THE ROLE OF THE CEREBELLUM IN COGNITION

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THE ROLE OF THE CEREBELLUM IN COGNITION

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Table of Contents

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Changes in Resting-State Functional Connectivity of Cerebellum in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: A Case-Control Study

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This case-control study is aimed to investigate the correlation of altered functional connectivity (FC) in cerebellum with cognitive impairment in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD). The morphometric and resting-state FC MRI analysis including 46 participants with AD, 32 with aMCI and 42 age-matched normal controls (NCs) were conducted. We compared the cerebellar gray matter volume and cerebellar FC with cerebral cortical regions among three groups. To investigate the relationship of cerebellar FC with cognition, we measure the correlation of significant altered FC and individual cognitive domain. No significant morphometric differences of cerebellum was observed across three groups. The patients with AD had weaker cerebral cortical FCs in bilateral Crus I and left VIIb compared to NCs, and in bilateral Crus I compared to patients with aMCI. For patients with aMCI, the weaker FC were found between right Crus I, left VIIb and cerebral cortical regions compared to NCs. The strength of left cerebellar FC positively correlated with specific cognitive subdomains, including memory, executive function, visuospatial function, and global cognition in AD and aMCI. These findings demonstrated the alteration of cerebellar FC with cerebral cortical regions, and the correlation of cerebellar FC and cognitive impairment in AD and aMCI.

Keywords: Alzheimer's disease, amnestic mild cognitive impairment, cerebellum, functional connectivity, resting state fMRI

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, leading to a heavy burden on patients, family and society. The hallmark of the pathology of AD is the deposition of amyloid-β (Aβ) in the cerebrum. The cerebellum has been recognized as essential only for the motor control and being free of Aβ deposition (Guo et al., 2016; Jacobs et al., 2018). Therefore, for a long time, the cerebellum was considered as a "standby" in AD, and was widely used as reference region for the calculation of standardized uptake value ratio (SUVR) in molecular imaging studies (Clark et al., 2011).

However, increasing evidences demonstrate that the cerebellum is also associated with the regulation of cognition by way of the cerebrocerebellar circuits (Schmahmann et al., 2019). With the advancement of staining techniques, pathological studies also found the deposition of Aβ, neurofibrillary tangles and increased microglia on cerebellar cortex in AD (Rudzinski et al., 2008; Sepulveda-Falla et al., 2014). Increasing neuroimaging studies reported the cerebellar atrophy and functional alteration in AD (Bai et al., 2011; Wang et al., 2011; Lou et al., 2015; Mascali et al., 2015; Guo et al., 2016; Jacobs et al., 2018; Olivito et al., 2020). However, till now, the studies about the changes of cerebellum in AD patients are still limited, and results are not consistent. This inconsistency may be due to the poor overlap of cerebellar subregions in parcellation by conventional whole-brain methods. Moreover, most previous studies focused on the relation between cerebellum and global cognitive function, the specific cognitive domain correlates with the alteration of cerebellum remains uncertain. More evidence is needed to illustrate the role of cerebellum in AD.

We hypothesized that altered cerebellar volume and functional connectivity (FC) correlated with cognitive dysfunction, and correlated with cognitive impairment in AD continuum. As amnestic mild cognitive impairment (aMCI) has a high incidence of conversion to AD, aMCI also provides a good model to investigate subtle change at the initial stage of the AD continuum (Petersen et al., 2001). Comparing the change of cerebellum among normal controls (NCs), patients with aMCI and AD, could help us to illustrate the processing of change in different cognitive status. With a cerebellum-specific spatially unbiased infratentorial template (SUIT), we performed voxel-based morphometry (VBM) analysis to compare the cerebellar volume between patients across different cognitively populations, including AD, aMCI and NCs. In addition, we used resting-state functional MRI (rs-fMRI) to investigate the FC between cerebellum and cerebral cortical regions, and the relations between altered FC and specific cognitive domains were calculated.

MATERIALS AND METHODS

Study Design and Participants

This is a retrospective case-control study. Participants were recruited in preparation for this study from the memory clinic of China-Japan Friendship Hospital from 2014 to 2019. Participants with structural and rs-fMRI images were enrolled using the inclusion and exclusion criteria below. Patients with AD met the diagnostic criteria of probable AD dementia according to the new National Institute on Aging-Alzheimer's Association criteria of 2011 (McKhann et al., 2011). The inclusion criteria for AD included: (1) significant episodic memory problems reported by the patient, relative or caregiver, which was corroborated by the score of Rey Auditory Verbal Learning Test (AVLT); (2) impaired performance on general cognition test (Mini-Mental State Examination (MMSE) score < 24) and activities of daily living (ADL); (3) medial temporal lobe atrophy on visual atrophy rating scale (Scheltens et al., 1992). Patients with aMCI participants satisfied with the Petersen's criteria and the National Institute on Aging-Alzheimer's Association criteria for MCI due to AD (van den Burg and Kingma, 1999; Petersen et al., 2014). The inclusion criteria were as follows: (1) memory complaint; (2) scoring lower than 1.5 standard deviations of the age- and education-adjusted norm on the score of AVLT; (3) normal performance on general cognition test (MMSE score $\geq$ 24) and ADL. The NCs included family members of patients, who did not have cognitive complaints or significant decline on the neuropsychological testing, and with MMSE score $\geq$ 24. The NCs were matched with AD and aMCI participants in gender and age.

Exclusion criteria for all participants included: (1) current or previous history of significant neurological disorder that could cause cognitive decline, including stroke, epilepsy, head trauma, intracranial mass or normal pressure hydrocephalus; (2) history of addictions or other psychiatric disorders, including schizophrenia, bipolar disorder or depression; (3) other severe medical problems, including chronic heart failure and chronic respiratory insufficiency; (4) left handed.

Clinical and Neuropsychological Assessment

All participants underwent neurological evaluation and comprehensive neuropsychological assessment. The neuropsychological assessments included general cognitive status and a series of detailed cognitive tests for specific cognitive domains, including memory, language, executive function, attention and visuospatial function (**Supplementary Material 1** provide the details). The *z* score of each cognitive domain and the composite cognitive *z* score (average of the five individual cognitive domains) were computed based on normative data from 114 healthy control participants with similar age, education, and gender distribution (age: 69.8 $\pm$ 6.4; Male/Female: 47/67, education 14.8 $\pm$ 2.8 years, no history of neurological or psychiatric illness) in our center. Neuropsychiatric symptoms and functional impairment were assessed by caregiver-based questionnaires: Neuropsychiatric Inventory (NPI) and ADL, respectively (Cummings, 1997). The APOE genotype was determined from genotyping of isolated DNA from blood. The participants who had at least 1 APOE ε4 allele were considered as APOE ε4 carriers.

MRI Data Acquisition and Preprocessing

The rs-fMRI images and T1-weighted MRI images were acquired using a 3.0 T MR imaging system (GE Healthcare, Discovery MR750, Milwaukee, WI, United States) in the Radiology Department of China-Japan Friendship Hospital. The parameters of sagittal three-dimensional T1-weighted images with fast spoiled gradient-echo sequences (FSPGR) were as follows: echo time (TE) = 3.0 ms, repetition time (TR) = 6.9 ms, slice thickness = 1.0 mm, FOV = 256 mm × 256 mm, acquisition matrix = 256 × 256, and flip angle = 12°. The parameters of axial resting-state data were as follows: TE = 30 ms, TR = 2,000 ms, slice thickness = 3.0 mm, 33 slices, field of view (FOV) = 240 mm × 240 mm, in plane matrix = 64 × 64, flip angle = 90°, and 240 phases.

Structural three-dimensional (3-D) T1 images were first processed using the SUIT toolbox[1] implemented in the Statistical Parametric Mapping software version 12 (SPM12)[2] toolbox (Diedrichsen et al., 2009). Each cerebellum was separated by a Bayesian algorithm into gray matter (GM) and white matter (WM), normalized to the Montreal Neurological Institute (MNI) space using the high-resolution probability template in SUIT. The intensity of each voxel was modulated to conserve the regional differences in the total amount of GM. All the images were smoothed with a 4-mm full-width at half-maximum (FWHM) Gaussian kernel.

The rs-fMRIs were preprocessed with the Data Processing Assistant for Resting-State fMRI (DPARSF) and the Resting-State fMRI Data Analysis Toolkit (REST). First, the first 10 volumes were discarded for the signal equilibrium and adaptation of subjects to the scanning noise. The remaining 230 volumes were corrected for timing difference and realigned to the first volume to correct for possible movement. The frame-wise displacement (FD) (Jenkinson) was calculated to evaluate the mismatch of volume-to-volume superimposed head position. The mean FD for the all the participants were 0.21 ± 0.14 mm. The data of 6 subjects (4 AD, and 2 NC) were excluded in this step due to excessive head motion (greater than 2.5 mm, greater than 2.5° angular rotation or mean FD > mean FD + 2SD). After removing the 6 subjects, the FD showed no significant different among the different groups (AD: 0.19 ± 0.09 mm, aMCI: 0.18 ± 012 mm; NC: 0.19 ± 0.09 mm, F-value estimated by one-way ANOVA was 0.45, $p = 0.64$). To normalize the resting images, the T1 images were registered to their corresponding functional images and were then segmented into GM, WM, and cerebrospinal fluid tissue (CSF) probabilistic maps using a unified segmentation algorithm. Second, a GM population template was derived from the whole image data set with the DARTEL technique. Third, non-linear warping of the segmented images was then performed to match the MNI space DARTEL template. Spatial smoothing was then performed with an isotropic 4-mm FWHM Gaussian kernel. Next, linear detrending and temporal band-pass filtering (0.01–0.1 Hz) were applied to remove low-frequency drifts and high-frequency noise. Finally, the nuisance variables (including 6 head motion parameters and their derivatives, the WM and CSF signal, and the linear term) were regressed out.

