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Disrupted functional connectivity of the cerebellum with default mode and frontoparietal networks in young adults with major depressive disorder

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ABSTRACT

Cerebellar dysconnectivity has repeatedly been documented in major depressive disorder (MDD). The cerebellum is composed of multiple functionally distinct subunits, and whether those subunits show similar or distinct dysconnectivity patterns with the cerebrum in MDD, is still unclear and needs to be further clarified. In this study, 91 MDD patients (23 male and 68 female) and 59 demographically matched healthy controls (22 male and 37 female) were enrolled to explore the cerebellar-cerebral dysconnectivity pattern in MDD by using the cutting-edge cerebellar partition atlas. Results showed that MDD patients exhibit decreased cerebellar connectivity with cerebral regions of default mode (DMN), frontoparietal networks (FPN), and visual areas. The dysconnectivity pattern was statistically similar across cerebellar subunits, with no significant diagnosis-by-subunit interactions. Correlation analyzes showed that cerebellar-dorsal lateral prefrontal cortex (DLPFC) connectivity is significantly correlated with anhedonia in MDD patients. Such dysconnectivity pattern was not affected by sex, which, however, should be further replicated in larger samples. These findings suggest a generalized disrupted cerebellar-cerebral connectivity pattern in MDD across all cerebellar subunits, which partially accounts for depressive symptoms in MDD, thus highlighting the pivotal role of the disrupted connectivity of cerebellum with DMN and FPN in the neuropathology of depression.

1. Introduction

The cerebellum was traditionally considered as a "motor structure", however, the non-motor functions of the cerebellum (eg., emotional and cognitive functions) have been observed over the past decade (Diedrichsen et al., 2019; Schmahmann et al., 2019), which has increasingly attracted scientific interests in how the cerebellum contributes to the pathology of psychiatric disorders. Against this background, studies have shown that cerebellar dysfunction may contribute to a wide range of mental disorders (Hariri, 2019; Romer et al., 2018), such as autism spectrum disorder (D'Mello et al., 2015), schizophrenia (Cao et al., 2022), bipolar disorder (Luo et al., 2018), as well as major depressive disorders (MDD) (Depping et al., 2018).

The abnormalities of cerebellar structure and function have repeatedly been reported in MDD patients. Structural MRI studies have shown increased or decreased cerebellar volumes in MDD patients (Depping et al., 2016; Peng et al., 2011; Yucel et al., 2013), including area IX, VIIA, Crus I, and anterior vermis, which were considered as areas of "affective / cognitive cerebellum" (Depping et al., 2018). Functional MRI studies have also demonstrated abnormal cerebellar function in MDD patients. Task-induced fMRI has shown abnormal cerebellum activation in MDD patients performing cognitive (Chantiluke et al., 2012; Tepfer et al., 2021), emotional (Wong et al., 2019), and rewarding tasks (Dichter et al., 2012; Tepfer et al., 2021). Meanwhile, several resting-state fMRI studies have also found that MDD patients have altered cerebellar local spontaneous neural activity (Guo et al., 2013a;

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Lai and Wu, 2016; Yue et al., 2015) and functional connectivity (FC) (Guo et al., 2015; Ji et al., 2021; Zhu et al., 2020), especially to default mode network (DMN) and cognitive control network (CCN). Moreover, Ma et al. have reported that altered cerebellar-cerebral FC can serve as a promising classification feature to discriminate MDD from healthy controls (Ma et al., 2013). Although cerebellar dysfunction in MDD demonstrates a robust result across numerous studies, heterogeneous results were substantially observed. Some studies found both increased and decreased cerebellar-cerebral FC (Alalade et al., 2011; Liu et al., 2012) but others only found decreased FC (Guo et al., 2013b; Zhu et al., 2020). In addition, contradictory results have also been found. For example, Guo et al. found increased cerebellar-DMN connectivity in MDD patients (Guo et al., 2015), while other studies found decreased cerebellar-DMN connectivity (Alalade et al., 2011; Guo et al., 2013b; Liu et al., 2012; Zhu et al., 2020), which should be further clarified (see Table 1 for more details).

Depping et al. (2018) suggested that the insufficiently accurate seed selection in the previous studies may potentially explain the inconsistent results due to the cerebellar lobules being polymodal structures with segregated and functionally distinct subregions. Specifically, the cerebellum is composed of multiple functional subunits, which communicate with various cerebral structures and are therefore involved in several distinct functions such as motor, emotional, and cognitive functions. However, functional regions within the cerebellum do not respect lobular boundaries; different functional subregions may be in the same lobules, and sometimes extend beyond. Therefore, it is vital to consider these topographical details when placing the seed regions for connectivity analyses. Given the numerous challenges mentioned above, accurate functional parcellation of the cerebellum rather than preselected seed regions would be helpful to clarify this problem.

Meanwhile, previous studies only focused on a handful of predefined regions of interest (ROIs) in the cerebellum to explore cerebellar-cerebral connectivity, such as regions that were involved in cognition and emotion, while other functional regions have been ignored. It is still unclear whether all cerebellar subunits showed dysconnectivity to the cerebrum in MDD or limited to subunits that involve emotional and cognitive functions, given that MDD is primarily characterized by mood dysregulation and cognitive impairment. Whether different subunits show similar or distinct functional dysconnectivity patterns that relate to the pathophysiology of the disorder remains to be determined. Based on the above shortcomings, it is, therefore, necessary to clarify the cerebellar-cortical connectivity in MDD patients across different cerebellar subunits by using a more accurate functional parcellation of the cerebellum. To the best of our knowledge, no study has utilized a

Table 1
Summary of rs-fMRI studies for cerebellar-cerebral FC which compared MDD with HC.

Study (year)	N (Male)	Mean age (range)	Index	Seed selection	Main findings
Alalade et al. 2012	11 (1)	64.90±4.50	rs-FC	13 ROIs -5 mm radius spheres *Executive network* B. Crus I: ±12, -78, -28 B. Crus II: -36, -70, -46; 36, -68, -44 B. Lobule VI: ±36, −52, −34 *Default-Mode Network* B. Crus I: -32, -76, -34; 34, -80, -36 *Affective-Limbic Network* B. Lobule VI: ±26, -64, -34 L. Vermis: -4, -80, -34 *Motor Network* B. Lobule V: 22, -52, -22; -20, -50, -24	MDD vs. HC ↓ Cerebellum ECN-vmPFC/dmPFC/dlPFC/rACC ↓ Cerebellum DMN-caudate/putamen/fusiform gyrus ↓ Cerebellum ALN-vmPFC/vlPFC/precuneus/IPC ↓ Cerebellum motor network-vlPFC/dlPFC ↑ Cerebellum ECN-dmPFC/insula/putamen/precentral cortex/middle occipital ↑ Cerebellum ALN-middle temporal/motor cortex ↑ Cerebellum motor network-dmPFC/dACC
Liu et al. 2012	20 (6)	28.40±8.20	rs-FC	9 ROIs -WFU_PickAtlas Vermis, B. Crus I, Crus II B. Lobule VI, VIIb	MDD vs. HC ↓ Cerebellar-DMN ↓ Cerebellar-ECN
Guo et al. 2013a	24 (13)	25.58±7.45	fALFF rs-FC	fALFF-based seed selection L. Crus I: -48, -66, -36, size=50 L. lobule VI: -24, -60, -27, size=21	MDD vs. HC ↑ fALFF in left Crus I / lobule VI ↑ Left Crus I-right hippocampus ↓ Left Crus I-left IPL
Guo et al. 2013b	TRD: 23 (11) TSD: 22 (12)	TRD: 27.35 ±7.26 TSD: 28.09 ±9.91	rs-FC	13 ROIs - 6 mm radius spheres MNI coordinate same with *Alalade* et al., *2012*	MDD vs. HC ↓ Cerebellar-DMN/PFC ↑ Cerebellar-VRN/parahippocampal gyrus TRD showed more decreased FC than TSD
Ma et al. 2013	24 (8)	31.89±10.99 (18–52)	rs-FC	9 ROIs - WFU_PickAtlas Vermis, B. Crus I, Crus II B. Lobule VI, VIIb	Cerebellar-cerebrum rs-FC reliable identify depressed patients from controls
Guo et al. 2015	44 (22)	27.52±8.57	rs-FC	2 ROIs - 6 mm radius spheres L. Crus I: -32, -76, -34 R. Crus I: 34, -80, -36	MDD vs. HC ↑ Right Crus I-DMN
Zhu et al. 2020	50 (19)	42.10±10.50 ±	Dynamic-FC	13 ROIs - 6 mm radius spheres MNI coordinate same with *Alalade* et al. *2012*	MDD vs. HC ↓ dynamic FC of Cerebellar-vmPFC/dlPFC/STG/VA

