obtain brain images that were checked for the absence of brain structural or signal abnormalities. All of the above scans were performed in a single session. During the scanning, the subjects were simply instructed to close their eyes, relax, and stay awake.

Data preprocessing

Functional imaging data were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and DPABI_V2.3_170105 (http://restfmri.net/forum/DPARSF). For each subject, we discarded the first ten volumes to allow for adaptation to the scanning environment. Then, we performed the following steps: (1) slice-timing correction to correct for the acquisition delay; (2) realignment to estimate head motions within the R-fMRI scan. All subjects in this study satisfied the head motion criteria of translation < 1.5 mm in x, y, or z direction and rotation < 1.5° for each axis. In this study, no significant difference in the mean frame-wise displacement Jenkinson (FD-J) of head motion was found between the three groups (FD-J_{BD} = 0.05 ± 0.03, FD-J_{MDD} = 0.05 ± 0.03, FD-J_{HC} = 0.05 ± 0.02; F = 0.47, p = 0.62); (3) spatial normalization to the EPI template in the standard MNI space with a resampled voxel size of $3 \times 3 \times 3$ mm^3; and (4) spatial smoothing with a 4-mm full-width half maximum isotropic Gaussian kernel. Finally, we performed a linear trend removal and temporal band-pass filtering (0.01–0.08 Hz) on the time series of each voxel. In the calculations, we regressed out nuisance covariates, including head motion profiles (Friston 24-parameter model) (Friston et al. 1996), white matter signal, global signal, and cerebrospinal fluid signal.

Table 1 Demographic and clinical characteristics of the patients with bipolar disorder (BD) and major depressive disorder (MDD) as well as the healthy controls (HC)

Characteristics	MDD (n = 33)	BD (n = 32)	HC (n = 43)	p value	Post-hoc (p value)
Gender [a] (male/female)	11/22	18/14	18/25	0.17	N.A.
Age [b] (years old)	30.8 ± 8.6	28.3 ± 9.6	29.5 ± 9.9	0.56	N.A.
Years of education [b]	13.2 ± 2.9	14.0 ± 2.8	14.9 ± 2.8	0.05	N.A.
Disease duration [c] (months)	39.2 ± 50.7	44.4 ± 58.0	N.A.	0.70	N.A.
HDRS score [c]	26.6 ± 4.4	27.8 ± 4.4	N.A.	0.29	N.A.
YMRS score [c]	3.1 ± 4.1	2.0 ± 1.8	N.A.	0.17	N.A.
Onset age [c] (years old)	27.4 ± 9.7	23.3 ± 10.9	N.A.	0.12	N.A.
Total number of episodes [c]	2.0 ± 2.2	2.4 ± 1.3	N.A.	0.37	N.A.
Cerebellar volume [b] (cm^3)	90.0 ± 9.6	85.6 ± 10.3	92.5 ± 11.8	0.03	0.02[d]

Mean and standard deviation (SD) are reported unless otherwise specified. [a] χ^2 test, [b] one-way analysis of variance, [c] two-sample t test, [d] post-hoc comparisons showed significant differences between the BD and HC groups. *HDRS*, Hamilton Depression Rating Scale; *YMRS*, Young Mania Rating Scale; *N.A.*, non-applicable

Functional connectivity analysis

The present study examined seed-based cerebro-cerebellar functional connectivity in the BD and MDD patients using REST_V1.9_140508 (http://resting-fmri.sourceforge.net). In the cerebrum, we selected six spheres as regions of interest (ROIs; three per hemisphere) of 5 mm in radius as the most typical seed regions in specific networks, which correspond to those in previous studies (McCarthy et al. 2013; Sheline et al. 2010). These seeds were centered in the bilateral subgenual anterior cingulate cortex (sACC, $x = \pm 10$, $y = 35$, $z = -2$), dorsolateral prefrontal cortex (DLPFC, $x = \pm 36$, $y = 27$, $z = 29$), and precuneus (PREC, $x = \pm 7$, $y = -60$, $z = 21$), each of which corresponds respectively to the bilateral affective network, cognitive control network, and default mode network. Because of the obligatory recruitment of the cerebellum in motor function (Stoodley and Schmahmann 2010), we also defined the ROIs centered in the bilateral postcentral gyri (M1, $x = \pm 46$, $y = -15$, $z = 40$) as seeds of the motor network (Sierakowiak et al. 2015). The time series for each seed was extracted by averaging across all the voxels within each ROI. For each seed, we created the voxel-wise connectivity maps for each subject by computing the Pearson's correlation coefficients between the time series for the given seed in the cerebrum and each voxel in the cerebellum. Eight connectivity maps were obtained for each subject and were converted to z-scores by applying Fisher's r-to-z transformation to improve the normality of the distribution (Fox et al. 2005).

To confirm that the seeds used to identify the networks of interest were located appropriately, we used the seeds to construct voxel-wise functional connectivity maps in the cerebrum for the healthy subjects. A one-sample t test was used to detect the network pattern in the HC group ($p < 0.001$ corrected for false discovery rate, FDR). The significant network connection patterns are shown in Figure S1 in the Supplementary Materials.

Finally, we also used an independent component analysis, a fully data-driven multivariate blind source separation method that requires no prior assumptions, to select the core regions of the intrinsic networks to perform a validation analysis. The method and main results can be found in the Validation analysis, Results, and Figure S2 in the Supplementary Materials.

Statistical analysis

A one-way analysis of variance (ANOVA) was used to test group differences in age, education level, cerebellar volume, and mean frame-wise displacement Jenkinson (FD-J) of the imaging data. A χ^2 test was used to compare group differences in gender. A two-sample t test was used to compare differences in clinical indices, such as total number of episodes, disease duration, disease onset age, HDRS total score, and YMRS total score, between the two patient groups.