Seed ROIs

Previous studies revealed that the posterior lobe (VI, VIIb, VIII), ansiform lobe (Crus I, Crus II), and flocculonodular lobe (IX, X) of cerebellum are especially associated with cognition (Barton and Harvey, 2000; Whiting and Barton, 2003; Prevosto et al., 2010; Stoodley and Schmahmann, 2010). Therefore, these lobules were included as seed ROIs. The masks of these ROIs were extracted from the probabilistic cerebellar atlas used in SUIT (Diedrichsen et al., 2009; **Figure 1**). For each participant, the voxel of each seed was extracted to obtain the average seed point time series. A correlation coefficient map for each seed was produced by correlating the coefficients between the reference time series and the time series from all other brain voxels, which was then transformed to Fisher z-values.

Statistical Analysis

Data were analyzed using SPSS 22.0 (IBM Corp., Chicago, IL, United States). Demographic and clinical variables were checked for normality of distribution using Kolmogorov–Smirnov tests. Variables revealing normal distribution were compared across groups via ANOVA followed by Bonferroni *post hoc* tests if ANOVA was significant ($p < 0.05$). Group comparisons of NPI and ADL between AD and aMCI were performed using Student's t test. Gender and ApoE4 status data were analyzed using a Chi-square test. $p < 0.05$ was regarded as significant.

The resulting images were subsequently entered into a VBM analysis to perform the one-way ANOVAs to identify differences among groups in the cerebellum. Age, gender, and total intracranial volume were included as nuisance covariates. Statistical analyses were performed on smoothed GM maps within the framework of the general linear model. A one-way ANOVA model was used for assessing between group differences in regional GM cerebellar volumes. Age, sex, and years of education were included as covariates in our analysis.

ANOVA analysis was used to compare the whole-brain FC of each seed among the three different groups. The age, gender, education level, head movement parameters, and total intracranial volume were used as covariates. False discovery rate (FDR) correction was performed with a threshold of 0.05. The z-values of FC were extracted to perform the *post hoc t* test in order to identify the inter-group differences between AD and NC, aMCI and NC, and aMCI and AD. Bonferroni correction was performed to adjust for the multiple testing, with a p value of <0.0167 (0.05/3) considered statistically significant for these comparisons.

Due to the small sample size of individual group, we combined the patients with aMCI and AD together to investigate the association between all the significant different FC and the five individual cognitive subdomain. When combined aMCI and AD groups together, the z scores of each cognitive subdomain did not present a normal distribution (Shapiro-Wilk test, $p < 0.05$), therefore, the Spearman's correlation was used. The Bonferroni correction was used for multiple comparisons correction with $p < 0.01$ (0.05/5) was considered significant.

Confirmatory Analysis Based on the ADNI Dataset

The Alzheimer's disease Neuroimaging Initiative (ADNI) database[3] was used to verify the results obtained from our data. Participants who with availability of T1-weighted MRI and rs-fMRI images were selected in the confirmatory study. The T1-weighted MRI images were performed as follows TE = 3.13 ms, TR = 6.77 ms, voxel size = 1 mm isotropic, FOV = 256 mm × 256 mm, acquisition matrix = 256 × 256. The parameters of rs-fMRI data were as follows: TE = 30 ms,

[1] http://www.diedrichsenlab.org/imaging/suit.htm

[2] http://www.fil.ion.ucl.ac.uk/spm/

[3] adni.loni.usc.edu

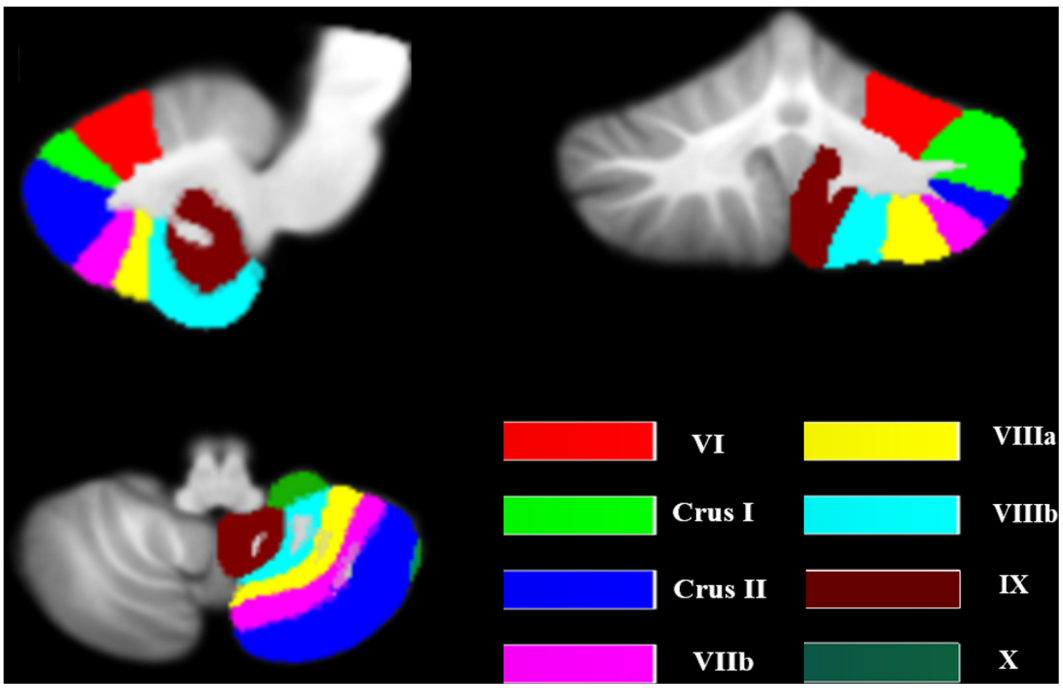

FIGURE 1 | The seeds of the cerebellum. The image was transformed into the space of the SUIT atlas and was overlapped by the seeds. The different colors show the lobular parcellation.

TR = 3,000 ms, 48 slices, voxel size = 3.3125 mm isotropic, FOV = 256 mm × 256 mm, and 140 phases. The full details of imaging data[4] can be found on the ADNI web site. 189 participants were recruited, however, 11 participants were excluded because of the poor quality of rs-fMRI data or excessive head motion. Finally, subjects with AD (n = 54), MCI (n = 57) and NC (n = 67) were selected. Details of the diagnostic criteria were from the ADNI web site[5].

RESULTS

Demographic and Neuropsychological Results

From June 2014 to June 2019, we recruited 46 subjects with AD, 32 aMCI, and 42 NCs with the aforementioned procedures (**Figure 2**). **Table 1** shows the clinical and neuropsychological data. No significant differences in age, gender and education level. Regarding the cognitive performance, the AD group had significantly lower scores than both the aMCI and NC groups on general cognitive test and all the cognitive subdomains except attention. aMCI subjects had significantly lower score on memory, language and executive function than NC subjects. The patients with AD scored significantly higher score on the ADL and NPI compared to patients with aMCI.

[4]http://adni.loni.usc.edu/methods/documents/mri-protocols

[5]http://www.adni-info.org/Scientists/AboutADNI.aspx

Cerebellar Morphometry

No significant group difference in volume of any cerebellar lobular was found among three groups with predefined threshold.

Seed-Based FC

Table 2 and **Figure 3** illustrate the significant difference clusters in the FC for each seed among three groups. The patients with AD had weaker cerebral cortical FCs in bilateral Crus I, left VIIb compared to NCs. The weakened cerebellar FCs with visual cortex [Brodmann area, (BA) 18, 19), including precuneus and cuneus, were found in left VIIb and IX in AD. The left Crus I in AD had weaker correlations with dorsal lateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex (ACC) (BA 9, 32, 45, 46). The weakened correlations with associative visual cortex (ASC), fusiform gyrus (FG) and middle temporal gyrus (MTG) (BA19, 21, 37) were found in right Crus I. Among cerebral cortical FCs mentioned above, the weakened FCs in bilateral Crus I still showed significant compared to patients with aMCI. For patients with aMCI, the right Crus I, and Left VIIb and IX was found with significantly weaker cerebral cortical FC compared to NCs.

Cerebral cortical FC in other seeds of cerebellum was not significantly different among three groups.