Notes: Only studies that using resting-state fMRI to directly focus on patient's cerebellar functional connectivity were included in this table. ↑ represents increased FC, ↓ represents decreased FC.

Abbreviations: ROI, region of interest; MNI, Montreal Neurological Institute space; MDD, major depressive disorder; HC, healthy controls; fALFF, fractional amplitude of low frequency fluctuations; FC, functional connectivity; TRD, treatment-resistant depression; TSD, treatment sensitive depression; IPL, inferior parietal lobule; DMN, default mode network; ECN, executive control network; ALN, affective-limbic network; VRN, visual recognition network; vm/vlPFC, ventral medial/lateral prefrontal cortex; dm/dlPFC, dorsal medial/lateral prefrontal cortex; IPC, r/dACC, rostral/dorsal anterior cingulate cortex; inferior parietal cortex, STG, superior temporal gyrus; VA, visual area; L, left; R, right; B, bilateral.

functional parcellation of the cerebellum to systematically explore cerebellar-cortical connectivity in MDD patients. In addition to differences in cerebellar seed selection, subject's developmental stages in previous studies show variation, including young adults, middle-aged, and elderly, which may contribute to inconsistent results (see detail in Table 1), since previous evidence suggests that human brains undergo dynamic reorganizations during the lifespan (Song et al., 2012).

Moreover, sex differences in the cerebellum were observed in healthy individuals. Some evidence indicates sex differences in cerebellar volume (Hicks et al., 2022; Ruigrok et al., 2014; Steele and Chakravarty, 2018). Steele and Chakravarty (2018) found that females had a larger Crus II (non-motor regions) volume while males had a larger volume of motor-connected lobules, including H V and VIIIA/B. A recent study also found sex differences in cerebellum volume across most anterior and posterior cerebellar lobules (Hicks et al., 2022). Meanwhile, sex differences in cerebellar functions were also observed. Males and females showed different functional activation in cerebellar lobules when stimulated with conditioned warning and safety cues, with enhanced activated lobules in females were mostly representative of sensorimotor networks, while in males were mostly representative of frontoparietal and ventral attention networks (Labrenz et al., 2015). To the best of our knowledge, it has been noticed that the lifetime prevalence of MDD shows an approximate 2:1 ratio for females over males, and females showed more severe depressive symptoms than males. Previous studies have reported abnormal cerebellar-cerebral functional connectivity in MDD patients; however, it is still unclear whether cerebellar-cerebral dysconnectivity patterns in MDD vary across sex. Given the important role of the cerebellum in the pathology of MDD, it is therefore immediately relevant to determine whether the cerebellar-cerebral dysconnectivity pattern in MDD was affected by sex, which could deepen our understanding of the contribution of the cerebellum to the pathology of MDD.

To clarify these issues, we attempt to use a cutting-edge cerebellum functional atlas; Cole-Anticevic Net Partition (Ji et al., 2019), to explore cerebellar dysconnectivity in MDD patients. This atlas is considered to have better spatial accuracy regarding functional systems, which divides the cerebellum into nine functional subunits corresponding to putative networks defined for the cerebral cortex, including the visual system (VIS), sensorimotor system (SMN), cingulo-opercular system (CON), dorsal-attention system (DAN), language system (LAN), frontoparietal system (FPN), auditory system (AUD), default-mode system (DMN), and multimodal system (MM) (see Fig. 1). This net partition for the cerebellum represents a cerebellar extension of the established Glasser's cortical multi-modal parcellation atlas (Glasser et al., 2016). Subjects who were young adults (ranging in age from 18 to 35 years old) were enrolled in the current study to eliminate the potential confounding effects caused by variations in the participants' developmental stages. In the current study, we attempted to determine whether different functional subunits of the cerebellum show similar or distinct dysconnectivity patterns with the cerebrum in MDD patients by using a front-edge atlas with high spatial accuracy, and to clarify the association of cerebellar-cerebral functional dysconnectivity with depressive symptoms, contributing to the understanding of the role of cerebellar function in the neuropathology of MDD. Based on previous studies, in which both hyper and hypo cerebellar-cerebral functional connectivity were observed in MDD patients, we hypothesized that different cerebellar subunits may show different cerebellar-cerebral dysconnectivity patterns in MDD patients. Furthermore, we attempt to explore whether the dysconnectivity pattern between the cerebellum and cerebrum in MDD may be affected by sex, given that the potential effect of sex on cerebellar functions in healthy individuals has been observed in previous studies.

2. Methods

2.1. Participants

Participants included 91 MDD patients and 59 HC in the present study, with age, sex ratio ($\chi^2 = 2.46$, $p = 0.117$), and estimated intelligence score matched among four groups. MDD patients were recruited from the psychological clinic at the Second Xiangya Hospital of Central South University, Changsha, China. The diagnosis was established by two experienced psychiatrists using Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I). Exclusion criteria for patients were: diagnosis of other axis I psychiatric disorders and a history of major medical or neurological problems. HC were recruited from local colleges and communities in Changsha. Exclusion criteria were a history of any psychiatric disorders and any major medical or neurological problems.