For any given seed, we used a one-sample t test to identify voxels in the cerebellum that exhibited significant correlations with the seed for each group. The significance level was set at $p < 0.01$ with a FDR correction (Benjamini and Hochberg 1995). A union mask was created from the union set of the one-sample t test results of the three groups for each seed. Then, within the union mask for each seed, a one-way analysis of covariance (ANCOVA) was used to compare differences in the cerebro-cerebellar connectivity between the three groups. Correction for multiple comparisons was performed using a cluster-level threshold at an uncorrected voxel-wise $p < 0.05$ and a minimum cluster size threshold to maintain a corrected threshold at a cluster level of $a < 0.01$. The cluster size thresholds are shown in Table S1. Cluster extents were computed via 1000 Monte Carlo simulations implemented in the 3dClustSim program (AFNI, https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). A post-hoc ANCOVA was used to extract the mean functional connectivity value of each cluster that showed a difference between the three groups to identify the significance of pair-wise group (BD vs. MDD, BD vs. HC, and MDD vs. HC) differences in connectivity ($p < 0.05$, least significant difference test for multiple comparisons, LSD). In the calculations, we regressed out age, gender, education level (Castellazzi et al. 2014), and head motions (Power et al. 2012). Because altered cerebellar volume in BD and MDD had been reported in a previous study (Wise et al. 2017), we first calculated the cerebellar volume for each subject and then regressed it out as a covariate in the one-sample t test and ANCOVA.

ROC analysis

Receiver operating characteristic (ROC) curves analyses were conducted to determine whether the connectivity differences between the three groups could serve as biomarkers for discriminating the BD patients from the MDD patients or distinguishing the two patient groups from the HC. This analysis was performed using a public MATLAB code (https://cn.mathworks.com/matlabcentral/fileexchange/19950-roc?out=roc-varargin-, Giuseppe Cardillo).

We also estimated the partial correlations between the cerebro-cerebellar connectivity and the clinical variables, including the number of depressive episodes, disease duration, disease onset age, and HDRS total score in the BD and MDD patients by regressing out age, gender, cerebellar volume, and education level. The significant results were set at the threshold at $p < 0.05$ (FDR corrected).

Results

Demographic and clinical characteristics

The demographic information and clinical characteristics are listed in Table 1. No significant differences were found in age, gender, or education level between the three groups. The two patient groups had no significant differences in disease duration, onset age, total number of episodes, total HDRS score, or total YMRS score. Significant group differences in cerebellar volume were found between the three groups ($F = 3.53$, $p = 0.03^*$). The post-hoc ANOVA showed that the BD group had a significantly smaller cerebellar volume than the HC group (BD $= 85.6 \pm 10.3$, HC $= 92.5 \pm 11.8$, $p = 0.02^*$). No significant difference in cerebellar volume was found either between the BD and the MDD or between the MDD and the HC.

Functional connectivity

Figure 1 displays significant differences in the cerebro-cerebellar connectivity circuits derived from the seed-based functional connectivity analysis between the three groups ($p < 0.05$, $a = 0.01$, 3dClustSim corrected). We found three distinct cerebro-cerebellar circuits showing significant differences between the three groups: one connecting the right sACC and cerebellar vermis IV_V; another connecting the right DLPFC to the left cerebellar lobule Crus I; and the third connecting the left precuneus and left cerebellar lobule IX. Specifically, the negative connectivity between the right sACC and cerebellar vermis IV_V was weaker, whereas the positive connectivity values in the other two circuits (the right DLPFC—left cerebellar lobule Crus I circuit, and the left precuneus—left cerebellar lobule IX circuit) were weaker in the BD compared to that in the HC. In addition, the MDD also showed weaker positive connectivity between the left precuneus and left cerebellar lobule IX and weaker negative connectivity between the right sACC and cerebellar vermis IV_V compared to the HC. We also found that the two cerebro-cerebellar circuits, including the right DLPFC—left cerebellar lobule Crus I circuit and the left precuneus—left cerebellar lobule IX circuit, showed significant or marginal difference in connectivity between the BD and the MDD. In addition, the three groups showed no significant difference in connectivity between the bilateral postcentral gyri and cerebellum. Detailed information about the abnormal cerebro-cerebellar connectivity is listed in Table 2.

ROC analysis

Next, to examine the robustness of the ability to distinguish between each of the patient groups and the HC group, we plotted the ROC curves for each of the cerebro-cerebellar connectivities that showed significant differences between the three

groups. For the abnormal connectivity between the right sACC and cerebellar vermis IV_V, the accuracies for discriminating the BD patients from the HC as well as the MDD patients from the HC were 59% ($p = 0.09$) and 71% ($p < 0.00^{**}$), respectively. For the abnormal connectivity between the right DLPFC and left cerebellar lobule Crus I, the accuracies for discriminating the BD patients from the HC and from the MDD patients were 73% ($p < 0.00^{**}$) and 69% ($p < 0.00^{**}$), respectively.

The abnormal connectivity between the left precuneus and left cerebellar lobule IX showed the greatest ability to distinguish the MDD patients from the HC at 76% ($p < 0.00^{**}$). In addition, the discriminatory accuracies of the connectivity between these same areas, the left precuneus and left cerebellar lobule IX, were 65% ($p < 0.01^{**}$) for discriminating the BD patients from the HC and 64% ($p = 0.02^*$) for discriminating the BD from the MDD patients. Detailed information about the ROC curves for each of the cerebro-cerebellar connectivities is shown in Fig. 2 and Table 3.

We also estimated the correlations between differences in connectivity and clinical variables. However, no significant correlation was found for either the MDD or BD patients ($p < 0.05$, FDR corrected).

Discussion

This study analyzed cerebro-cerebellar functional connectivity in patients with MDD and BD. The main findings were as follows: (1) Both the BD and MDD patients showed weaker negative connectivity between the right sACC and cerebellar vermis IV_V than the HC. (2) Both the BD and MDD patients showed weaker positive connectivity between the left precuneus and left cerebellar lobule IX than the HC, but the connectivity in the left precuneus—left cerebellar lobule IX loops was much weaker in the MDD than the BD. (3) The BD group showed weaker positive connectivity between the right DLPFC and left cerebellar lobule Crus I than either the MDD patients or the HC group. We identified differences in cerebro-cerebellar functional connectivity in patients with BD or MDD. In addition, differences in the extent of the differences in the cerebro-cerebellar circuits, which are involved in affective or cognitive functioning, in BD and MDD suggest that cerebro-cerebellar functional circuits play different roles in the mechanisms of BD from those in MDD.