Cognitive Correlations of Cerebellar FC

Cognitive correlates of the FC findings in patients with AD and aMCI were investigated for all reported significant cerebellar-cerebral cortical FCs after controlling for age, gender and education (**Table 3** and **Figure 4**). For left Crus I,

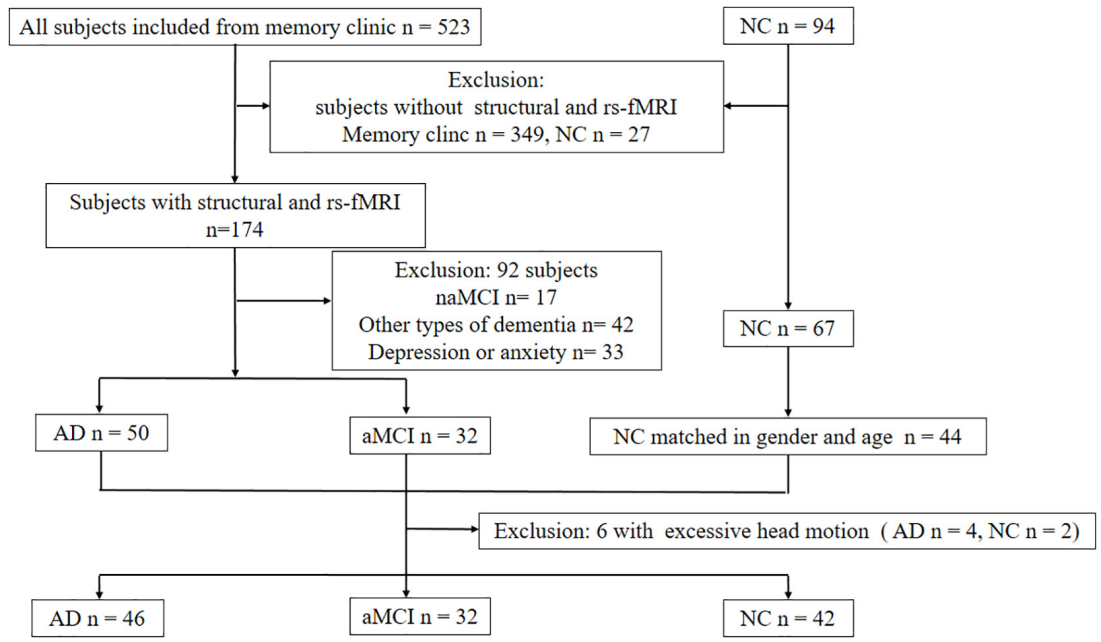

FIGURE 2 | Diagram showing the number and flow of subjects in this study. Abbreviations: NC: normal control; aMCI: amnestic mild cognitive impairment; naMCI: non-amnestic mild cognitive impairment; rs-fMRI: resting-state functional MRI.

TABLE 1 | Demographic and neuropsychological data.

	Normal controls	Amnestic MCI	Alzheimer's disease	*p* (ANOVA)
N	42	32	46	
Age, years	69.86 ± 6.66	70.84 ± 7.54	73.17 ± 7.09	0.083
Gender (Male,%)[4]	18 (42.86%)	16 (50.0%)	19 (41.30%)	0.732
Education, years	14.35 ± 3.05	13.68 ± 3.43	12.74 ± 4.32	0.153
MMSE	29.29 ± 0.86	26.16 ± 1.65	18.52 ± 3.48	<0.001[1, 2, 3]
MoCA	27.09 ± 1.48	21.72 ± 2.87	14.02 ± 4.26	<0.001[1, 2, 3]
NPI[5]	-	6.41 ± 5.21	12.17 ± 11.99	0.013
ADL[5]	-	23.59 ± 3.43	34.02 ± 8.37	<0.001
APOE ε4 carrier (n,%)[4]	11 (23.81%)	18 (59.38%)	29 (63.04%)	<0.001
Composite cognitive z score	0.04 ± 0.44	−1.03 ± 0.73	−2.02 ± 1.01	<0.001[1, 2, 3]
z-memory	0.12 ± 0.71	−2.10 ± 0.49	−2.70 ± 0.83	<0.001[1, 2, 3]
z-language	0.26 ± 0.62	−1.29 ± 1.28	−2.00 ± 1.13	<0.001[1, 2, 3]
z-executive function	−0.05 ± 0.76	−0.62 ± 1.31	−1.16 ± 1.01	<0.001[1,3]
z-attention	−0.07 ± 0.95	−0.30 ± 1.32	−0.63 ± 1.03	0.053
z-visuospatial	−0.10 ± 0.86	−0.85 ± 1.12	−3.21 ± 2.43	<0.001[1, 3]

MMSE, mini-mental status examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; ADL, Activity of Daily Living.
(1). Post hoc analysis showed significant group differences between NC and AD.
(2). Post hoc analysis showed significant group differences between NC and aMCI.
(3). Post hoc analysis showed significant group differences between aMCI and AD.
(4). Values were mean ± standard deviation. Comparisons using Chi-square test.
(5). Values were mean ± standard deviation (sd). Comparisons using Student's t test.

the strength of FC with left DLPFC and ACC (BA 9, 32), positively correlated with executive function and visuospatial function (**Figures 4A,B**). The strength of FC between left Crus I and right DLPFC and IFG (BA 45, 46) correlated with global cognition, executive function and visuospatial function (**Figures 4C-E**). The FC of right Crus I with left ASC and FG correlated with memory (**Figure 4F**). No significant correlation with other cognitive subdomain was found. In the cerebral cortical FC with Left VII, IX, no significant correlation was found with individual cognitive domain and global cognition. The correlation for aMCI and AD subgroup is detailed in **Supplementary Table 2**.

TABLE 2 | Brain regions showing significant differences during one-way ANOVA on *z* value of functional connectivity maps of NC, aMCI, and AD groups.

Seed	Cluster voxels	Brain regions	Laterality	BA	MNI coordinate			Maxi-mum *F*
					x	*y*	*z*	
Left VIIb	13	Visual cortex (Pcu and Cu)	Right	18, 19	9	−84	27	18.24
Left Crus I	44	DLPFC and IFG	Right	45, 46	42	42	18	17.29
	19	DLPFC and ACC	Left	9, 32	−6	48	33	17.23
Right Crus I	23	MTG and FG	Right	21, 37	−45	−69	−12	25.18
	15	ASC and FG	Left	19, 37	60	−57	6	24.62

BA, Brodamann area; PCu, precuneus; Cu, cuneus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; MTG, middle temporal gyrus; FG, fusiform gyrus; ASC, associative visual cortex.

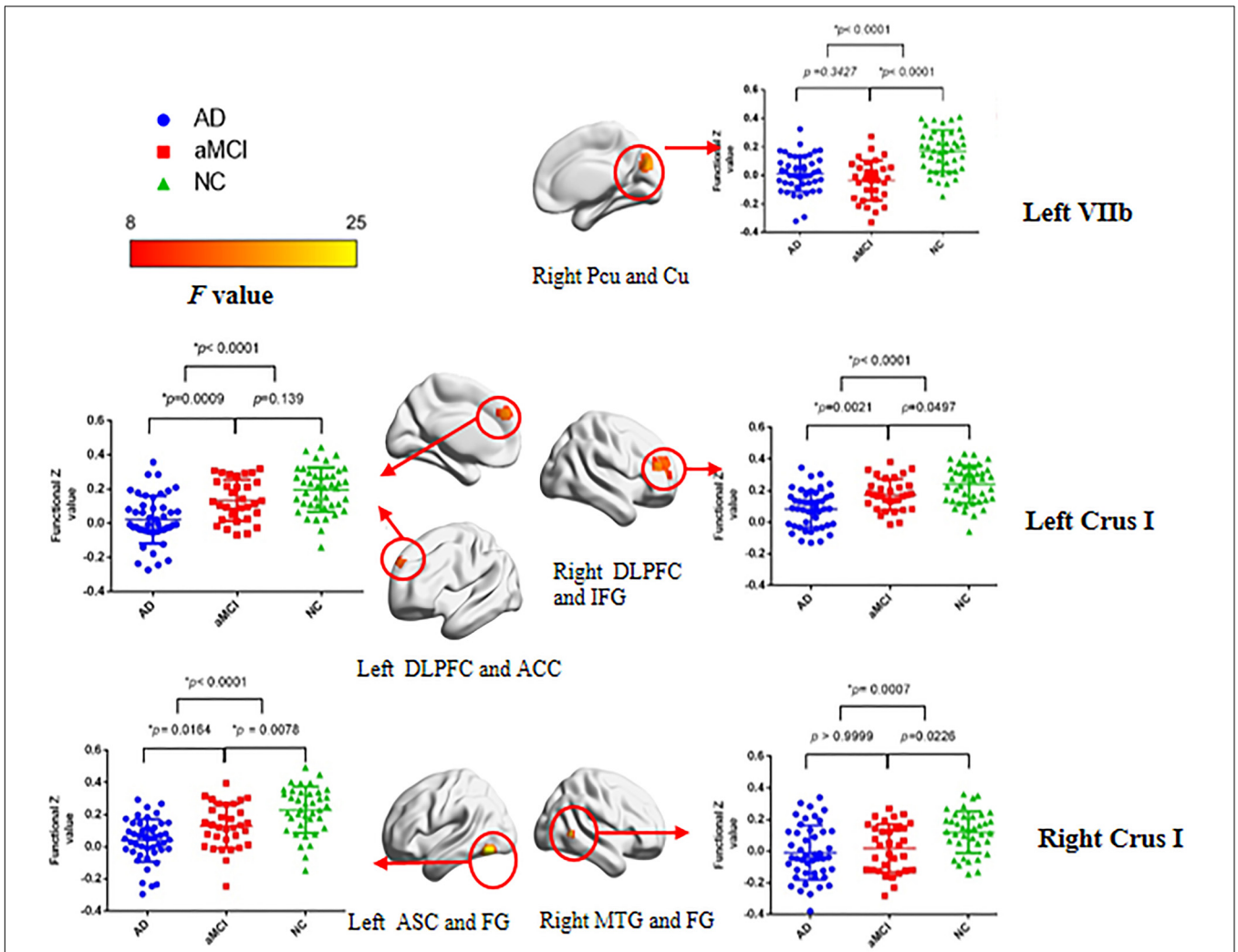

FIGURE 3 | Statistical parametric map and the scatterplot of the significant cerebral cortical clusters among three groups and the *post hoc* analysis between groups. Each row corresponds to a distinct cerebellar lobular seed region of interest. The difference remained significant after Bonferroni correction at *post hoc* analysis. Color bar represents *F* values. BrainNet Viewer (Beijing Normal University, http://www.nitrc.org/projects/bnv/) was used for the visualization of the results. L, left; R, right; Bi, bilateral; PCu, precuneus; Cu, cuneus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; ASC, associative visual cortex; MTG, middle temporal gyrus; FG, fusiform gyrus.

TABLE 3 | Spearman Correlation between cognition and cerebellar FC.