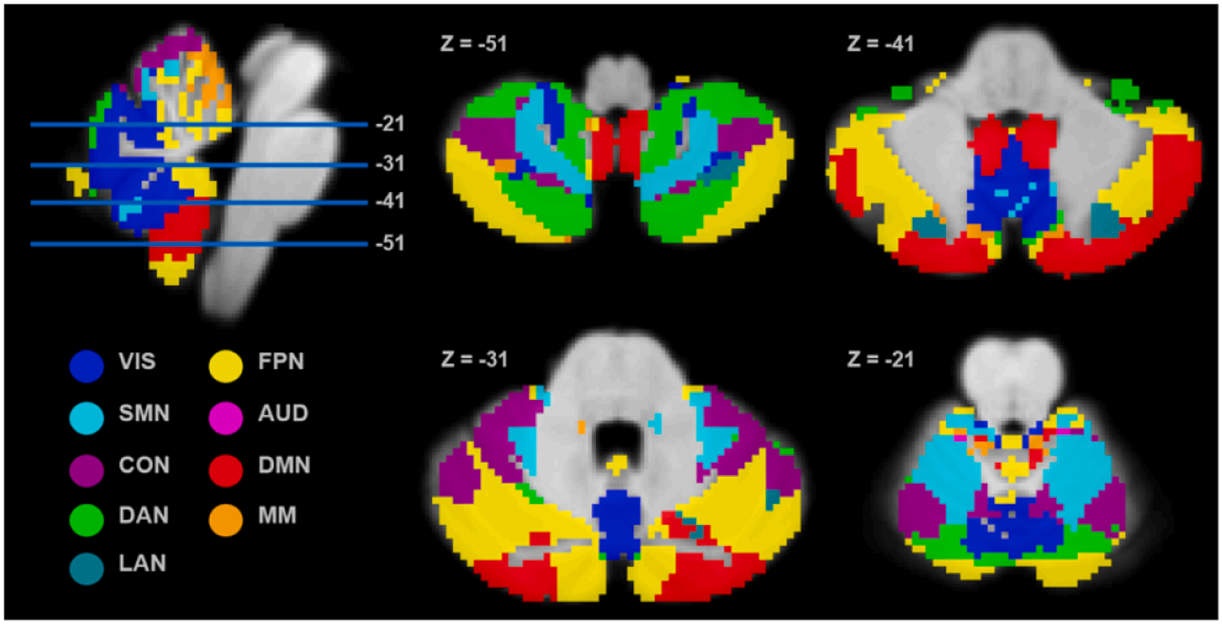

Fig. 1. Cerebellar seeds based on Cole-Anticevic Net Partition. VIS, visual; SMN, sensorimotor; CON, cingulo-opercular; DAN, dorsal-attention; LAN, language; FPN, fronto-parietal; AUD, auditory; DMN, default-mode; MM, multimodal.

All participants were right-handed, 18–35 years old, and had at least 9 years of education. The handedness was confirmed by the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Beck Depression Inventory (BDI) (Beck et al., 1961), Hamilton Depression Rating Scale-17 items (HAMD-17) (Hamilton, 1960), and the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) were used to assess depression and anxiety levels. The Temporal Experience of Pleasure Scale (TEPS) (Chan et al., 2012) was used for assessing trait anticipatory and consummatory anhedonia (see Supplementary Materials for details of these assessments). The age-adjusted scores of subtests (information, similarity, arithmetic, and digit span) of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-RC, administered by clinicians) (Gong, 1992) were used for controlling participants' intelligence levels. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (Grant No. 2016013). All participants agreed to participate and written informed consent was obtained.

2.2. MRI acquisition and processing

2.2.1. MRI acquisition

The MRI was conducted on a Siemens Skyra 3.0T magnetic resonance scanner at the Second Xiangya Hospital of Central South University. Subjects were asked to lie on the scanner, and foam pads were used to fix their heads to minimize head motion. The scanning sessions and the parameters were as follows: (1) three-dimensional T1-weighted, magnetization-prepared rapid gradient echo (MPRAGE) sagittal images: repetition time (TR) = 1900 ms; echo time (TE) = 2.01 ms; slices = 176; slice thickness = 1 mm; voxel size = 1.0 × 1.0 × 1.0 mm; flip angle = 9°; inversion time = 900 ms; field of view (FOV) = 256 mm; matrix = 256 × 256. (2) resting-state fMRI series using the echoplanar imaging sequence: TR = 2500 ms; TE = 25 ms; axial slices = 39; slice thickness / gap = 3.5 / 0 mm; voxel size = 3.8 × 3.8 × 3.5 mm, 200 vol; flip angle = 90°; FOV = 240 mm; matrix = 64 × 64. During the scanning, subjects were informed to keep their eyes closed but remain awake.

2.2.2. MRI processing

MRI data preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF V5.2) (Chao-Gan and Yu-Feng, 2010). The preprocessing procedures were as follows: (1) convert raw DICOM data to NIfTI format; (2) the first 10 vol were discarded to allow the magnetization to reach equilibrium and the participants to adapt to scanning noise; (3) slice-timing correction and realignment of head motion. Participants who demonstrated a maximum displacement greater than 2 mm or more than 2° of angular rotation were excluded from this study; (4) T1-weighted images of each participant were co-registered to the mean functional images; (5) functional images were normalized to the standard Montreal Neurological Institute (MNI) space using the transformation (co-registered T1 to standard MNI) parameters and resampled to 3 × 3 × 3 mm; (6) spatial smoothing with a 6 mm full-width half-maximum Gaussian filter; (7) linear detrending, regressing out of nuisance covariates (WM signal, CSF signal, and Friston-24 head motion parameters) were performed to remove low-frequency drift; (8) temporal bandpass filtering at 0.01–0.08 Hz was performed to reduce physiological high-frequency noise.

After preprocessing, seed-based whole-brain FC analysis was performed. The seed regions were defined based on Cole-Anticevic Net Partition Atlas (Ji et al., 2019), which divides the cerebellar into nine subunits corresponding to putative networks defined for the cerebral cortex (see Fig. 1). Each of the nine cerebellar subunits was used as the seed region once. Then, the average time series data from seed regions were extracted and seed-based whole-brain FC maps for all participants were subsequently generated by computing Pearson correlations (r scores) between the time course of the average signal in the seed region and all other brain voxels. Finally, Fisher's r-to-z transform was performed to convert the correlation coefficients to normally distributed z scores for further statistical analysis. In addition, the frame-wise displacement (FD) by Jenkinson et al. (2002) was calculated due to its consideration of voxel-wise differences in motion in its derivation. According to the recommendation (Yan et al., 2013), a "scrubbing routine" was used to censor any frame with an FD > 0.2 mm from the following seed-based FC calculation. Meanwhile, the mean FD was further controlled as a covariate in the group-level imaging statistical analysis.

2.3. Statistical analysis

2.3.1. Cerebellar connectivity analysis

The effects of MDD diagnosis and sex on cerebellar-whole brain connectivity were analyzed by 2 (diagnosis: MDD/HC) × 2 (sex: male/female) ANCOVAs with age, intelligence score, and mean FD as covariates. Statistical analyses were conducted with SPM12 for image analysis. All image comparisons (the main effect of diagnosis, the main effect of sex, and the interactive effect of diagnosis-by-sex) were corrected for multiple comparisons to reduce potential false positives, with a significant threshold of cluster-level $p < 0.05$, a family-wise error (FWE), starting from an uncorrected $p < 0.001$ at the voxel level. The overall dysconnectivity pattern in MDD patients was determined by the main effect of diagnosis on nine cerebellar subunits connectivity. To determine whether different cerebellar subunits would show similar or distinct dysconnectivity patterns in MDD patients and whether these patterns vary across sex, the interactive effects of diagnosis by cerebellar seeds were estimated by using ANCOVA models in males and females separately, controlling for age, intelligence score, and mean FD. In addition, considering the possible effect of antidepressant medications on resting-state brain function, we further compared MDD patients with medication to those without medication to examine whether they have significant differences in cerebellar-whole brain connectivity.

2.3.2. Correlation between cerebellar dysconnectivity and symptoms

To explore whether cerebellar-whole brain connectivity alterations in MDD patients were correlated with clinical characteristics, correlation analyses were performed. Considering the heterogeneity of depressive symptoms, we divided BDI into three sub-scales according to symptom dimensions (Finger and Argimon, 2013): Cognitive-Affective (items 1–3, 5–10, 13–14), Somatic (items 11, 15–20), and Anhedonia (items 4, 12, 21). We first extracted connectivity values for each participant from each cluster that survived after multiple comparison corrections based on group statistical maps of each cerebellar seed. Then, the relationships between these connectivity values and illness duration (Time of enrollment minus onset time of current major depressive episode), anxiety, depressive symptoms, and trait anhedonia were explored by applying partial correlation analyses across MDD patients (controlling for age, sex, and intelligence score). Benjamini-Hochberg FDR analysis was performed for the multiple comparison correction using MATLAB, with adjusted p-value (FDR q-value) < 0.05 considered statistically significant.