Common abnormalities in the connectivity of the BD and MDD

In this study, the BD and MDD groups both showed a similar and weaker negative cerebro-cerebellar connectivity between the right sACC and the cerebellar vermis IV_V, with part of cerebellar vermis VI, than the HC group (Fig. 1 and Table 2). In further ROC analyses, the accuracies of using altered

Fig. 1 Seed-based cerebro-cerebellar resting-state functional connectivity in patients with bipolar disorder (BD) and major depressive disorder (MDD) as well as healthy controls (HC). The seeds in the cerebrum, corresponding to the cognitive control network, default mode network, and affective network, are shown inside of the center annulus, and the clusters in the cerebellum that were significantly connected to the seeds are displayed outside of the center annulus. The bar plot shows the pair-wise contrasts in functional connectivity between the three groups. The bar height corresponds to the mean value of the functional connectivity and the error bar to the standard deviation for a given group. Abbreviations: sACC, subgenual anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PREC, precuneus; vermis IV_V, cerebellar vermis IV_V; Crus I, cerebellar lobule Crus I; IX, cerebellar lobule IX; CCN, cognitive control network; DMN, default mode network; AN, affective network; L (R), left (right) hemisphere. $*p < 0.05$; $**p < 0.01$
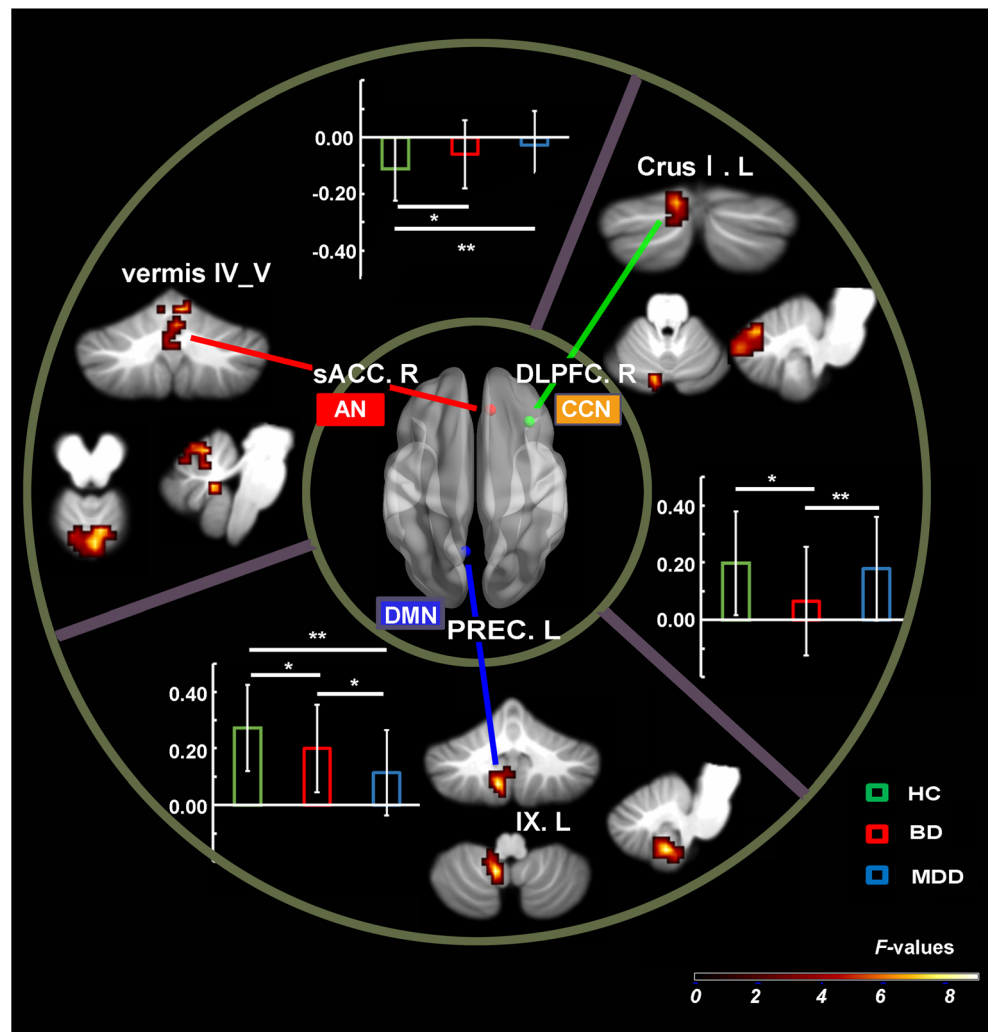
connectivity between the right sACC and cerebellar vermis IV_V to distinguish BD and MDD patients from the HC group were 59% ($p = 0.09$) and 71% ($p < 0.00^{**}$), respectively (Fig. 2 and Table 3). The cerebellar vermis has reciprocal connections with regions in the limbic system, such as the hippocampus and amygdala (Bernard et al. 2012). It has been proposed that the posterior vermis can be viewed as the "limbic cerebellum" (Schmahmann et al. 1998; Stoodley and Schmahmann 2010) and defined as part of the affective-limbic network (Alalade et al. 2011; Guo et al. 2013b; Liu et al. 2012). Baumann and Mattingley (2012) found stable activity of the cerebellar vermis during an emotional processing task, suggesting that it plays an important role in emotional processing. Previous studies found that malformations or damage to the cerebellar vermis are commonly linked to affective alterations (Tavano and Borgatti 2010) or impairments, such as blunting of emotion (Schmahmann and Sherman 1998), flattened affect, and reduced emotional expressivity (Sokolov et al. 2017; Young et al. 1978). Previous studies also found structural or functional abnormality of the cerebellar vermis in BD and MDD (Mills

et al. 2005; Minichino et al. 2014; Yucel et al. 2013), and impaired connection between the cerebellar vermis and ACC can be regarded as one of the most discriminative features for distinguishing MDD patients from an HC group (Ma et al. 2013). Therefore, it seems likely that the cerebellar vermis is involved in the pathophysiology of BD and MDD. Our finding of abnormal functional connectivity between the sACC and cerebellar vermis may further reveal dysfunction in the cerebro-cerebellar emotion processing circuit.