BA			Composite *z* score	Memory *z* score	Language *z* score	Executive *z* score	Attention *z* score	Visuospatial *z* score
Left VIIb	Right BA 18, 19	*r*	0.018	0.010	−0.085	0.057	−0.070	0.062
		p	0.876	0.930	0.457	0.619	0.548	0.594
Left Crus I	Left BA 9,32	*r*	0.270	0.159	0.161	**0.301***	0.094	**0.327***
		p	0.017	0.164	0.159	**0.007**	0.415	**0.004**
	Right BA 45, 46	*r*	**0.320***	0.191	0.252	**0.314***	0.054	**0.387***
		p	**0.004**	0.093	0.026	**0.005**	0.644	**0.001**
Right Crus I	Left BA 19, 37	*r*	0.204	**0.397***	0.272	0.241	0.095	−0.030
		p	0.073	**0.000**	0.016	0.034	0.413	0.795
	Right BA 21, 37	*r*	0.138	0.233	0.143	0.116	0.144	0.030
		p	0.230	0.040	0.213	0.313	0.213	0.794

*BA, Brodamann area. Bold and * means $p < 0.05$.*

Results of the Confirmatory Analysis on the ADNI Dataset

Results of the ADNI data showed similarities and differences with those obtained from our sample.

In the VBM analysis, compared with the NC group, the AD and aMCI groups had significant gray matter volume reduction in the left Crus I/II, and there is no difference between the AD and aMCI group (NC > AD: $p < 0.001$; NC > aMCI: $p < 0.001$; aMCI > AD: $p = 0.059$). **Supplementary Table 3** and **Supplementary Figure 1** show the details.

The seed-based FC analysis based on ADNI database showed that the cortical FC in left IX, left Crus I and bilateral Crus II are involved in aMCI group, with a later involvement of the right X lobe in AD group only. Similar to our sample, the weakened cortical cerebellar FCs involved left DLPFC, FG, bilateral precuneus and cuneus. Details are illustrated in **Supplementary Table 4** and **Supplementary Figures 2–5**.

DISCUSSION

This case-control study investigated the cerebellar anatomic and functional changes across three different cognitive status, including the NC, aMCI, and AD group. The strength of cerebellar FC with cerebral cortical areas were different among three groups, and it correlated with cognitive function in AD and aMCI. The results from ADNI cohort partially confirmed these findings.

The weakened FC was found between the left VIIb and contralateral precuneus and cuneus in AD. Precuneus is one of the core regions of default mode network (DMN) (Buckner et al., 2008). Aβ accumulation preferentially starts in several of the core regions of the DMN, including the precuneus at the early stage of AD (Palmqvist et al., 2017). From the perspective of clinical symptoms, the DMN has been found to be related to episodic memory in AD (Buckner et al., 2008; Sperling et al., 2009). Failure to detect the correlation with the cognitive performance, especially with the memory, could be due to the restricted range of this dependent variable in our aMCI cohort.

Compared to NC, the aMCI and AD group showed weaker FC of the left Crus I correlated with frontal lobe (bilateral DLPFC, left ACC and right IFG), while right Crus I with occipital and temporal lobule (bilateral FG, left ASC and right MTG). The role of Crus I in working memory, planning and organization have been highlighted by functional imaging studies (Buckner, 2013). In addition, the role of DLPFC in executive function had been clearly established. This is consistent with our result that the FC between left Crus I and bilateral DLPFC correlated with execution. Previous fMRI also demonstrated the crossed cerebro-cerebellar projections, language is heavily right lateralized and visuospatial function left lateralized. Interestingly, in this study, we found similar lateralization in Crus I, as the FC of left Crus I connected with the execution and visuospatial function, and right Crus I connected with the memory and language.

Crossed cerebellar diaschisis (CCD) is the remote effect of supratentorial dysfunction in the unilateral hemisphere inducing contralateral cerebellar hypometabolism (Lin, 1997), which could explain the weakened FC between cerebellum and cerebrum. The mechanism of CCD include the involvement of cortico-ponto-cerebellar and the cerebello-thalamo-cortical circuits (Dum and Strick, 2003; Di Lorenzo et al., 2013). Using diffuse tension imaging (DTI), Sofia Toniolo et al. provide the evidence of the impairment of microstructural fiber integrity of cerebellum WM tracts in AD (Toniolo et al., 2020). However, whether the focal change in the cerebellum is a form of Wallerian degeneration or the result of accumulation of AD pathological substrates in the cerebellum itself is still unknown. In this study, we did not find morphometric difference in any of the observed cerebral cortical regions across the three groups, also implicating altered FC could be due to the dysfunction of neurotransmitter or network connection, instead of being secondary to the atrophy.

In this study, we did not find significant differences in volumes of any cerebellar lobular in AD or aMCI group from the data of our center, though the results based on ADNI database showed the GM volume loss in left Crus I/II. The smaller sample size and the younger age of our cohort might account for the discrepancy. Using the SUIT template for cerebellar VBM parcellation, which is the same method as our study, Sofia Toniolo et al. also reported a progression of cerebellar GM volume loss throughout a continuous spectrum from aMCI stage to AD stage (Toniolo et al., 2018).

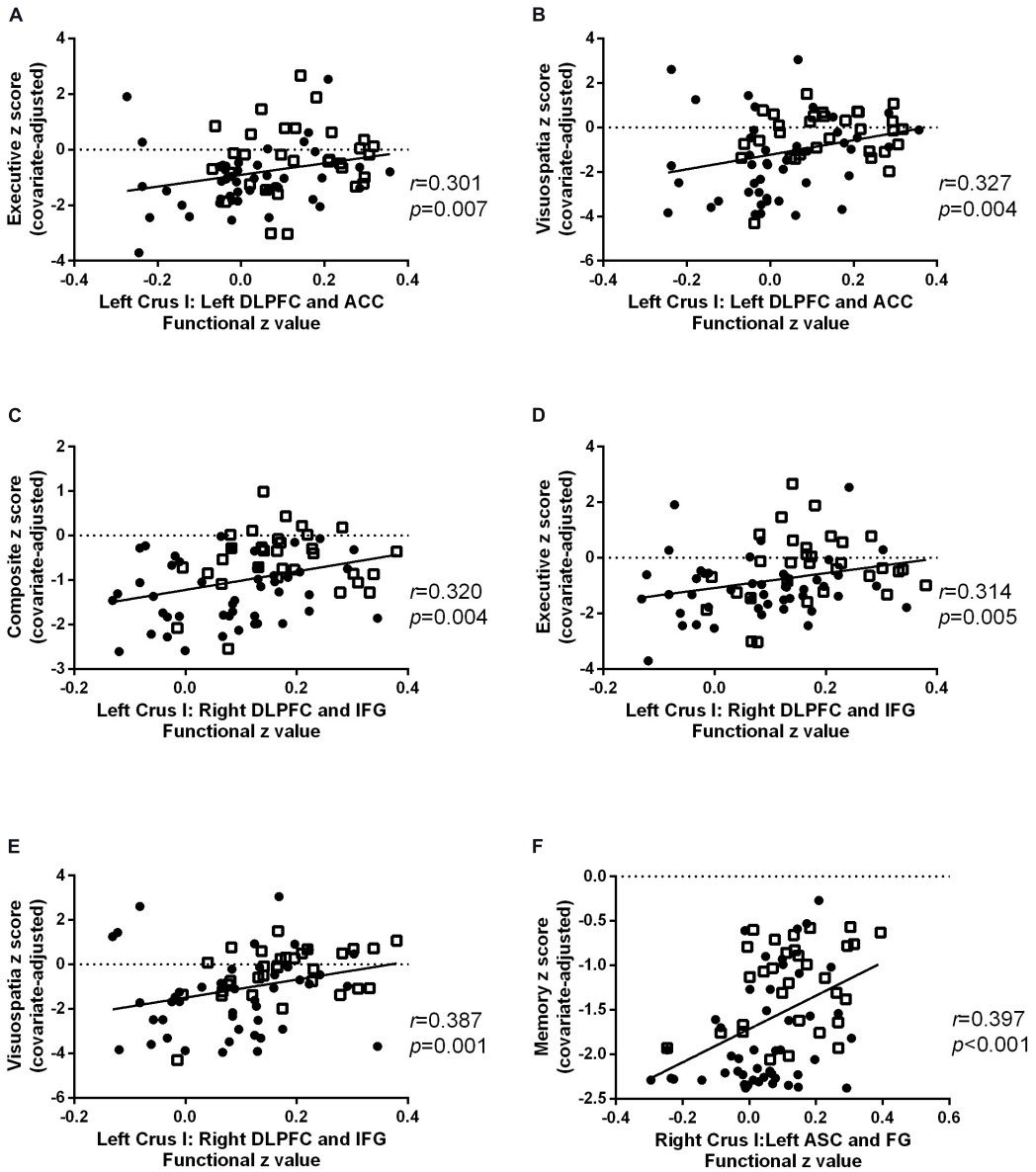

FIGURE 4 | Scatter plots for the significant cognitive-functional connectivity (FC) correlations in Alzheimer's disease (AD) (circles) and amnestic mild cognitive impairment (aMCI) (squares). The strength of FC with left dorsolateral prefrontal cortex (DLPFC) and inferior frontal gyrus (IFG) positively correlated with **(A)** executive and **(B)** visuospatial function. The FC of left Crus I and correlated with **(C)** global cognition, **(D)** executive function, and **(E)** visuospatial function. The FC of right Crus I with left associative visual cortex (ASC) and fusiform gyrus (FG) positively correlated with memory **(F)**.