3. Results

3.1. Demographical and clinical variables

Table 2 provides the demographical and clinical characteristics of four groups. Table 3 provides statistical results of diagnosis and sex effects on clinical characteristics.

3.2. Cerebellar dysconnectivity patterns in MDD

The seed-based whole-brain connectivity analysis showed a significant main effect of diagnosis. Compared to HC, MDD patients showed hypoconnectivity in all cerebellar subunits-cerebral connectivity (see Fig. 2). No increased connectivity survived after multiple comparison corrections. Decreased connectivity was predominantly observed

Table 2
Demographical and clinical characteristics among four groups.

Characteristics	MDD		HC		*F/t*	*p*	Post-hoc tests (Bonferroni corrected)
	Male (G1; $n = 23$)	Female (G2; $n = 68$)	Male (G3; $n = 22$)	Female (G4; $n = 37$)			
Age (years)	21.78 (3.85)	21.65 (3.34)	20.73 (3.53)	21.84 (3.82)	0.52	0.672	—
Intelligence score [a]	48.83 (8.78)	48.74 (6.43)	51.86 (4.00)	50.49 (7.91)	1.42	0.156	—
Duration (month)	10.93 (14.59)	10.66 (15.37)	—	—	0.07	0.940	—
Age onset	20.74 (4.18)	20.24 (4.00)	—	—	0.50	0.610	—
Medication (yes/no) [b]	13/10	26/42	—	—	—	—	—
HAMD [c]	16.78 (7.29)	19.23 (4.87)	2.00 (2.83)	2.43 (4.01)	92.48	< 0.001	G2&G1>G3&G4
BDI	25.96 (9.79)	30.68 (7.32)	8.00 (9.08)	6.30 (6.37)	101.92	< 0.001	G2>G1>G3&G4
STAI_S	52.61 (11.44)	58.97 (8.65)	36.55 (8.79)	36.46 (10.07)	60.19	< 0.001	G2>G1>G3&G4
STAI_T	57.13 (7.50)	63.34 (6.72)	39.36 (8.23)	38.81 (9.52)	104.42	< 0.001	G2>G1>G3&G4
TEPS total	64.13 (16.58)	69.10 (15.92)	83.50 (13.47)	86.19 (11.68)	17.31	< 0.001	G1&G2<G3&G4
TEPS_ANT	33.70 (9.81)	37.72 (9.09)	46.41 (9.71)	46.92 (6.58)	16.86	< 0.001	G1&G2<G3&G4
TEPS_CON	30.43 (8.29)	31.38 (8.93)	37.09 (6.62)	39.27 (6.70)	10.34	< 0.001	G1&G2<G3&G4
FD	0.04 (0.02)	0.05 (0.02)	0.05 (0.03)	0.04 (0.02)	1.25	0.293	—

Notes: Means with standard deviations in parentheses. *F/t*: variables of age, intelligence score, BDI, STAI and FD were tested by one-way ANOVA as indicated by *F*; variables such as illness duration, age onset and HAMD were tested by two-sample *t*-test as indicated by *t*. [a] Intelligence score: age adjusted scores of subtests of the short form of the WAIS-RC (including Information, Similarity, Arithmetic and Digit span), which is only used for controlling the participants' intelligence level, rather than an estimation of IQ. [b] Medication: number of patients taking psychopharmacology yes/no. "No" means that the patients were medication-naïve, or they did not take any antipsychotic medicine at least for one month prior to the day when they were enrolled. "Yes" mean they were using medicine when enrolled (14 selective serotonin reuptake inhibitor; 3 serotonin and norepinephrine reuptake inhibitor; 1 tricyclic, 4 atypical antipsychotics). [c] HAMD: 16 of 22 participants in G3, and 21 of 37 participants in G4 completed HAMD assessment.
Abbreviations: MDD, major depressive disorder; HC, healthy controls; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; STAI_S, Spielberger State-Trait Anxiety Inventory_State Form; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; TEPS, Temporal Experience of Pleasure Scale; TEPS_ANT, anticipatory subscale; TEPS_CON, consummatory subscale; FD, Frame Displacement.

Table 3
Diagnosis and Sex effect on clinical characteristics.

Characteristics	MDD		HC		Effect of diagnosis		Effect of sex		Effect of diagnosis × sex	
	Male ($n = 23$)	Female ($n = 68$)	Male ($n = 22$)	Female ($n = 37$)	*F (P)*	Eta^2	*F (P)*	Eta^2	*F (P)*	Eta^2
HAMD [a]	16.78 (7.29)	19.23 (4.87)	2.00 (2.83)	2.43 (4.01)	202.43 (< 0.001)	0.62	0.99 (0.32)	—	2.02 (0.16)	—
BDI	25.96 (9.79)	30.68 (7.32)	8.00 (9.08)	6.30 (6.37)	217.39 (<0.001)	0.60	1.15 (0.29)	—	5.13 (0.25)	0.03
STAI_S	52.61 (11.44)	58.97 (8.65)	36.55 (8.79)	36.46 (10.07)	117.71 (<0.001)	0.45	2.79 (0.10)	—	4.54 (0.35)	0.03
STAI_T	57.13 (7.50)	63.34 (6.72)	39.36 (8.23)	38.81 (9.52)	213.61 (<0.001)	0.60	3.93 (0.05)	0.03	5.71 (0.02)	0.04
TEPS_total	64.13 (16.58)	69.10 (15.92)	83.50 (13.47)	86.19 (11.68)	42.64 (<0.001)	0.23	2.38 (0.13)	—	0.09 (0.76)	—
TEPS_ANT	33.70 (9.81)	37.72 (9.09)	46.41 (9.71)	46.92 (6.58)	45.47 (<0.001)	0.24	2.33 (0.13)	—	0.97 (0.33)	—
TEPS_CON	30.43 (8.29)	31.38 (8.93)	37.09 (6.62)	39.27 (6.70)	21.83 (<0.001)	0.13	1.39 (0.24)	—	0.27 (0.60)	—

Notes: Means with standard deviations in parentheses. Age and intelligence score were taken as covariates. [a] HAMD: 16 of 22 participants in G3, and 21 of 37 participants in G4 completed HAMD assessment.
Abbreviations: MDD, major depressive disorder; HC, healthy controls; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; STAI_S, Spielberger State-Trait Anxiety Inventory_State Form; STAI_T, Spielberger State-Trait Anxiety Inventory_Trait Form; TEPS, Temporal Experience of Pleasure Scale; TEPS_ANT, anticipatory subscale; TEPS_CON, consummatory subscale

between the cerebellum and cerebral regions of DMN (eg., middle and inferior temporal gyrus, angular, precuneus), FPN (superior parietal gyrus, dorsal lateral prefrontal cortex), and visual area (occipital cortex, fusiform gyrus) across all cerebellar subunits. Hypoconnectivity within the cerebellum was also observed (eg., crus1 and lobule 8).