Of note, in the HC group, the connectivity between the sACC and cerebellar vermis was negative, which may be regarded as anti-correlated connectivity. Fox et al. (2005) suggested that anti-correlations play a role in segregating neuronal processes that subserve opposing goals or competing representations. In our study, both the BD and MDD patients showed weaker negative connectivity between the sACC and cerebellar vermis compared to the healthy controls, a finding which indicates dysregulated cerebro-cerebellar interactions, which are involved in affective functioning. These dysregulations may be related to a negative processing bias

Table 2 Group differences in cerebro-cerebellar functional connectivity between the patients with major depressive disorder (MDD) and those with bipolar disorder (BD) as well as the healthy controls (HC)

| Seed region in cerebrum	Peak location in cerebellum	Cluster size (# voxels)	Peak coordinate in the MNI space			F value	BD Mean (SD)	MDD Mean (SD)	HC Mean (SD)	Post-hoc (p value)		
			x	y	z					BD vs. MDD	BD vs. HC	MDD vs. HC
Affective network												
sACC. R	vermis IV_V	111	6	−60	−12	7.79	−0.06 (0.12)	−0.03 (0.12)	−0.11 (0.11)	0.286	0.030	0.001
Cognitive control network												
DLPFC. R	Crus I. L	66	−9	−78	−24	7.07	0.07 (0.19)	0.18 (0.18)	0.20 (0.18)	0.013	0.002	0.542
Default mode network												
PREC. L	IX. L	63	−9	−54	−51	8.71	0.20 (0.15)	0.11 (0.15)	0.27 (0.15)	0.049	0.043	0.000

A one-way ANCOVA within the union mask was used to assess between-group differences in cerebro-cerebellar functional connectivity at the threshold of $p < 0.05$, $a = 0.01$ (3dClustSim corrected) with the post-hoc least significant difference (LSD) test ($p < 0.05$) for multiple comparisons correction. *sACC*, subgenual anterior cingulate cortex; *DLPFC*, dorsolateral prefrontal cortex; *PREC*, precuneus; *vermis IV_V*, cerebellar vermis IV_V; *Crus I*, cerebellar lobule Crus I; *IX*, cerebellar lobule IX; *L (R)*, left (right) hemisphere; *SD*, standard deviation

that manifests as defective disengagement from enhanced attentional capture and negative events in BD and MDD.

Different abnormalities in connectivity between the BD and MDD

We found that both the BD and MDD patients showed weaker positive connectivity between the left precuneus and left cerebellar lobule IX (Fig. 1 and Table 2) compared to the HC. In addition, the weaker positive connectivity between the left precuneus and left cerebellar lobule IX provided the highest ability for distinguishing the MDD from the HC with an accuracy of about 76% ($p < 0.00^{**}$) (Fig. 2 and Table 3). Sang et al. (2012) found that both the anterior and posterior default mode network were correlated with cerebellar lobule IX. Habas et al. (2009) indicated that cerebellar lobule IX may play an important role in the default mode network. Thus, we infer that abnormal connectivity between the left precuneus and left cerebellar lobule IX may reflect dysfunction within the cerebro-cerebellar default mode network in the BD and MDD patients. An aberrant default mode network may lead to dysfunctional self-referential and affective processing in the form of an excessively negative self-focus (Greicius et al. 2003; Gusnard et al. 2001; Raichle et al. 2001), which has been found in BD and MDD patients in previous studies (Kaiser et al. 2015; Ongur et al. 2010; Sheline et al. 2010; Zhu et al. 2012). Our finding of weaker connectivity between the left precuneus and left cerebellar lobule IX in the MDD patients is consistent with several previous studies (Guo et al. 2013b; Liu et al. 2012) that also found reduced connectivity in the cerebellar-cerebral default mode network. Although no research has investigated cerebro-cerebellar default mode network connectivity in BD patients, hypoactivity in the default mode network in BD patients has been reported (Houenou et al. 2011; Ongur et al. 2010). In the present study, we also found weaker connectivity within the cerebro-cerebellar default mode network in the MDD patients compared with the BD patients. This is in line with previous studies that also found a relatively weaker connectivity of the precuneus within the default mode network in MDD patients than in BD patients (Liu et al. 2015). Rive et al. (2016) used default mode network functional connectivity patterns to distinguish depressed subjects with MDD from depressed subjects with BD, suggesting that the nature of default mode network abnormalities differs between the two mood disorders while they are in a depressed state. In our study, depressed subjects with MDD or BD, despite having no significant difference in clinical symptoms such as YMRS scales or HDRS scales, still had different connectivities within the cerebro-cerebellar default mode network. This difference may reflect scarring effects due to the experience of previous (hypo) manic episodes in BD (Rive et al. 2016). Hence, our findings of abnormal connectivity within the cerebro-cerebellar default mode network may provide a reference for clinical diagnosis of the two disorders.

Fig. 2 Receiver operating characteristic (ROC) curves show the classification power of different resting-state functional connectivities for between-group discriminations in the patients with bipolar disorder (BD), the patients with major depressive disorder (MDD), and the healthy controls (HC). The black arrow indicates the point with simultaneously optimized sensitivity and specificity. **a** functional connectivity of the left PREC—left cerebellar lobule IX; **b** functional connectivity of the right sACC—cerebellar vermis IV_V; **c** functional connectivity of the right DLPFC—left cerebellar lobule Crus I. Abbreviations: PREC, precuneus; sACC, subgenual anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; AUC, area under the curve; Sen, sensitivity; Spe, specificity; TPR, true positive rate; FPR, false positive rate. *$p < 0.05$; **$p < 0.01$
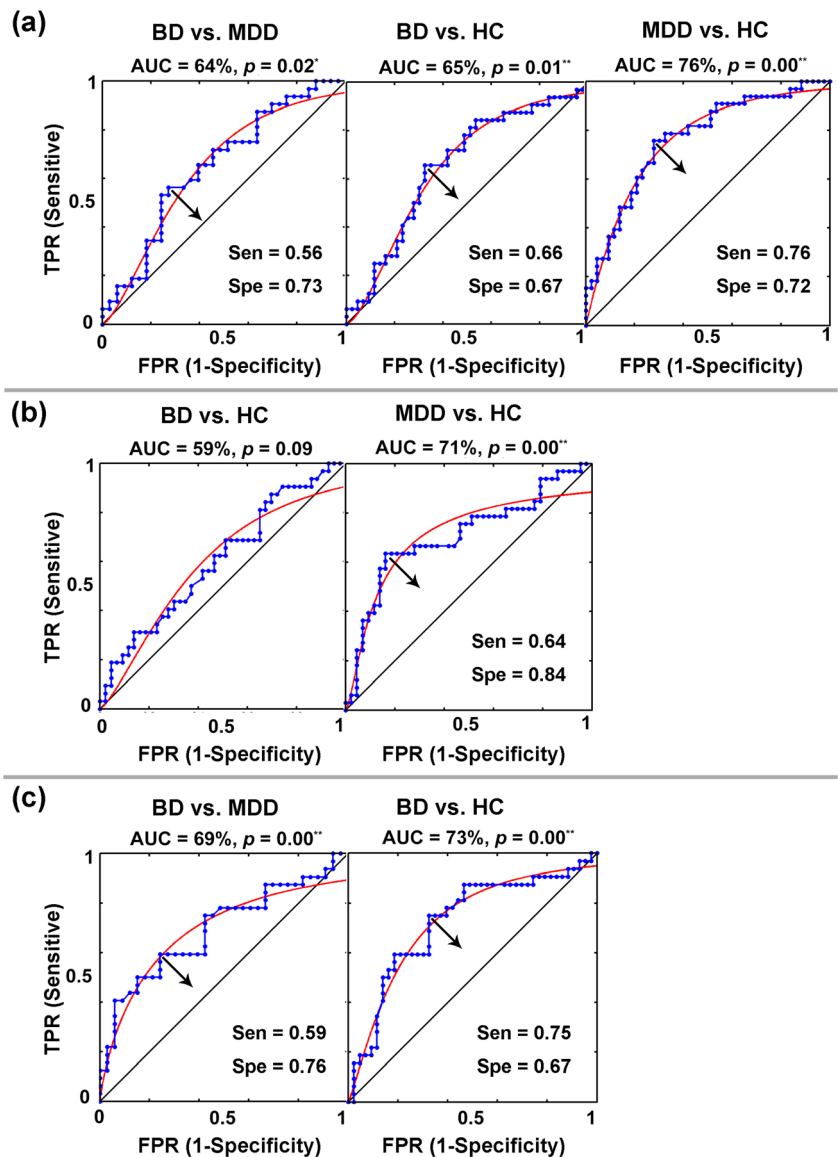
Specific abnormalities in connectivity of the BD patients