To investigate the mechanism of cerebellar involvement in AD and aMCI is important for the diagnosis and treatment. Recent strategies of diagnosis and treatment for AD continuum are based on identification and quantification of the pathological biomarkers. Molecular neuroimaging study with selective radioligands, including Aβ and phosphorylated tau, is an important method for the quantification of these biomarkers (Jack et al., 2018). The most used parameter is the SUVR between a target region and a reference region (Fleisher et al., 2011). The selection of reference region directly affects the value of SUVR, which therefore is important for the diagnosis. The cerebellum has been the most widely used reference region in AD (Clark et al., 2011; Maass et al., 2017; Stern et al., 2019). However, if the cerebellum is involved in the pathogenesis of AD continuum, it may not be an optimal choice for the reference region. Furthermore, using the repetitive transcranial magnetic stimulation (rTMS) of cerebellum, Di Lorenzo et al. (2020) revealed the impairment of cerebellar-cortical plasticity by showing the long term potentiation (LTP) was impaired in AD patients. For the treatment, as the cerebellum is easily accessible with non-invasive stimulation tools, it may be used as a novel target for neuromodulation in AD in the future.

There are some limitations to this study. First, as a retrospective case-control study, the identification of the aMCI and AD groups was not based on pathological evidence, such as Aβ PET, which is still expensive for some patients in China. However, in this study, the prevalence of APOE ε4 carriers in AD and aMCI was 61.70 and 59.38%, respectively, which is similar to that of a previous study with large sample of Aβ biomarker positive individuals (66% in AD and 64% in MCI) (Mattsson et al., 2018). Second, though we included the aMCI group as the prodromal stage of AD, this was still a cross-sectional study. In the future, longitudinal studies are needed to investigate the dynamic changes in the cerebellum throughout disease progression.

CONCLUSION

In conclusion, these findings suggest the functional changes of the cerebellum indicating the critical role cerebellum in the cognitive impairment in aMCI and AD. This was important because using the cerebellum as the reference region for ligand neuroimaging studies could bring the possible biased results.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://dx.doi.org/10.17632/tc7xmjbmfw.3.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committees of China-Japan Friendship Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DP: conceptualization. ZZ, WS, and LW: methodology. ZZ, RZ, SZ, LW, and XD: formal analysis and investigation. ZZ: writing – original draft preparation. RZ and DP: writing – review and editing. DP: funding acquisition and supervision. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnsys.2021.596221/full#supplementary-material

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frontiers in Systems Neuroscience

REVIEW
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Functional Connectivity of the Cognitive Cerebellum

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Anatomical tracing, human clinical data, and stimulation functional imaging have firmly established the major role of the (neo-)cerebellum in cognition and emotion. Telencephalization characterized by the great expansion of associative cortices, especially the prefrontal one, has been associated with parallel expansion of the neocerebellar cortex, especially the lobule VII, and by an increased number of interconnections between these two cortical structures. These anatomical modifications underlie the implication of the neocerebellum in cognitive control of complex motor and non-motor tasks. In humans, resting state functional connectivity has been used to determine a thorough anatomo-functional parcellation of the neocerebellum. This technique has identified central networks involving the neocerebellum and subserving its cognitive function. Neocerebellum participates in all intrinsic connected networks such as central executive, default mode, salience, dorsal and ventral attentional, and language-dedicated networks. The central executive network constitutes the main circuit represented within the neocerebellar cortex. Cerebellar zones devoted to these intrinsic networks appear multiple, interdigitated, and spatially ordered in three gradients. Such complex neocerebellar organization enables the neocerebellum to monitor and synchronize the main networks involved in cognition and emotion, likely by computing internal models.

Keywords: neocerebellum, crus 1–2, cognition, functional connectivity, resting-state, intrinsic networks

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INTRODUCTION

The cerebellum has been classically involved in sensorimotor planning, execution, control, automation, and learning. However, in the last 30 years, a growing number of studies has broadened its role to cognitive and emotional processing. Anatomical tracing in monkeys showing cerebellum interconnections between neocerebellum and associative brain areas organized in closed loops (Schmahmann and Pandya, 1997; Strick et al., 2009) in agreement with human tractograms reviewed in Habas and Manto (2018), human clinical studies leading to the description of a "cerebellar cognitive affective syndrome" (Schmahmann and Sherman, 1998), and activation functional MRI (Stoodley et al., 2012; Stoodley and Schmahmann, 2018) have firmly supported the enlarged functional implication of the cerebellum in cognition. Moreover, from a phylogenetical standpoint, increased neocerebellar (posterior lobule) volume (MacLeod et al., 2003) and folding

(Sereno et al., 2020), as well as an increased number of associative, mainly prefrontal, cerebello-cortical connections have been observed during the macroevolution history from great apes to humans (Ramnani et al., 2006; Balsters et al., 2010; Smaers, 2014). In other words, the neocerebellar expansion (lobules VII–VIII, especially crus 1–2) is parallel to the associative, mainly prefrontal, expansion in hominoids and humans.

In humans, two complementary imaging methods have been applied to delineate the cerebellar networks subserving cognitive functions. As mentioned above, diffusion imaging coupled with tractography strove to identify neocerebellar afferents and efferents connecting the cerebellum with associative cortices, thalamus, and striatum. The second method, on which we will exclusively focus, consists in determining the brain "resting-state" static and dynamic functional connectivity (rssFC). These methods allowed identifying the associative cortices functionally connected with the neocerebellum, and the whole network the neocerebellum takes part in.

FUNCTIONAL CONNECTIVITY METHODS

"Resting-state" static and dynamic functional connectivity detects temporal correlations between spontaneous BOLD signal fluctuations in a specific frequency domain (0.01–0.1 Hz) across brain areas belonging to specific—genetically prewired—networks during the brain "resting state." Several algorithms (Bastos and Schoffelen, 2016) have been utilized to determine cerebellar rssFC, such as correlational, independent component, amplitude of low-frequency fluctuations, and regional homogeneity analyses. The most widely used ones are the seed-based correlational analysis and independent component analysis (ICA). The first method computes the r Pearson correlation coefficient between the BOLD time-series of a region of interest (ROI) and the time-series of the rest of the brain. It generates a specific temporal correlational map between the ROI and the functional interconnected brain areas. The second method consists of an exploratory multivariate data-driven approach. ICA decomposes the MRI dataset into statistically independent spatial maps, part of which can represent distinct large-scale networks whose neural nodes exhibit synchronized activity. The other part corresponds to different kinds of noise such as head or eye movements, breathing, heart rate, or spinal fluid pulsation. rssFC studies have identified the associative brain areas specifically connected with the neocerebellum, using seed-based method, and allowed to group these areas in functional networks, called intrinsically connected networks (ICNs), using ICA. However, these methods assume a stationary resting-state brain activity across the whole MRI exam and, thus, fail to describe the temporal dynamics of network recruitment. Dynamic functional connectivity methods have been developed to overcome this important limitation (Hutchison et al., 2013) such as the sliding window, time-frequency, paradigm-/parameter-free mapping, coactivation patterns (CAPs), or innovation-driven coactivation pattern (iCAP) methods (Preti et al., 2017). Put in a nutshell, the former technique relies on the segmentation of the BOLD time series in intervals of equal duration (usually around 30 s). Functional connectivity is then calculated for each interval separately, highlighting the temporal evolution of within- and between-network reconfiguration. Conversely, the CAP method associated with K-mean clustering consists in a point process analysis tracking brief (around 5–10 s) recurring coactivation or co-deactivation patterns by computing the rate of BOLD peaks or trough co-occurrence between an ROI and the rest of the brain voxels. In addition, the iCAP method specifically deals with transient encoding, in the BOLD fluctuations, onsets of network (de-)activations (Karahanoğlu and Van De Ville, 2015). All these methods permit to capture time-varying states characterized by synchronized networks and to quantify their duration (dwell time), the frequency of their occurrence, and the frequency of state-to-state transitions. Dynamic functional connectivity studies revealed that resting-state brain activity is a highly non-stationary process characterized by dynamic within- and across-network reconfiguration into recurring, sometimes overlapping, patterns (CAPs) and correlated with specific phases of the spontaneous low-frequency BOLD signal (Gutierrez-Barragan et al., 2019).

FUNCTIONAL CONNECTIVITY AND GRAPH ANALYSIS

Graph analysis can be applied to functional connectivity in order to decipher network topological organization (Bullmore and Sporns, 2009). Brain circuits are regarded as graphs composed of a set of nodes (brain areas) interconnected by edges (functional and/or structural links). An edge between region A and region B is said to be "oriented or directed" if A exerts a causal effect on B (effective connectivity), as measured, for instance, by dynamic causal modeling or Granger causality. Such edges can also be weighted, for example, by the internode correlation coefficient. Several metrics have been defined to thoroughly describe the complex architecture of functional brain networks, such as connection or adjacency matrix, node connectivity degree, node connection strength, internodal path length, shortest path length, etc. (Bullmore and Sporns, 2009; Sporns, 2018). Networks encompass modules interconnected by specific nodes, called provincial hubs, and networks are bridged by connector hubs. Modules are implicated in local specialized information processing, whereas connector hubs contribute to information transferring and integration. Most networks display a specific architecture, called small-world architecture, which is intermediate between random (short path length between nodes) and regular organization (high clustering among nodes). Such small word architecture optimizes regional information processing and distributed integration. Small-world organization has been demonstrated in resting-state networks (Achard et al., 2006; van den Heuvel et al., 2008), and its graph properties varied in relation with the frequency of the BOLD fluctuations (Thompson and Fransson, 2015). Therefore, resting-state networks also undergo dynamic topological reconfiguration.