No significant diagnosis-cerebellar subunit interactions were observed in both males or females, which suggests that different cerebellar subunits are likely to have similar dysconnectivity pattern in MDD patients, and this similar dysconnectivity pattern across different cerebellar subunits does not differ across sex. Specifically, in MDD patients, all cerebellar subunits except for AUD showed decreased connectivity with temporal cortex (especially inferior and middle temporal gyrus). The VIS, SMN, CON, DAN, FPN, DMN, and MM systems showed decreased connectivity with parietal cortex. Hypoconnectivity with prefrontal cortex was found in cerebellar CON, LAN, FPN, DMN, AUD, and MM systems. The VIS, CON, DAN, and MM exhibited decreased connectivity with visual cortex (occipital cortex and fusiform). Meanwhile, hypoconnectivity within the cerebellum was observed in CON, DAN, LAN, and MM. Details of altered brain regions and their corresponding cerebellar seeds are listed in Table 2 (statistical maps of each cerebellar system, please see Fig. S1). Additional analysis showed that there was no significant difference between MDD patients with medication and those without medication in all cerebellar subunits-whole brain connectivity (see Table S1).

In addition to the effects of diagnosis, we also found the main effects of sex. Increased connectivity was found in females compared to males. The brain regions were observed in superior temporal gyrus, insula, cingulate cortex, as well as inferior frontal gyrus (see Table 2). In the current study, no significant interactive effect of diagnosis by sex on cerebellar-cerebral functional connectivity was observed.

3.3. Correlations between cerebellar dysconnectivity and clinical characteristics

We further tested whether the cerebellar-whole brain connectivity alterations in MDD patients were correlated with clinical characteristics. We did not find significant correlations between illness duration and cerebellar connectivity ($p > 0.05$). For the depressive symptoms, the BDI_anhedonia score was significantly correlated with the connectivity between cerebellar LAN seed and right superior frontal gyrus (DLPFC.R)

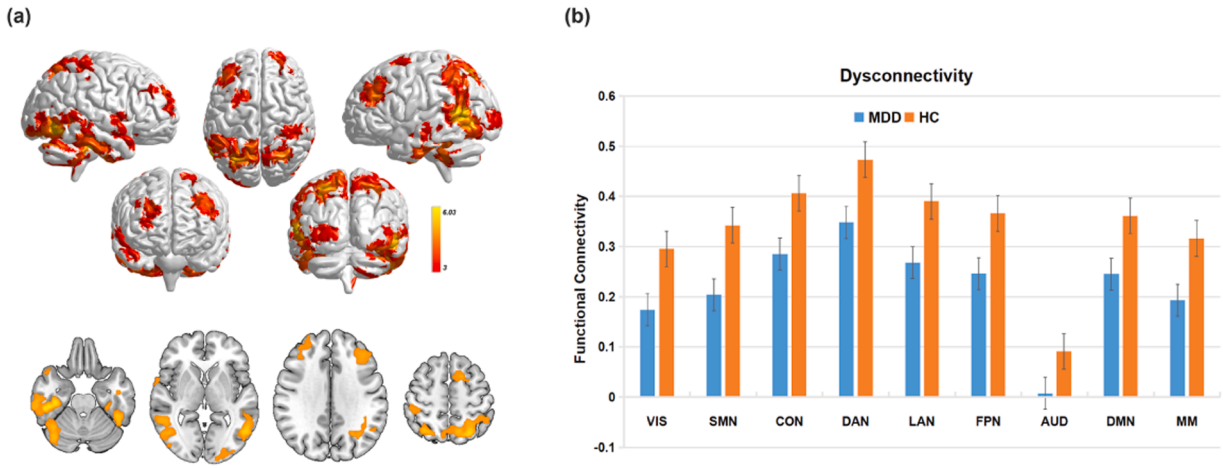

Fig. 2. Main effects of diagnosis of all cerebellar connectivity across nine cerebellar systems. (a) Union regions showing decreased connectivity in MDD patients compared with HC across all cerebellar systems, controlling for age, intelligence score, and FD (FWE corrected $p < 0.05$). (b) Mean connectivity of regions in panel a. VIS, visual; SMN, sensorimotor; CON, cingulo-opercular; DAN, dorsal-attention; LAN, language; FPN, fronto-parietal; AUD, auditory; DMN, default-mode; MM, multimodal.

($r = 0.421$, $p < 0.001$, FDR$q < 0.05$, see Fig. 3) after strict multiple comparisons correction. TEPS total was significantly correlated with cerebellar FPN seed-DLPFC.L connectivity ($r = -0.284$, $p = 0.007$), and with cerebellar DMN seed-DLPFC.L connectivity ($r = -0.297$, $p = 0.005$). TEPS_ANT was also significantly correlated with cerebellar FPN seed-DLPFC.L connectivity ($r = -0.285$, $p = 0.007$), and with cerebellar DMN seed-DLPFC.L connectivity ($r = -0.289$, $p = 0.006$) (see Supplementary Materials, Fig. S2 for scatterplots). However, these correlations did not survive after multiple comparisons correction (all FDR$q > 0.1$). No significant correlations were observed for STAI_T, STAI_S, HAMD, BDI total, cognitive-affective, and somatic scores after multiple comparisons correction (all FDR$q > 0.1$) (for all correlations, please see Supplementary Materials, Table S2).

4. Discussion

In the present study, we systematically examined the patterns of cerebellar functional dysconnectivity in MDD patients by using a novel atlas, providing an overall insight into cerebellar functional abnormalities in MDD at resting state. We found a similar dysconnectivity pattern in MDD across all cerebellar subunits, and not limited to those involved in cognitive and emotional functions. Specifically, compared with HC, MDD patients show decreased cerebellar functional connectivity primarily with the DMN and FPN regions, (such as lateral temporal cortex, angular, parietal cortex, and lateral prefrontal cortex), as well as visual areas (including occipital cortex and fusiform gyrus) Table 4. Decreased connectivity within the cerebellum was also observed. No significantly increased connectivity was found across all cerebellar subunits. Meanwhile, females showed higher cerebellar connectivity with the sensory

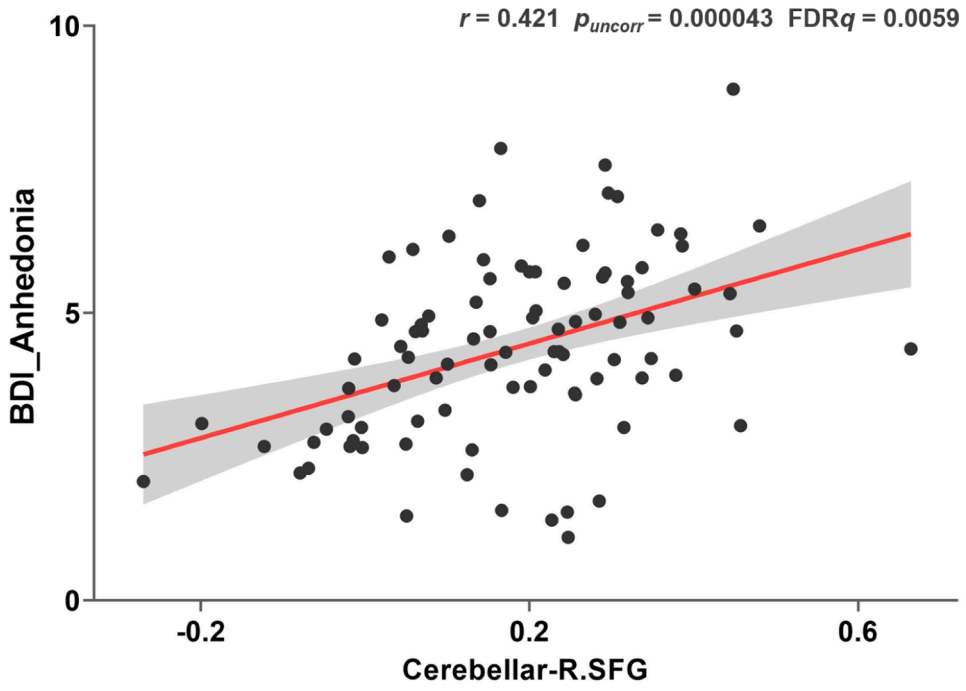

Fig. 3. Partial correlation between cerebellar-right superior frontal gyrus (DLPFC) hypoconnectivity and BDI_anhedonia scores in MDD patients, after controlling for age, gender, and intelligence score.