We found that the BD patients showed weaker positive connectivity between the right DLPFC and left cerebellar lobule Crus I than the MDD patients or the HC group (Fig. 1 and Table 2). Stoodley et al. (2012) indicated that the cerebellar lobule Crus I may be involved in cognitively demanding tasks along with the prefrontal and parietal cortices. Other studies also reported that the Crus I lobule was part of the cognitive

Table 3 ROC analysis of altered functional connectivity between the BD patients, the MDD patients, and the healthy controls (HC)

Altered connectivity	BD vs. HC			MDD vs. HC			BD vs. MDD		
	AUC	Sen	Spe	AUC	Sen	Spe	AUC	Sen	Spe
sACC. R - vermis IV_V	59%	--	--	71%**	0.64	0.84	--	--	--
DLPFC. R - Crus I. L	73%**	0.75	0.67	--	--	--	69%**	0.59	0.76
PREC. L - IX.L	65%**	0.66	0.67	76%**	0.76	0.72	64%*	0.56	0.73

AUC, area under curve; *sACC*, subgenual anterior cingulate cortex; *DLPFC*, dorsolateral prefrontal cortex; *PREC*, precuneus; *vermis IV_V*, cerebellar vermis IV_V; *Crus I*, cerebellar lobule Crus I; *IX*, cerebellar lobule IX; L(R), left (right) hemisphere; −, no value; *AUC*, area under the curve; *Sen*, sensitivity; *Spe*, specificity. *$p < 0.05$; **$p < 0.01$

control network (Habas et al. 2009; Krienen and Buckner 2009). In a meta-analysis, Stoodley and Schmahmann (2009) identified the cerebellar lobule Crus I as being engaged in executive functions. Habas et al. (2009) suggested that the cerebellar lobule Crus I may contribute to the specific cerebro-cerebellar loops that are involved in executive control. Its replicable presence in the cognitive function of the cerebellar lobule Crus I and weaker connectivity between the right DLPFC and left cerebellar lobule Crus I in the BD patients compared to the HC in our study may indicate an imbalance in the homeostasis of the cerebro-cerebellar cognitive loops in BD patients (Aydemir et al. 2014; Bauer et al. 2014; Breakspear et al. 2015; Rogers et al. 2004; Wolkenstein et al. 2017). Previous studies found reduced engagement in the cognitive control network in BD patients when viewing positive face stimuli (Pavuluri et al. 2007) or positive autobiographical memory recall (Young et al. 2016) or during a target anticipation and feedback anticipation task (Urosevic et al. 2016). Disner et al. (2011) suggested that reduced connectivity within the cognitive control network may result in impaired top-down regulation of aberrant emotional processing in BD patients (Chai et al. 2011; Fernández-Corcuera et al. 2013; Reinke et al. 2013). Based on the previous studies mentioned above, we suggest that the altered connectivity between the right DLPFC and left cerebellar lobule Crus I is associated with dysfunction of the cerebro-cerebellar cognitive circuit in BD patients compared to HC.

We also found weaker connectivity between the right DLPFC and left cerebellar lobule Crus I in the BD than in the MDD patients in our study. Gildengers et al. (2012) found worse overall cognitive function in BD patients than in MDD patients. MacQueen and Memedovich (2017) also suggested a higher degree of cognitive impairment in BD patients than in MDD patients. Our finding of a weaker cerebro-cerebellar cognitive loop connection in the BD patients than in the MDD patients may indicate greater cognitive impairment in BD patients than in MDD patients. In addition, the accuracy of using altered right DLPFC-cerebellar lobule Crus I functional connectivity to distinguish the BD patients from the MDD patients or from the HC group are 69% ($p < 0.00^{**}$) and 73% ($p < 0.00^{**}$), respectively, according to the ROC analysis (Fig. 2 and Table 3). The specific alteration of the DLPFC-cerebellar lobule Crus I coupling pattern in the BD patients but not in the MDD ones encourages further investigations using neuroimaging tools to support the differential diagnosis of depression between the two affective disorders.

Overall, abnormal cerebro-cerebellar cognitive and affective loop connections were found in the BD and the MDD patients in our study. These results may indicate the contribution of interactions between the cerebrum and cerebellum to both cognitive and affective dysfunction in BD and MDD patients. The ROC analysis further showed that the altered connections between the cerebro-cerebellar cognitive circuit

and the affective circuit can be used to distinguish the BD patients from the MDD patients or the patient groups from the HC group (Fig. 2 and Table 3).