FUNCTIONAL CONNECTIVITY PHYSIOLOGICAL BASIS

The physiological mechanism underlying the endogenous hemodynamic low-frequency fluctuations remains a matter of debate. RssFC in the gray matter would derive from a region-specific complex combination of Fox and Raichle (2007): 1. (inter-) neuronal and astrocytic sources, such as spiking, quantal exocytosis, up–down neuronal states, energetic metabolism, extracellular sodium/potassium regulation (Krishnan et al., 2018), neuromodulation (Cole et al., 2013), microstates (Custo et al., 2017), topological network constraints (Deco and Corbetta, 2011), vasculature and extracerebral blood flow source (Tong et al., 2019), and behavioral sources (Lu et al., 2019). rssFC partly reflects the structural connectivity (SC) (Greicius et al., 2009) and can evolve with learning (epigenesis) in an age-dependent manner (Edde et al., 2020). Moreover, the cortical nodes of the resting-state networks display specific electroencephalographic power variation of infra-slow-to-gamma rhythms (Mantini et al., 2007; Grooms et al., 2017). In particular, there exists a strong correlation between infra-slow scalp potentials and the spontaneous BOLD signal (Hiltunen et al., 2014). Finally, biophysical models showed that the networks composed of coupled gamma oscillators linked by long-range structural connections with delay transmission yielded the emergence of endogenous low-frequency neural activity fluctuations (Cabral et al., 2017). In conclusion, rssFC is an emergent functional pattern of the brain activity, which is spatially and temporally multiscale organized from the cell to the network, and modulated by experience (training).

REGION OF INTEREST-BASED ASSOCIATIVE CEREBELLO-CORTICAL "RESTING-STATE" STATIC AND DYNAMIC FUNCTIONAL CONNECTIVITY

fMRI studies (Stoodley et al., 2012; Stoodley and Schmahmann, 2018) using task-based protocols clearly delineated different sensorimotor territories such as sensorimotor (anterior lobe: lobules II–VI and VIIIB), oculomotor (vermis of lobules VI–VII, and lobules IX–X), vestibular (lobules IX–X), visual (lobule VI vermal), and auditory (lobules V–VI and left crus 1) zones. Cognitive and emotional regions have also been described, especially in lobule VII (Stoodley et al., 2012; Stoodley and Schmahmann, 2018). Using rssFC between the cerebellum and prefrontal cortex, Krienen and Buckner (2009) have found functional coherence between crus 2-lobule VIIB and the dorsolateral prefrontal cortex, crus 1-lobule IX and the medial prefrontal cortex, and VI/crus 1 border-crus 1-VIIB/VIIIA border and the anterior prefrontal cortex. O'Reilly et al. (2010) and Sang et al. (2012) have also found functional links between lobule VIIA paravermal-crus 2, posterior parietal and cingulate cortices as well as precuneus, lobule VIIA paravermal-IX and the prefrontal cortex, lobule VIII and the visual MT area, lobules VIII–IX and hippocampus and amygdala, and crus 1–2–vermal VIIIb–lobule IX and caudate nucleus. Regarding the vermis, rssFC has been identified between crus 2 and the cuneus, lobule VIIB and anterior thalamus–precuneus–posterior cingulate cortex, lobule VIIIA and superior frontal gyrus, and lobule IX and superior frontal and median temporal gyri (Bernard et al., 2012). All these studies have shown strong and lateralized functional coherence between crus 1–2 and contralateral prefrontal cortex. There exists a homotopic relation between associative cortical surface and their cerebellar representation with an over-representation within the cerebellar cortex of associative brain areas (Buckner et al., 2011).

The ROI-based rssFC demonstrates widespread interconnections between the neocerebellum (lobule VII and VIII) and prefrontal, parietal, cingulate, temporal, and occipital cortices. Such functional connections might rely on cortico-pontine afferents and/or cerebello-thalamo-cortical efferents in agreement with anatomical tracing in animal (Schmahmann and Pandya, 1997; Strick et al., 2009) and human tractography (Habas and Manto, 2018).

REGION OF INTEREST-BASED DENTATO-CORTICAL "RESTING-STATE" STATIC AND DYNAMIC FUNCTIONAL CONNECTIVITY

Moreover, the human dentate nuclei, the main cerebellar output system to the brain and brainstem, exhibits rssFC with occipital (BA 19), parietal (BA 40), insular (BA 13), cingulate (BA 24), and prefrontal (BA6-8-9-32-46) cortices, the left dentate nucleus displaying more widespread efferents than the right one (Allen et al., 2005). The neocerebellar cortex, especially the prominent lobule VII, and the dentate nuclei constitute a supramodal zone interconnected with the major associative brain regions (O'Reilly et al., 2010) and, to a lesser extent, to affective and associative subcortical nuclei such as the amygdala and striatum. Finally, the interlobular rssFC could subserve a cross-network coordination within the cerebellum; for instance, crus 1–2 are correlated with lobule IX. This could functionally bridge executive network (EN) and default-mode network (DMN) (Bernard et al., 2012). Of interest, topological properties of the intracerebellar rssFC, such as small-world organization, depend upon intelligence coefficient and gender (especially in lobules VI–crus 1 on the left side and vermal VIII) (Pezoulas et al., 2018).

In conclusion, the cerebellum can influence, through dentate-thalamo-cortical projections, all the associative cortices.

INDEPENDENT COMPONENT ANALYSIS-BASED ASSOCIATIVE CEREBELLO-CORTICAL CLOSED LOOPS

The abovementioned cerebellar areas and functionally associated cortical areas take part in parallel cerebro-ponto/reticulo-cerebello-thalamo-cortical loops. More precisely, these ICNs

encompass (Habas et al., 2009; Krienen and Buckner, 2009; Brissenden et al., 2016) (**Figure 1**):

- the right and left frontoparietal EN passing through crus 1–2 (working memory, adaptive control, and task switching),
- the DMN passing through crus 1–2 and lobule IX (mind wandering, episodic memory, agentivity, navigation, self-reflection, and consciousness),
- the limbic salience network passing through lobules VI–VIIb/crus 1–2 (interoception, autonomic regulation, emotional processing, and bottom–up attention),
- the frontoparietal dorsal attentional network (DAN) passing through lobules VIIB–VIIIA (top–down attention and visual working memory),
- the language-dedicated network passing through the cerebellum (especially right crus 1–2) (Tomasi and Volkow, 2012).

Using another method (fuzzy-c means clustering algorithm), Lee et al. (2012) also reported during the resting state a ventral attentional network (VAN) previously described by Corbetta et al. (2000). VAN encompasses mainly the inferior and middle prefrontal, temporoparietal junctional, anterior insula, inferior parietal on the right side, and is involved in the bottom–up reorientation of attention. VAN passes bilaterally through parts of lobules VI and VIIIA and, to a lesser extent, lobules crus 1 and VIIIB (Guell et al., 2018; Guell and Schmahmann, 2020). This circuit can switch DAN activity to a novel object of interest. It is noteworthy that several nodes of VAN, such as anterior insula, also belong to the limbic salience network.

In conclusion, the neocerebellum can influence all the associative resting-state networks.

GRADIENT ORGANIZATION

It has been shown (Guell et al., 2018; Guell and Schmahmann, 2020) that EN, DMN, and DAN are represented three times in each hemisphere of the neocerebellar cortex (lobules VII–VIII–IX–X), and that these representations are included in functional gradients from attentional (DAN) and task-positive executive (CEN) processing to task-negative default-mode processing