Table 4
Diagnosis and Sex effects on Cerebellar System-Whole Brain Connectivity.

Brain region	Voxel	MNI coordinate			*Peak T* value	P_{FWE}
		x	*y*	*z*		
Main negative effect of diagnosis (MDD < HC)						
Cerebellar visual system						
R. inferior temporal gyrus, ext. inferior occipital gyrus (BA19/37)	172	51	-63	-6	4.86	< 0.001
R. fusiform, ext. inferior temporal gyrus (BA20)	61	36	-24	-24	4.69	0.048
L. middle temporal gyrus / inferior occipital gyrus (BA19/37)	188	-48	-66	-6	4.60	<0.001
L. superior parietal gyrus / inferior parietal, but supramarginal and angular gyri / precuneus (BA7/40)	290	-27	-63	54	4.50	<0.001
R. angular / superior parietal gyrus (BA7)	82	30	-60	39	4.20	0.015
L. middle occipital gyrus (BA18)	81	-24	-90	3	3.98	0.015
Cerebellar sensorimotor system						
L. middle temporal gyrus (BA21/37)	153	-57	-57	6	5.09	0.001
R. middle / inferior temporal gyrus (BA21/37)	146	51	-60	-6	4.24	0.001
L. superior parietal gyrus / inferior parietal, but supramarginal and angular gyri, ext. middle occipital gyrus (BA7)	158	-27	-63	54	4.18	<0.001
R. superior parietal gyrus, ext. angular (BA7/40)	118	33	-60	54	3.81	0.003
Cerebellar cingulo-opercular system						
R. cerebellum lobe 8, ext. 7b	162	12	-78	-48	6.03	< 0.001
L. middle temporal gyrus (BA37)	163	-57	-57	6	5.35	< 0.001
R. cerebellum lobe 8, ext. 10	109	30	-42	-48	4.97	0.003
L. cerebellum lobe 8, ext. 6, 10	113	-24	-39	-45	4.75	0.003
R. fusiform (BA20)	60	36	-24	-24	4.68	0.048
R. middle / inferior temporal gyrus (BA21/37)	124	48	-57	-6	4.61	0.002
L. superior parietal gyrus / precuneus, ext. middle occipital and inferior parietal, but supramarginal and angular gyri (BA5/7/19)	259	-33	-60	30	4.45	< 0.001
R. inferior temporal gyrus, ext. fusiform (BA20/36)	91	36	-3	-45	4.39	0.008
L. middle frontal gyrus (BA9/45/46)	73	-39	36	27	3.80	0.023
Cerebellar dorsal-attention system						
R. fusiform, ext. cerebellum lobe 8,10 (BA20)	168	36	-24	-24	5.26	< 0.001
R. inferior temporal / occipital gyrus, ext. fusiform, and cerebellum crus1, ext. lobe 6 (BA19/37)	353	39	-75	-21	5.12	< 0.001
L. inferior temporal gyrus / fusiform, ext. cerebellum lobe 6, 10 (BA20/37)	181	-33	-30	-30	4.89	< 0.001
B. precuneus / superior parietal gyrus, ext. R. angular, and L. inferior parietal gyrus, but supramarginal and angular gyri (BA7)	452	33	-63	54	4.75	< 0.001
L. inferior occipital gyrus / middle temporal gyrus (BA19/37)	133	-48	-69	-15	4.42	0.001
Cerebellar language system						
R. cerebellum crus1	61	39	-75	-24	4.46	0.047
R. inferior temporal gyrus, ext. fusiform (BA20)	100	48	-15	-36	4.29	0.005
R. superior frontal gyrus, ext. middle frontal gyrus (BA10/46)	67	27	60	15	3.88	0.033
Cerebellar frontoparietal system						
L. middle frontal gyrus (BA9/44/45/46/48)	245	-36	30	39	5.50	< 0.001
R. middle frontal gyrus (BA44/45/46/48)	101	33	30	30	4.00	0.001
L. inferior parietal gyrus, but supramarginal and angular gyri / angular (BA22, 39, 40)	410	-51	-48	48	4.53	< 0.001
R. inferior temporal gyrus (BA20)	202	63	-27	-30	4.68	< 0.001
L. inferior temporal gyrus (BA20)	65	-45	-15	-30	4.86	0.031
	68	-48	-42	-21	4.82	0.026
Cerebellar auditory system						
L. middle frontal gyrus, ext. superior frontal gyrus (BA6)	74	-24	6	63	4.10	0.015
Cerebellar default-mode system						
R. inferior / middle temporal gyrus (BA20/21)	206	63	-27	-30	5.12	< 0.001
L. inferior / middle temporal gyrus (BA20)	127	-54	-15	-33	4.97	0.001
L. inferior parietal, but supramarginal and angular gyri / angular (BA22/39/40)	125	-51	-48	51	4.15	0.001
L. middle frontal gyrus (BA9/44/46)	65	-36	27	39	4.11	0.033
Cerebellar posterior-multimodal system						
R. fusiform (BA20)	61	45	-30	-24	5.12	0.05
R. inferior / middle / temporal gyrus / inferior occipital gyrus, ext. fusiform, cerebellum crus1, and lobe 6 (BA19/37)	436	39	-78	-21	4.88	< 0.001
L. superior frontal gyrus / supplementary motor area (BA6/32)	105	-12	15	54	4.84	0.005
R. inferior temporal gyrus, ext. fusiform (BA20)	124	48	-18	-36	4.59	0.002
L. middle temporal gyrus (BA21/37)	172	-60	-60	12	4.54	< 0.001
R. postcentral gyrus, ext. inferior parietal, but supramarginal and angular gyri (BA2/3)	117	48	-33	54	4.52	0.003
L. inferior temporal gyrus (BA20/37)	73	-30	-30	-33	4.14	0.025
R. temporal pole: superior temporal gyrus / middle temporal gyrus (BA20/21/38)	85	51	3	-18	3.94	0.013
Main negative effect of sex (Male < Female)						
Cerebellar visual system						
L. superior temporal gyrus / postcentral gyrus (BA22/42/43/48)	136	-48	-30	18	4.39	0.001
R. insula, ext. rolandic operculum (BA48)	89	36	-9	15	4.38	0.010
B. median cingulate and paracingulate gyri / supplementary motor area (BA23/24)	89	-9	-9	48	4.08	0.010
Cerebellar cingulo-opercular system						
L. inferior frontal gyrus, triangular part / opercular part (BA44/45/48)	78	-45	21	15	3.98	0.017
Interactive effect of Diagnosis-by-Sex						
NS						

Notes: the significance level for these brain regions was set at $p < 0.05$, cluster-level FWE corrected with voxel-level starting from $p < 0.001$ uncorrected; age, intelligence score, and FD were taken as covariates.
Abbreviations: BA, Broadmann area; x, y, z, coordinates of peak locations in the Montreal Neurological Institute space (MNI); ext., extending to; L, left hemisphere; R, right hemisphere; B, bilateral hemisphere. NA, no significant.

and emotional processing cortices than males in both MDD and HC, such as postcentral gyrus, insula, and cingulate cortex. However, cerebellar dysconnectivity in MDD patients does not exhibit different patterns by sex. These findings suggest a common connectivity abnormality for the cerebellum in MDD, and cerebellar hypoconnectivity with DMN and FPN may play a crucial role in the neuropathology of MDD.