Limitations

The present study has several limitations. This study failed to find any significant brain-behavior correlation because we did not collect behavioral and cognitive measures for the BD and MDD patients. It is unknown whether the altered cerebro-cerebellar affective or cognitive circuits have direct causal relationships with the clinical symptoms in the depressed. Besides, the patients who were diagnosed as MDD in the present study were in severe depression and had never previously exhibited manic or hypo-manic symptoms. Because this study was not longitudinal, we cannot be sure that none of the MDD patients will never turn out to have BD. The next limitation was that we applied a 3dClustSim correction for the multiple comparisons correction, which was set at an uncorrected voxel-wise $p < 0.05$ and a minimum cluster size threshold to maintain a corrected threshold at a cluster level of $a < 0.01$. Because our uncorrected threshold was relatively lenient, we cannot claim that the false positive error was strongly controlled. Another limitation was that we did not perform an inter-rater reliability analysis. In the present study, the diagnosis for each patient was made according to the Structured Clinical Interview for DSM-IV (SCID-IV) by two experienced psychiatrists (Y.J. and S.Z.). One of the two psychiatrists has had 6 years of clinical experience, and the other has had 20 years. In addition, in the present study, the total number of episodes included depressive, manic, hypomanic, and mixed episodes for the BD patients. Future studies should record the separate numbers of depressive, manic, hypomanic, and mixed episodes for the BD patients. Finally, we did not analyze the causal relationship of these core functional networks between the cerebrum and cerebellum. Understanding the dynamic interaction processes can help to reveal the role of the cerebellum in high level cognitive and affective functions in MDD and BD patients.

Conclusion

This study analyzed abnormal cerebro-cerebellar connectivity in BD and MDD patients. We found common patterns of weaker negative connectivity in the cerebro-cerebellar affective circuit and weaker positive connectivity in the cerebro-cerebellar default mode network in both the BD and MDD groups. In addition, we found that the MDD patients showed weaker connectivity within the cerebro-cerebellar default mode network than the BD patients. The significantly weaker positive connectivity in the cerebro-cerebellar cognitive circuit is specific to BD patients. Our results suggested that

MDD and BD are characterized by common and distinct patterns of cerebro-cerebellar connectivity differences. This combination of differences and similarities has the potential to inform the development of diagnostic biomarkers for the two mood disorders. Our findings provide further evidence for the important role of the cerebellum in the pathophysiological models of BD and MDD patients.

Compliance with ethical standards

This study was approved by the Ethics Committee of First Affiliated Hospital of Jinan University, Guangzhou, China.

Conflict of interest The authors declare that they have no conflicts of interest.

References

Alalade E, Denny K, Potter G, Steffens D, Wang L (2011) Altered cerebellar-cerebral functional connectivity in geriatric depression. PLoS One 6:e20035

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, Kalnin A, Lowe MJ (2005) Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol Psychiatry 57:1079–1088. https://doi.org/10.1016/j.biopsych.2005.02.021

Arnone D, Job D, Selvaraj S, Abe O, Amico F, Cheng Y, Colloby SJ, O'Brien JT, Frodl T, Gotlib IH, Ham BJ, Kim MJ, Koolschijn PCMP, Périco CAM, Salvadore G, Thomas AJ, van Tol MJ, van der Wee NJA, Veltman DJ, Wagner G, McIntosh AM (2016) Computational meta-analysis of statistical parametric maps in major depression. Hum Brain Mapp 37:1393–1404. https://doi.org/10.1002/hbm.23108

Aydemir O, Cubukcuoglu Z, Erdin S, Tas C, Onur E, Berk M (2014) Oxidative stress markers, cognitive functions, and psychosocial functioning in bipolar disorder: an empirical cross-sectional study. Rev Bras Psiquiatr 36:293–297. https://doi.org/10.1590/1516-4446-2013-1299

Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC (2014) Inflammatory mediators of cognitive impairment in bipolar disorder. J Psychiatr Res 56:18–27. https://doi.org/10.1016/j.jpsychires.2014.04.017

Baumann O, Mattingley JB (2012) Functional topography of primary emotion processing in the human cerebellum. Neuroimage 61:805–811

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate - a practical and powerful approach to multiple testing. J R Stat Soc 57:289–300

Bernard JA, Seidler RD, Hassevoort KM, Benson BL, Welsh RC, Wiggins JL, Jaeggi SM, Buschkuehl M, Monk CS, Jonides J, Peltier SJ (2012) Resting state cortico-cerebellar functional connectivity networks: a comparison of anatomical and self-organizing map approaches. Front Neuroanat 6

Brady RO Jr, Tandon N, Masters GA, Margolis A, Cohen BM, Keshavan M, Ongur D (2017) Differential brain network activity across mood states in bipolar disorder. J Affect Disord 207:367–376. https://doi.org/10.1016/j.jad.2016.09.041

Breakspear M, Roberts G, Green MJ, Nguyen VT, Frankland A, Levy F, Lenroot R, Mitchell PB (2015) Network dysfunction of emotional and cognitive processes in those at genetic risk of bipolar disorder. Brain 138:3427–3439. https://doi.org/10.1093/brain/awv261

Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 106:2322–2345. https://doi.org/10.1152/jn.00339.2011

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215–222

Castellazzi G, Palesi F, Casali S, Vitali P, Sinforiani E, Wheeler-Kingshott CA, D'Angelo E (2014) A comprehensive assessment of resting state networks: bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. Front Neurosci 8:223. https://doi.org/10.3389/fnins.2014.00223

Chai XJ, Whitfield-Gabrieli S, Shinn AK, Gabrieli JDE, Nieto Castañón A, McCarthy JM, Cohen BM, Öngür D (2011) Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 36:2009–2017. https://doi.org/10.1038/npp.2011.88

Clark L, Sahakian B, Frank E, Kupfer D (2008) State-of-Science Review: SR-B15 Neurocognition and Neuroimaging in Major Depressive Disorder and Bipolar Depression: Implications for Treatment and Functional Outcome

Cole MW, Schneider W (2007) The cognitive control network: integrated cortical regions with dissociable functions. Neuroimage 37:343–360

Cordova-Palomera A et al (2016) Environmental factors linked to depression vulnerability are associated with altered cerebellar resting-state synchronization. Sci Rep 6:37384. https://doi.org/10.1038/srep37384

DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW (1999) MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology 21:63–68. https://doi.org/10.1016/S0893-133X(99)00026-3

Depping MS, Nolte HM, Hirjak D, Palm E, Hofer S, Stieltjes B, Maier-Hein K, Sambataro F, Wolf RC, Thomann PA (2017) Cerebellar volume change in response to electroconvulsive therapy in patients with major depression. Prog Neuro-Psychopharmacol Biol Psychiatry 73:31–35. https://doi.org/10.1016/j.pnpbp.2016.09.007