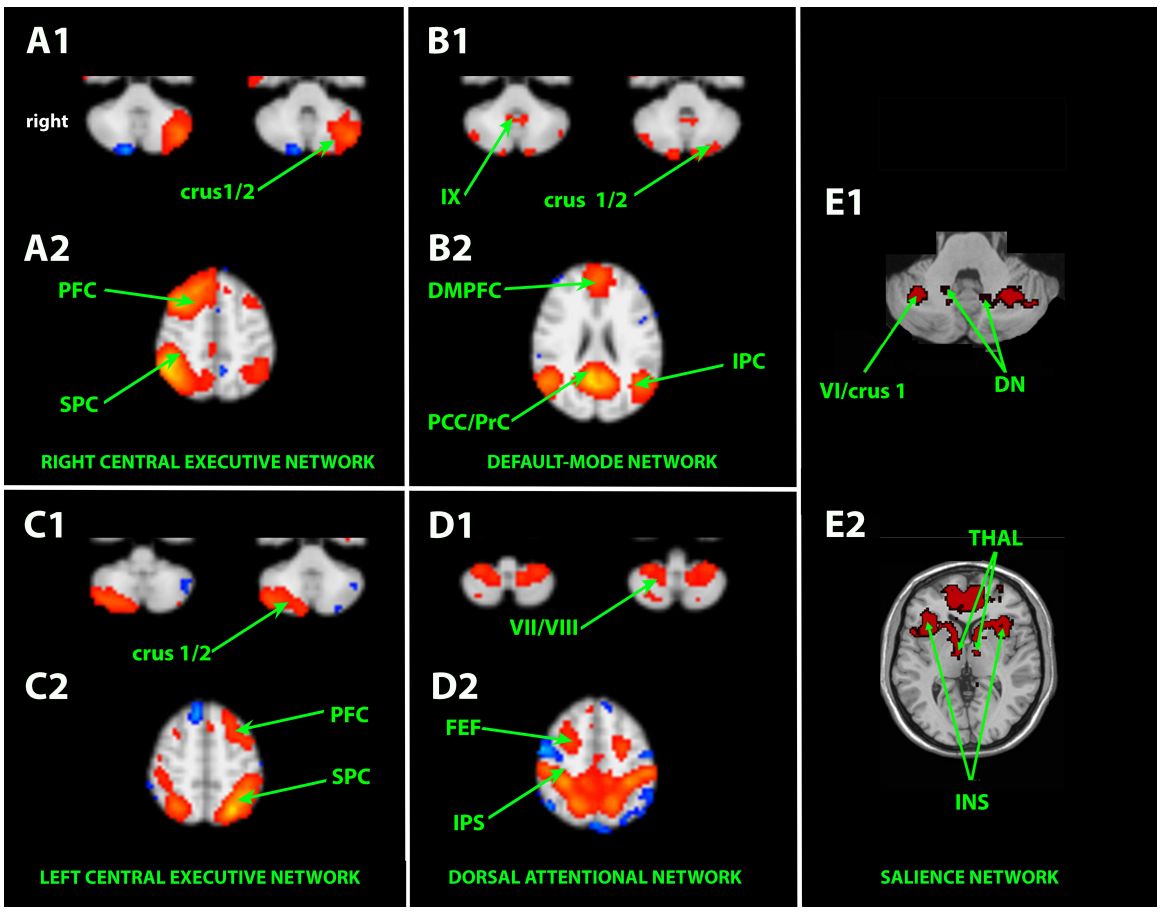

FIGURE 1 | Independent component analysis (ICA)-based resting-state associative cortico-cerebello-cortical networks. A1–B1–C1–D1–E1: axial slices passing through the neocerebellum. A2–B2–C2–D2–E2: axial slices passing through the brain. DMPFC, dorsomedial prefrontal cortex; DN, dentate nucleus; FEF, frontal eye field; INS, insula; IPC, inferior parietal cortex; PCC/PrC, posterior cingulate cortex/precuneus; PFC, prefrontal cortex; SPC, superior parietal cortex; Thal, thalamus. Cerebellar lobules are numbered with Latin numerals. Crus 1/2 corresponds to the hemisphere of lobule VIIA.

(DMN). These three gradient-based representations are found in lobules VI–crus 1, lobules VIIB–crus 2, and lobules IX–X. The rostro-caudal direction of the first representation and the opposite direction of the second representation imply that the crus 1–2 intersection encompasses partial overlapping of the first and second DMN representations. These anatomical gradients mirror hierarchical cognitive control of the prefrontal and parietal cortices (D'Mello et al., 2020). Furthermore, this anatomo-functional gradient organization may reflect the phylogenetical coupling between telencephalization and neocerebellar development with progressive complexification of motor abilities requiring more executive control (attention, anticipation, and regulation) and behavioral integration (emotion-related behaviors) until the cerebellum could also monitor non-motor tasks. The differential role of these multiple representations and whether adjacent contiguous representations, as in the DMN case, would participate in a coordinated computation through, for instance, intracerebellar interconnections, remains to be determined.

EMOTIONAL CEREBELLUM

It is worth noting that the "emotional cerebellum" belongs to SN and DMN, and includes, in particular, the vermis of lobule VII, in accord with the "constructivist" or "scaffolding" hypothesis, claiming that no specific network is dedicated, at least, to emotion such as lateral and medial pain matrix (Iannetti and Mouraux, 2010). Emotions rest on the transient collaboration of distinct intrinsic networks with specific hubs such as insula and anterior cingulate cortex (Menon and Uddin, 2010) and subserving the multidimensional (autonomic, affective, cognitive, mnesic, and motor) aspects of emotion.

STRIATO-CEREBELLAR INTERCONNECTION

Of interest, several studies found structural and functional connectivity between the cerebellum and the limbic ventral striatum. For instance, Pelzer et al. (2013) found dentato-thalamo-striato-pallidal and sub-thalamo–pontine nuclei–cerebellar connections passing through crus 2/lobules VIII–IX, using probabilistic tractography. Functional coherence was recorded between lobule IX (DMN) and the ventral tegmental area (Murty et al., 2014), and between lobule VII–IX (EN, DMN, and SN) and nucleus accumbens (Cauda et al., 2011). In this vein, a serial reaction time task was accompanied by FC strengthening of a cerebello (crus 1 and dentate nucleus)-thalamo-lenticular nucleo-cortical network during explicit and implicit learning (Sami et al., 2014). Therefore, SC and FC tightly and directly interconnect the (neo-)cerebellum and basal ganglia, which explains why a reward signal can be detected in granule cells and climbing fibers (Wagner and Luo, 2020). Although the role of this latter signal requires further investigations, it has been speculated that the basal ganglia would send to the cerebellum a value estimation of the cerebellar forward model-based selection of cortical planned or executed mental actions (Caligiore et al., 2017). In other words, striatal reinforcement learning could not only modulate the cortical activity but also the cerebellar error-based supervised learning.

LOBULE VII "RESTING-STATE" STATIC AND DYNAMIC FUNCTIONAL CONNECTIVITY

Two main networks occupying the most voluminous neocerebellar lobule (VII) are represented by EN and DMN, with an EN predominance. The DMN-related cerebellar zone within crus 1–2 is surrounded by the EN-related cerebellar zone. It has been demonstrated that there exists a greater individual variability in the spatial organization of ICNs within the neocerebellum than in the corresponding cortex, despite a group-level identical spatial pattern, and that the resting state cerebellar fluctuations of EN and DMN lag behind the cortex ones by hundreds of milliseconds (Marek et al., 2018). Marek et al. (2018) hypothesized that the cerebral cortex would transmit information to the neocerebellum using infra-slow activity conveyed by cortico-ponto-cerebellar afferents, and the cerebellum would respond by sending a signal back to the cortex through the cerebello-thalamo-cortical efferents using delta rhythm (0.5–4 Hz). It is noteworthy that delta rhythms are involved in learning-dependent timing (Dalal et al., 2013), and in the latter assumption, part of the endogenous fluctuations could subserve information processing.

Intermittent theta burst magnetic stimulation applied to the neocerebellum induced DMN and EN reconfiguration in terms of functional connectivity and frequency of their associated electroencephalogram signal (Halko et al., 2014; Farzan et al., 2016). The stimulation of vermian lobule VII influenced the DAN with enhanced power in beta/gamma oscillations, whereas the stimulation of the hemisphere of lobule VII modulated the activity of DMN with diminished frontal theta activity. The absence of EN implication could be ascribed to the prominent recruitment of DMN during the resting state. This study illustrated that neocerebellum can differentially alter electrophysiological activity of networks.

Dynamic rssFC, studying time-varying rssFC, coupled with SC reveals the highest rssFC/SC similarity in the posterior lobe compared with the anterior one and a low rssFC variability (Fernandez-Iriondo et al., 2020). These last findings might explain the specific and constant recruitment of DMN and EN during mind wandering (Fox et al., 2016), and the high and temporally stable constraints exerted by SC onto the rssFC of the cognitive circuits. Moreover, the CAPs method was applied to the resting-state BOLD fluctuations (Liu and Duyn, 2013). When the left intraparietal sulcus belonging to DAN was seeded, several CAPs were found in distinct non-overlapping neocerebellar regions showing activation or deactivation. Thus, different transient states of a specific circuit can recruit distinct cerebellar subregions.

FUNCTIONAL CONSIDERATIONS AND SYNTHESIS

The polymodal neocerebellum (lobules VII, VIII, and IX) is massively interconnected with associative cortices, as well as with the striatum and amygdala, and it partakes in all associative resting-state circuits with an overrepresentation of EN. Each circuit contributes to a triple functional gradient-based representation within the cerebellar cortex. These resting-state circuits are also characterized by a specific BOLD and electrophysiological signature. The slow BOLD fluctuations, at least for CEN, lag behind the cortical oscillations. This resting-state functional architecture can also be modulated by experience and individual mental abilities. For instance, enhanced functional coherence between crus 1–2 and the right CEN is positively correlated with task goal maintaining (Reineberg et al., 2015). However, functional connectivity analyses *per se* cannot specify which precise functional action is exerted by such networks. It is assumed that "[. . .] resting state networks represent a finite set of spatiotemporal basis function from which task-networks are then dynamically assembled and modulated during different behavioral states" (Mantini et al., 2007) even if intrinsic networks, especially DMN, can be actively recruited by mind wandering during the brain resting state. The associative function of the human neocerebellum can only be inferred from task-based fMRI paradigms and from clinical studies. Task-based fMRI meta-analysis has shown involvement of the neocerebellum, including lobules VI, VII, and VIII, in executive, linguistic, and emotional functions (Stoodley et al., 2012). In addition, cerebellar stroke patients exhibited cognitive deficits due to posterior lobe, mainly lobules VII–VIII, and dentate nucleus lesions (Stoodley et al., 2016). Such deficits corresponded to components of the Schmahmann's cognitive and affective syndrome (Schmahmann and Sherman, 1998). Furthermore, from a computational standpoint, because of the structural and histological homogeneity of the cerebellum organized in microcomplexes, it is postulated that motor and associative cerebellum may accomplish the same algorithmic function. Substantial data support the view that the cerebellum may elaborate internal models and especially forward models (Wolpert et al., 1998; Sokolov et al., 2017). Such models would allow prediction of the consequences of intended mental activity during movement (sensory consequence of planned or executed motor action) (Ito, 2005) or cognition (Ito, 2008), and, consequently, would control and optimize the accuracy of the current performance, particularly during supervised learning. The cerebello-cortical closed loops would likely help coordinate or (de-)synchronize cortical areas through the thalamus reviewed in Habas et al. (2019) and to sequence their activity (Molinari et al., 2008). In other words, the cerebellum would act as a general modulator, or "universal transform" (Sereno and Ivry, 2019), generating internal models (functional unicity of microcomplexes) for all motor and associative/emotional domains (functional heterogeneity due to its wide interconnections with the cerebral cortex). Finally, it is noteworthy that task-free and task-based functional parcellations of the cerebellum can exhibit some small regional differences (King et al., 2019): for example, several tasks such as hand movement, working memory and language activation recruit bilateral homologous cerebellar zones, although these zones belong to lateralized resting-state networks. Moreover, if task-free intrinsic connectivity can predict task-evoked activations, small differences can be noted between the former one and the task-state functional connectivity (Cole et al., 2021). Idiosyncratic mental strategies to solve the current tasks may explain these differences observed in functional connectivity.