The current study indicates a common dysconnectivity pattern across different cerebellar systems in MDD patients, suggesting that broad functional disturbances in the entire cerebellum occur in MDD. Anatomical tracing studies have revealed a communication loop between the cerebellum and cerebral cortex (Strick et al., 2009), which provides a possible explanation for this common dysconnectivity. The pontine projections (the key nodes are pontine nuclei and inferior olive) transit almost the entire cerebral cortical signal, including signals from motor areas and prefrontal, parietal, superior temporal, and parahippocampal areas, to the cerebellum (Diedrichsen et al., 2019), and the cerebellar cortex sends its output back to the cerebral cortex via dentate nucleus and thalamus (Dum and Strick, 2003; Kelly and Strick, 2003). Therefore, functional deficits in these key nodes of the cortico-cerebellar loop may lead to generalized dysconnectivity patterns between cerebellum and cerebral cortical, even if in the different cerebellar subunits. Although this is only speculative, a diffusion kurtosis and perfusion imaging study supported this possibility to some extent and revealed that patients with unipolar depression and bipolar disorder during the depressive period showed microstructural abnormalities in the middle cerebellar peduncles, and dentate nuclei of the cerebellum (Zhao et al., 2016), which are the critical structures of cognitive and affective functions related to the prefrontal-thalamic-cerebellar circuit (Buckner, 2013). It should be further clarified whether these brain structures play a certain role in the observed cerebellar dysconnectivity in MDD. In addition, the "Universal Cerebellar Transform (UCT)" theory may also be a possible explanation of observed similar cerebellar dysconnectivity across different cerebellar subunits in MDD, suggesting that these common dysconnectivity patterns may be due to a singular neurobiological dysfunction: Universal Cerebellar Impairment (Guell et al., 2018). The theory of UCT holds that this singular mechanism emerges from essentially uniform cerebellar anatomy but performs its computation on different channels of information processing subserved by anatomically precise connections linking focal cerebellar regions with different cerebral areas. That is, although the cerebellum can be divided into different functional subunits according to different manifestations; they share a common underlying mechanism (Schmahmann, 1991). As a result, the common cerebellar dysconnectivity pattern that we have observed may represent a general dysfunction of cerebellar connectivity based on the common neurobiological process.

The decreased connectivity between the cerebellum and regions of DMN and FPN was observed in the current study, which is consistent with most of the previous studies (Alalade et al., 2011; Guo et al., 2013a, 2013b; Liu et al., 2012; Ma et al., 2013; Zhu et al., 2020). In previous studies, abnormalities of DMN (Sheline et al., 2009; Yan et al., 2019) and FPN (Rogers et al., 2004; Sheline et al., 2010) have also been reported in MDD. The DMN is supposed to play a role in emotional processing, self-referential mental activity, episodic memory retrieval, and internal-directed attention (Raichle, 2015). In the present study, decreased connectivity of the cerebellum with DMN in MDD patients showed primarily in middle and inferior temporal gyrus (lateral temporal cortex, LTC), precuneus, and angular. The temporal lobe has been illustrated to be involved in emotional regulation, memory processing, and social cognition (Beauregard et al., 2006; Gallagher and Frith, 2003), especially, the inferior temporal gyrus was proven to be involved in emotional processing and social cognition (Rolls and Stringer, 2001). Functional abnormalities of temporal gyrus in MDD have been demonstrated in several studies (Cui et al., 2017; Guo et al., 2014), and were thought to play important roles in the pathophysiology of MDD (Yan et al., 2021). Due to the pivotal role of the temporal cortex, it is not surprising that the temporal cortex is the region most widely observed in MDD patients showing decreased coupling to different cerebellar subunits in our study. Relative to the functions of LTC, the precuneus and angular are associated with self-related processes and mentalizing (Nejad et al., 2013; Seghier, 2013). Abnormal functions of precuneus and angular were found in MDD patients, which may be associated with cognitive bias (such as rumination thought and low self-esteem) (Cheng et al., 2018) and deficits of "theory of mind" (Wolkenstein et al., 2011) in MDD patients. Given the multifaceted role of these DMN regions, the observed hypoconnectivity of cerebellar-DMN may be able to interpret the abnormalities of emotional regulation, memory functions, and the impairments in integrating contextual information for self-perception and self-interpretation of the outside world in MDD patients (Lai et al., 2017; Yan et al., 2021).

Decreased connectivity of the cerebellum with FPN regions in MDD patients was also observed in the present study, showing primarily in dorsal lateral prefrontal cortex (DLPFC) and superior parietal gyrus (SPG). FPN contributes to executive control, the ability to deliberately guide action based on goals (Dixon et al., 2018). Abnormal communication within FPN may underlie deficits in cognitive control, which are commonly observed in MDD (Rogers et al., 2004; Stange et al., 2017), especially in DLPFC. As a core region of FPN, DLPFC is another region widely observed in the current study showing decreased connectivity with different cerebellar subunits in MDD patients. DLPFC is a well-acknowledged cognitive control region that is suggested to play a key role in emotion regulation via its interactions with brain regions involved in emotion generation such as the amygdala (Ochsner et al., 2012). Previous studies also suggested that DLPFC is associated with reward processing (Cohen et al., 2009; Staudinger et al., 2011), which is thought to modulate striatal reward encoding during reappraisal of reward anticipation (Staudinger et al., 2011). The abnormal reward processing is the core feature of MDD. In our study, cerebellar LAN system-R.SFG (DLPFC) connectivity was found to be positively correlated with state anhedonia symptoms in MDD patients. The initial correlation analyses also showed negative correlations between TEPS total / TEPS_ANT anticipation pleasure with cerebellar DMN system-DLPFC.L /cerebellar FPN system-DLPFC.L, suggesting its importance in anhedonia of MDD, although they did not survive after multiple comparison corrections. That is, MDD patients with more severe anhedonia showed more "normal" cerebellar-DLPFC connectivity, which may be interpreted as a compensatory mechanism or protective mechanism. A recent study supports this possibility and showed that MDD with severe anhedonia exhibited higher network efficiency of left SFG than MDD with mild anhedonia, suggesting a possibility of a compensatory mechanism (Zhang et al., 2022). Meanwhile, the SPG also plays an important role in many cognitive, perceptive, and motor-related processes (Wang et al., 2015), and was found decreased connectivity with the cerebellum in our study. Therefore, the observed hypoconnectivity of cerebellar-FPN may be able to interpret the abnormalities of cognitive control in MDD patients.