Depping MS, Wolf ND, Vasic N, Sosic-Vasic Z, Schmitgen MM, Sambataro F, Wolf RC (2018) Aberrant resting-state cerebellar blood flow in major depression. J Affect Disord 226:227–231. https://doi.org/10.1016/j.jad.2017.09.028

Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N (2009) A probabilistic MR atlas of the human cerebellum. Neuroimage 46:39–46

Disner SG, Beevers CG, Haigh EA, Beck AT (2011) Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci 12:467–477. https://doi.org/10.1038/nrn3027

Fernández-Corcuera P, Salvador R, Monté GC, Salvador Sarró S, Goikolea JM, Amann B, Moro N, Sans-Sansa B, Ortiz-Gil J, Vieta E, Maristany T, McKenna PJ, Pomarol-Clotet E (2013) Bipolar depressed patients show both failure to activate and failure to de-

activate during performance of a working memory task. J Affect Disord 148:170–178

Fischer AS, Keller CJ, Etkin A (2016) The clinical applicability of functional connectivity in depression: pathways toward more targeted intervention. Biol Psychiatry Cogn Neurosci Neuroimaging 1: 262–270. https://doi.org/10.1016/j.bpsc.2016.02.004

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102: 9673–9678

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R (1996) Movement-related effects in fMRI time-series. Magn Reson Med 35:346–355

Gildengers AG, Butters MA, Chisholm D, Anderson SJ, Begley A, Holm M, Rogers JC, Reynolds CF III, Mulsant BH (2012) Cognition in older adults with bipolar disorder versus major depressive disorder. Bipolar Disord 14:198–205. https://doi.org/10.1111/j.1399-5618.2012.00995.x

Goya-Maldonado R, Brodmann K, Keil M, Trost S, Dechent P, Gruber O (2016) Differentiating unipolar and bipolar depression by alterations in large-scale brain networks. Hum Brain Mapp 37:808–818

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100:253–258. https://doi.org/10.1073/pnas.0135058100

Guo W, Liu F, Liu J, Yu L, Zhang Z, Zhang J, Chen H, Xiao C (2013a) Is there a cerebellar compensatory effort in first-episode, treatment-naive major depressive disorder at rest? Prog Neuro-Psychopharmacol Biol Psychiatry 46:13–18

Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C, Chen H, Zhao J (2013b) Abnormal resting-state cerebellar-cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression. Prog Neuro-Psychopharmacol Biol Psychiatry 44:51–57

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 98:4259–4264. https://doi.org/10.1073/pnas.071043098

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 29:8586–8594

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62

He H et al (2017) Co-altered functional networks and brain structure in unmedicated patients with bipolar and major depressive disorders. Brain Struct Funct 222:1–14

Hirschfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 64:161–174

Houenou J, Frommberger J, Carde S, Glasbrenner M, Diener C, Leboyer M, Wessa M (2011) Neuroimaging-based markers of bipolar disorder: evidence from two meta-analyses. J Affect Disord 132:344–355. https://doi.org/10.1016/j.jad.2011.03.016

Judd LL et al (2012) Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J Affect Disord 138:440–448

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015) Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72:603–611

Krienen FM, Buckner RL (2009) Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 19: 2485–2497

Li M, Das T, Deng W, Wang Q, Li Y, Zhao L, Ma X, Wang Y, Yu H, Li X, Meng Y, Palaniyappan L, Li T (2017) Clinical utility of a short resting-state MRI scan in differentiating bipolar from unipolar depression. Acta Psychiatr Scand 136:288–299. https://doi.org/10.1111/acps.12752

Liu L, Zeng LL, Li Y, Ma Q, Li B, Shen H, Hu D (2012) Altered cerebellar functional connectivity with intrinsic connectivity networks in adults with major depressive disorder. PLoS One 7:e39516

Liu Y, Wu X, Zhang J, Guo X, Long Z, Yao L (2015) Altered effective connectivity model in the default mode network between bipolar and unipolar depression based on resting-state fMRI. J Affect Disord 182:8–17. https://doi.org/10.1016/j.jad.2015.04.009

Ma Q, Zeng LL, Shen H, Liu L, Hu D (2013) Altered cerebellar-cerebral resting-state functional connectivity reliably identifies major depressive disorder. Brain Res 1495:86–94

MacQueen GM, Memedovich KA (2017) Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatry Clin Neurosci 71:18–27. https://doi.org/10.1111/pcn.12463

Mamah D, Barch DM, Repovs G (2013) Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. J Affect Disord 150:601–609

Manelis A, Almeida JR, Stiffler R, Lockovich JC, Aslam HA, Phillips ML (2016) Anticipation-related brain connectivity in bipolar and unipolar depression: a graph theory approach. Brain 139:2554–2566

McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, Johnson K, Fagan A, Gill M, Meaney J, Frodl T (2013) Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. JAMA Psychiatry 70:1329–1337

Menon V (2011) Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15:483–506. https://doi.org/10.1016/j.tics.2011.08.003

Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68:241–251

Mills NP, Delbello MP, Adler CM, Strakowski SM (2005) MRI analysis of cerebellar vermal abnormalities in bipolar disorder. Am J Psychiatry 162:1530–1533. https://doi.org/10.1176/appi.ajp.162.8.1530

Minichino A, Bersani FS, Trabucchi G, Albano G, Primavera M, Delle CR, Biondi M (2014) The role of cerebellum in unipolar and bipolar depression: a review of the main neurobiological findings. Riv Psichiatr 49:124–131

Moulton EA, Elman I, Pendse G, Schmahmann J, Becerra L, Borsook D (2011) Aversion-related circuitry in the cerebellum: responses to noxious heat and unpleasant images. J Neurosci 31:3795–3804. https://doi.org/10.1523/JNEUROSCI.6709-10.2011

Oertel-Knöchel V, Reuter J, Reinke B, Marbach K, Feddern R, Alves G, Prvulovic D, Linden DEJ, Knöchel C (2015) Association between age of disease-onset, cognitive performance and cortical thickness in bipolar disorders. J Affect Disord 174:627–635

Ongur D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 460: 425–449. https://doi.org/10.1002/cne.10609

Ongur D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, Renshaw PF (2010) Default mode network abnormalities in bipolar disorder and schizophrenia. Psychiatry Res 183:59–68