In addition, abnormalities in cerebellar-visual areas (occipital cortex and fusiform) were also observed, especially in fusiform gyrus, which is related to high-level visual functions such as face perception, object recognition, and reading (Weiner and Zilles, 2016). These alterations may be associated with deficits in visual functions of MDD (Chang et al., 2011; Fam et al., 2013). Regions showing decreased FC within the cerebellum are primarily located in posterior lobule (eg., lobe VI, VIIB, VIII, Crus 1), which were considered to be more involved in emotional and cognitive functions rather than motor function (Stoodley and Schmahmann, 2009). The decreased FC within the cerebellum may indicate

reduced or disrupted function in the computation of error or conflict information presented in the cerebellum (Cao et al., 2022). Moreover, contrary to our hypothesis, no significantly increased connectivity was found, which is inconsistent with previous studies that reported both increased and decreased FC (Alalade et al., 2011; Guo et al., 2013a; Liu et al., 2012). As mentioned above, the differences in seed region selection and heterogeneity of patients may partially account for these inconsistencies. In addition, we did not find altered FC of cerebellar and limbic regions, such as amygdala, hippocampus, and ventral striatum. However, a previous study has emphasized that the cerebellum may be involve the modulation of emotional processing through cerebellar-limbic connections (Minichino et al., 2014) to contribute to the neural mechanism of MDD. The possible reason is that cerebellar dysconnectivity with these regions is more sensitive when engaging in tasks, rather than at rest, as found in previous task-state studies (Chantiluke et al., 2012; Dichter et al., 2012). Future work could be performed on task-induced fMRI to fully investigate the matter. Furthermore, the variability in instructions to keep eyes closed or open during rs-fMRI may have also influenced the conflicting results in previous studies. For example, participants in one study (Alalade et al., 2011) were instructed to "rest without moving, keep their eyes open, and focus on a fixation cross presented in the center of the screen inside the scanner". Another study (Liu et al., 2012) asked the participants to "keep their eyes closed and do not think anything", while other studies asked participants to keep their eyes closed but remain awake (Guo et al., 2013a, 2015, 2013b; Ma et al., 2013; Zhu et al., 2020), which is consistent with our study. Numerous studies have proven that different resting conditions (eyes open, eyes closed, or fixated) affect resting-state FC (Fernandez et al., 2022; Han et al., 2023; Patriat et al., 2013), and different instructions ("let your mind wander" or "think of nothing") induce distinct psychological states during fMRI scan (Kawagoe et al., 2018). Although it is difficult to determine whether and how much the different conditions and instructions could account for the conflicting results of the current topic given that there are still different results even if they have the same instruction (keep eyes closed but remains awake), it should be taken seriously, and strictly controlled in further study to eliminate potential confounding effects.

We did not find the effect of sex on cerebellar-cerebral dysconnectivity pattern in MDD patients, suggesting that the disrupted cerebellar-cerebral connectivity pattern was not affected by sex in our sample. However, we only recruited participants who are young adults, it is unclear whether there are sex differences in cerebellar-cerebral dysconnectivity patterns in MDD with other age groups, which should be further investigated in a larger sample. Despite this, we found general sex differences in cerebellar-cerebral connectivity both in MDD patients and HC. Females showed higher FC of cerebellar with insula and regions involving sensory than males, which may be related to higher emotional responses, interoceptive awareness (Menon and Uddin, 2010), and sensitivity to external information (Blankenburg et al., 2011) in females than males. For example, females often show an advantage in tasks that reflect verbal processing, the increased cerebellar-superior temporal gyrus (STG) and left inferior frontal gyrus, triangular part (IFG_{Tri}, is Broca area, and involvement in language processing) may partially account for this difference. Insula involves disparate cognitive, affective, and regulatory functions, including interoceptive awareness, emotional responses, and empathic processes (Menon and Uddin, 2010). Sex difference in insula has been reported in a recent study (Brennan et al., 2021). It is unclear whether the increased connectivity of the cerebellar with insula contributes to higher depression vulnerability in females, which should be proven by establishing a direct link, while the abnormal function of insula has been documented in MDD patients (Li et al., 2017; Namkung et al., 2017), suggesting the difficulties in cognitive and emotional integration in affective disorders (Menon and Uddin, 2010). Although these issues need to be further studied, the observed sex differences of cerebellar-insula connectivity in our study may be interpreted to be associated with the differences in various motivations and drives, as well as emotional and affective experiences between males and females (Khalsa et al., 2018).

Taken together, the current observation of the cerebellar hypoconnectivity in MDD deepens our understanding of the cerebellum's contribution to the pathology of MDD. Cerebellum communicates with various cerebral structures through dentate nuclei in the output loop and pontine nuclei in the input loop (Stoodley and Schmahmann, 2010), and therefore involves motor, emotional, and cognitive functions. Thus, the generalized reduction in FC of the cerebellum with DMN and FPN in MDD may reflect impaired cognitive and emotional processing as well as abnormal communication of cerebellar-cerebral information necessary to guide behavior. Meanwhile, dysconnectivity patterns between the cerebellum and cerebrum did not differ by sex, although there are general sex differences in cerebellar-cerebral communication both in MDD and HC.

Several limitations should be noted concerning our results. First, the current study is a cross-section design, we could not clarify whether this cerebellar dysconnectivity already existed before MDD onset, which limits the determination of causality. Future research would especially benefit from longitudinal design to clarify how the abnormalities of cerebellar-cerebral connectivity contribute to the pathology of MDD. Second, we included medicated patients and the potential effects of antidepressant medications on resting-state brain function are still unclear. Although there is no significant medication effect on cerebellar connectivity (see Supplementary Tables S2) in the present results, the data from drug-naive MDD patients may be valuable to analyze in future studies. Third, even though we only used the "age-adjusted intelligence score" as a covariate to control for potential confounding caused by differences in intelligence levels, rather than used it as an estimation of IQ, it may not be an accurate reflection of premorbid intelligence level since MDD patients have been proven to have to perform worse in some subtests than healthy individuals (e.g., working memory measured by digital span). The more appropriate indexes should be used to construct intelligence scores in future studies. Finally, we only recruited young adult MDD patients, which limits the generalizability of our findings. It should be noticed that growing evidence showed developmental stages' influence brain functions (Song et al., 2012). Thus, the cerebellar dysconnectivity pattern may be different across different age groups, which should be further clarified.

5. Conclusions

In conclusion, the current study used the cutting-edge parcellation atlas of the cerebellum in MDD patients and found a common disrupted connectivity pattern with the cerebrum across all cerebellar subunits, not limited to those involved in cognitive and emotional functions, which are primarily characterized by the decreased coupling of the cerebellum with the DMN, FPN regions of the cerebrum. This dysconnectivity pattern was not affected by sex in the current sample, however, this should be further replicated in larger samples to fully understand the influence of sex. The altered FC of cerebellar-DLPFC was associated with anhedonia symptoms in MDD. The findings of our study draw an in-depth picture of cerebellar dysconnectivity in MDD patients, and provide further evidence for the pivotal role of the disrupted cerebellar-cerebral connection in the neuropathology of depression, especially in the DMN and FPN regions.

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Data availability statement

The data that support the findings of the study are available on

request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CRediT authorship contribution statement

Xiang Wang: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Jie Xia:** Data curation, Writing – review & editing. **Weiyan Wang:** Methodology, Writing – review & editing. **Jingjie Lu:** Data curation, Writing – review & editing. **Qian Liu:** Data curation, Writing – review & editing. **Jie Fan:** Writing – review & editing. **Tamini Soondrum:** Writing – review & editing. **Quanhao Yu:** Data curation. **Changlian Tan:** Conceptualization, Supervision. **Xiongzhao Zhu:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declared no potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115192.

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