O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H (2010) Distinct and overlapping functional zones in the cerebellum

defined by resting state functional connectivity. Cereb Cortex 20: 953–965. https://doi.org/10.1093/cercor/bhp157

Pavuluri MN, O'Connor MM, Harral E, Sweeney JA (2007) Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. Biol Psychiatry 62:158–167

Phillips JR, Hewedi DH, Eissa AM, Moustafa AA (2015) The cerebellum and psychiatric disorders. Front Public Health 3(66)

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142–2154

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98:676–682

Reinke B, Ven V, Matura S, Linden DE, Oertel-Knochel V (2013) Altered intrinsic functional connectivity in language-related brain regions in association with verbal memory performance in euthymic bipolar patients. Brain Sci 3:1357–1373. https://doi.org/10.3390/brainsci3031357

Rive MM, Redlich R, Schmaal L, Marquand AF, Dannlowski U, Grotegerd D, Veltman DJ, Schene AH, Ruhé HG (2016) Distinguishing medication-free subjects with unipolar disorder from subjects with bipolar disorder: state matters. Bipolar Disord 18:612–623

Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, Fukuda M, Kato N (2004) Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. Neurosci Res 50:1–11. https://doi.org/10.1016/j.neures.2004.05.003

Samudra N, Ivleva EI, Hubbard NA, Rypma B, Sweeney JA, Clementz BA, Keshavan MS, Pearlson GD, Tamminga CA (2015) Alterations in hippocampal connectivity across the psychosis dimension. Psychiatry Res 233:148–157

Sang L, Qin W, Liu Y, Han W, Zhang Y, Jiang T, Yu C (2012) Resting-state functional connectivity of the vermal and hemispheric subregions of the cerebellum with both the cerebral cortical networks and subcortical structures. Neuroimage 61:1213–1225

Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579

Schmahmann JD, Loeber RT, Marjani J, Hurwitz AS (1998) Topographic organization of cognitive functions in the human cerebellum: a meta-analysis of functional imaging studies. Neuroimage 7:S721

Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, Kabani N, Toga A, Evans A, Petrides M (1999) Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. Neuroimage 10:233–260

Sheline YI, Price JL, Yan Z, Mintun MA (2010) Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A 107:11020–11025

Shen Z, Cheng Y, Yang S, Dai N, Ye J, Liu X, Lu J, Li N, Liu F, Lu Y, Sun X, Xu X (2016) Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset. Neuroimage Clin 12:492–498. https://doi.org/10.1016/j.nicl.2016.08.016

Shinn AK, Roh YS, Ravichandran CT, Baker JT, D Ö, Cohen BM (2017) Aberrant cerebellar connectivity in bipolar disorder with psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging 2:438–448

Sierakowiak A, Monnot C, Aski SN, Uppman M, Li TQ, Damberg P, Brene S (2015) Default mode network, motor network, dorsal and ventral basal ganglia networks in the rat brain: comparison to human networks using resting state-fMRI. PLoS One 10:e0120345

Sokolov AA, Miall RC, Ivry RB (2017) The cerebellum: adaptive prediction for movement and cognition. Trends Cogn Sci 21:313–332

Stoodley CJ, Schmahmann JD (2009) Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44:489–501

Stoodley CJ, Schmahmann JD (2010) Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 46:831–844

Stoodley CJ, Valera EM, Schmahmann JD (2012) Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage 59:1560–1570

Strick PL, Dum RP, Fiez JA (2009) Cerebellum and nonmotor function. Annu Rev Neurosci 32:413–434. https://doi.org/10.1146/annurev.neuro.31.060407.125606

Tavano A, Borgatti R (2010) Evidence for a link among cognition, language and emotion in cerebellar malformations. Cortex 46:907–918

Urosevic S, Luciana M, Jensen JB, Youngstrom EA, Thomas KM (2016) Age associations with neural processing of reward anticipation in adolescents with bipolar disorders. Neuroimage Clin 11:476–485

Wang Y, Zhong S, Jia Y, Zhou Z, Wang B, Pan J, Huang L (2015) Interhemispheric resting state functional connectivity abnormalities in unipolar depression and bipolar depression. Bipolar Disord 17:486–495

Wang Y, et al (2017) Altered cerebellar functional connectivity in remitted bipolar disorder: a resting-state functional magnetic resonance imaging study. Aust N Z J Psychiatry :4867417745996

Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, Amico F, Cheng Y, Cole JH, de Azevedo Marques Périco C, Dickstein DP, Farrow TFD, Frodl T, Wagner G, Gotlib IH, Gruber O, Ham BJ, Job DE, Kempton MJ, Kim MJ, Koolschijn PCMP, Malhi GS, Mataix-Cols D, McIntosh AM, Nugent AC, O'Brien JT, Pezzoli S, Phillips ML, Sachdev PS, Salvadore G, Selvaraj S, Stanfield AC, Thomas AJ, van Tol MJ, van der Wee NJA, Veltman DJ, Young AH, Fu CH, Cleare AJ, Arnone D (2017) Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. Mol Psychiatry 22:1455–1463. https://doi.org/10.1038/mp.2016.72

Wolkenstein L, Kanske P, Bailer J, Wessa M, Hautzinger M, Joormann J (2017) Impaired cognitive control over emotional material in euthymic bipolar disorder. J Affect Disord 214:108–114. https://doi.org/10.1016/j.jad.2017.03.007

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429–435

Young KD, Bodurka J, Drevets WC (2016) Differential neural correlates of autobiographical memory recall in bipolar and unipolar depression. Bipolar Disord 18:571–582

Yucel K, Nazarov A, Taylor VH, Macdonald K, Hall GB, Macqueen GM (2013) Cerebellar vermis volume in major depressive disorder. Brain Struct Funct 218:851–858. https://doi.org/10.1007/s00429-012-0433-2

Zeng LL, Shen H, Liu L, Wang L, Li B, Fang P, Zhou Z, Li Y, Hu D (2012) Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. Brain 135:1498–1507

Zhao L, Wang Y, Jia Y, Zhong S, Sun Y, Zhou Z, Zhang Z, Huang L (2016) Cerebellar microstructural abnormalities in bipolar depression and unipolar depression: a diffusion kurtosis and perfusion imaging study. J Affect Disord 195:21–31

Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, Yao S (2012) Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol Psychiatry 71:611–617. https://doi.org/10.1016/j.biopsych.2011.10.035

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