CONCLUSION

"Resting-state" static and dynamic functional connectivity sheds light on the genetically prewired and epigenetically tuned resting-state networks underlying the cognitive function of the neocerebellum for motor and non-motor tasks. RssFC demonstrated in humans that the major part of the cerebellum (lobules VII–VIII and dentate nucleus) is functionally interconnected with non-motor associative cortices and constitutes a major relay of all associative resting-state networks. These cerebello-cortical functional interconnections partly reflect the underlying structural hardware. Further studies are required to determine whether this cerebello-cortical coherence would also reflect information processing/transferring between the cerebellum and its targets during the resting state. However, this "functional tracing" method does not furnish any explanation concerning the exact functional or algorithmic role of the neocerebellum in the cognitive domain. It can only suggest that the cerebellar computation based on supervised and predictive control through internal models—the current prevalent hypothesis about the cerebellar function—is the same for networks in charge of movements and networks in charge of executive and emotional processing. Finally, the advances in our understanding of the organization of ICNs would lead to a better understanding of the pathogenesis and therapy of major disorders of the brain such as Parkinson's disease (Mueller et al., 2019) or genuine disorders of the cerebellar circuitry itself (Iang et al., 2019). The understanding of node shaping and synchronizing activities of the cortical areas (Habas et al., 2019) will benefit from refinements in the techniques currently applied, such as neurostimulation.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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A Focus on the Cerebellum: From Embryogenesis to an Age-Related Clinical Perspective

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The cerebellum and its functional multiplicity and heterogeneity have been objects of curiosity and interest since ancient times, giving rise to the urge to reveal its complexity. Since the first hypothesis of cerebellar mere role in motor tuning and coordination, much more has been continuously discovered about the cerebellum's circuitry and functioning throughout centuries, leading to the currently accepted knowledge of its prominent involvement in cognitive, social, and behavioral areas. Particularly in childhood, the cerebellum may subserve several age-dependent functions, which might be compromised in several Central Nervous System pathologies. Overall, cerebellar damage may produce numerous signs and symptoms and determine a wide variety of neuropsychiatric impairments already during the evolutive age. Therefore, an early assessment in children would be desirable to address a prompt diagnosis and a proper intervention since the first months of life. Here we provide an overview of the cerebellum, retracing its morphology, histogenesis, and physiological functions, and finally outlining its involvement in typical and atypical development and the age-dependent patterns of cerebellar dysfunctions.

Keywords: age-related clinical findings, anatomy, cerebellar, cerebellum, circuitry, neurodevelopment, neuroimaging, neurophysiology

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INTRODUCTION: THE CEREBELLUM THROUGH HISTORY

The cerebellum, also known as "little brain," has been an object of interest and research for centuries. Throughout history, many prominent personalities, as recently discussed by Voogd and Koehler (2018), have been trying to reveal the cerebellum complexity to achieve a better understanding of this peculiar structure. Among those who contributed in implementing the knowledge on structural and functional aspects of the cerebellum, it is worth mentioning the French anatomist Vieussens (1641–1715), whose compendium "Neurographia Universalis" (Vieussens, 1685), written in Latin, provided an ahead of time description of the Central Nervous System (CNS; Manto and Huisman, 2018). This work, albeit still far from thorough, pointed out some relevant notions, such as the functional independence of the spinal cord from the rest of the CNS, and contributed in characterizing the *centrum ovale* (namely the central white matter of the cerebrum) and other

structures, such as the "superior medullary velum" of the cerebellum, also known as "Vieussen's valve" (JAMA, 1968; Loukas et al., 2007).

A major contribution to the topic came during the 18th century thanks to the work of the Italian professor of medicine, surgery, and obstetrics Vincenzo Malacarne, who, in his publications, among which is worth recalling "*Nuova esposizione della vera struttura del cervelletto umano*" (1776), provided a complete description of the human cerebellum anatomy (comprising the number of lobes and folia), introduced the terms tonsil, pyramid, lingual, and uvula, to date still in use and proposed a correlation between the number of cerebellar lamellae and the expression of intellectual faculties, hence asserting the existence of a strict relation between cerebellar underdevelopment and cretinism (Zanatta et al., 2018).

Further knowledge spread during the 19th century, through the meticulous research carried out by numerous scientists who contributed to improving the description of symptoms and signs of cerebellar lesions; for example, Rolando and Magendie emphasized the role of cerebellum in controlling, respectively, posture/movement and equilibrium, Luciani reported atonia, asthenia, astasia, and dysmetria as possible neurological cerebellar signs, Babinski described adiadochokinesia and pointed out the role of the cerebellum in synergia, while Sherrington linked the cerebellum to proprioception and modulation of reflexes (Manto and Huisman, 2018). Between 1917 and 1939, Holmes provided a thorough description of neurological signs and symptoms deriving from cerebellar lesions, such as disturbances of muscle tone (hypotonia) and voluntary movement, static tremor, asthenia and fatigability, astasia, vertigo, disturbances of ocular movements and nystagmus, abnormal speech, and reflexes (Holmes, 1917, 1939).

Innovations on the morphology and functionality of the cerebellum were continuously achieved throughout the 20th century, leading progressively to the currently accepted notions such as the division in 10 lobules, first proposed by Larsell (1970), the functional subdivision into a medial, an intermediate, and a lateral zone (Dow and Moruzzi, 1958), and cerebellar prominent involvement, not only in sensorimotor functions, but also in cognitive, social and behavioral areas (Roostaei et al., 2014).

ANATOMY OF THE CEREBELLUM

The cerebellum is a small structure of the hindbrain, weighing approximately from 136 to 169 *g* and representing about the 11% of brain weight in adult humans and 5–6% in neonates (Solov'ev, 2016). Despite its small size, it contains almost 80% of the global brain neurons and plays an important role in sensorimotor, cognitive, and affective functions (Roostaei et al., 2014).

Cerebellar Gross Anatomy

The cerebellum is located in the posterior cranial fossa. It is separated, anteriorly, from the pons and the medulla oblongata by the fourth ventricle, and, superiorly, from the cerebrum by the Tentorium Cerebelli (an invagination of the dura mater). It globally presents two faces: the superior one is convex, crossed by the superior vermis and shows, laterally, the upper surfaces of the two cerebellar hemispheres; the inferior one is allocated in the posterior cranial fossa and presents a depression, in whose depth the inferior vermis is placed. A roughly ellipsoidal circumference separates these two faces, and opens anteriorly in the hilum of the cerebellum, from which the three cerebellar peduncles (superior, middle, and inferior) emerge. These latter represent the structures through which the afferents and efferences of the cerebellum pass and reach their targets (Voogd, 2003; Cattaneo, 2013; Roostaei et al., 2014).

The cerebellum surface is globally composed of numerous parallel leaflike subdivisions, called folia (Voogd and Glickstein, 1998), giving it an onion-like aspect. Two main transversal fissures (the fissura prima, anteriorly, and the horizontal fissure, posteriorly) delineate three main lobes (the anterior lobe, the posterior lobe, and the flocculonodular lobe), each one subdivided in lobules (**Figure 1**; Larsell, 1970; Manni and Petrosini, 2004). Besides, considering the medio-lateral perspective, the cerebellum presents a central part, the vermis, and two lateral cerebellar hemispheres. Both the anterior and posterior lobes contain a part of the vermis and of the two hemispheres. Moreover, the flocculonodular lobe constitutes *per se* the so-called vestibulocerebellum/archicerebellum, the oldest one phylogenetically-wise (Manni and Petrosini, 2004). The medial zone (vermis) and the intermediate ones (paravermis) form the spinocerebellum, so called because of the sensorimotor afferents coming from the spinal cord. The lateral zones constitute the cerebrocerebellum, whose name is due to the presence of afferents/efferences from/to the cortex (Kandel et al., 2013; Roostaei et al., 2014).

Overall, on a phylogenetical basis, it is possible to distinguish among three parts: the archicerebellum, the paleocerebellum and the neocerebellum (**Figure 1**; Manni and Petrosini, 2004).

The archicerebellum is strictly connected with the vestibular nuclei (for this reason it also called "vestibulocerebellum"; Voogd et al., 1996), sending outputs to these structures directly, thus bypassing the deep nuclei (Roostaei et al., 2014). It is also involved in equilibrium, ocular movements, and vestibulo-ocular reflex regulation. The medial zone (nodulus) primarily controls the axial musculature, while the lateral parts (floccules) are mostly involved in eye pursuit movements and hand-eye coordination (Manni and Petrosini, 2004). Both the paleocerebellum and the neocerebellum include a part of the spinocerebellum and the cerebrocerebellum. Specifically, the paleocerebellum (corresponding to the anterior lobe), mostly regulates tone and posture, whereas the neocerebellum (corresponding to the posterior lobe) controls voluntary movements, as well as automatic and semi-automatic ones (Manni and Petrosini, 2004; Cattaneo, 2013; Roostaei et al., 2014).

The vermis receives visual, auditory and vestibular inputs, as well as sensorimotor ones from head, trunk and proximal portions of limbs, and it sends outputs, through the fastigial nucleus, to the cortex and the brainstem, generating the medial descending tracts (which control limbs and proximal muscles). The paramedian zones receive sensorimotor inputs from the distal parts of limbs and send outputs, through the interposed nucleus, to the corticospinal and rubrospinal

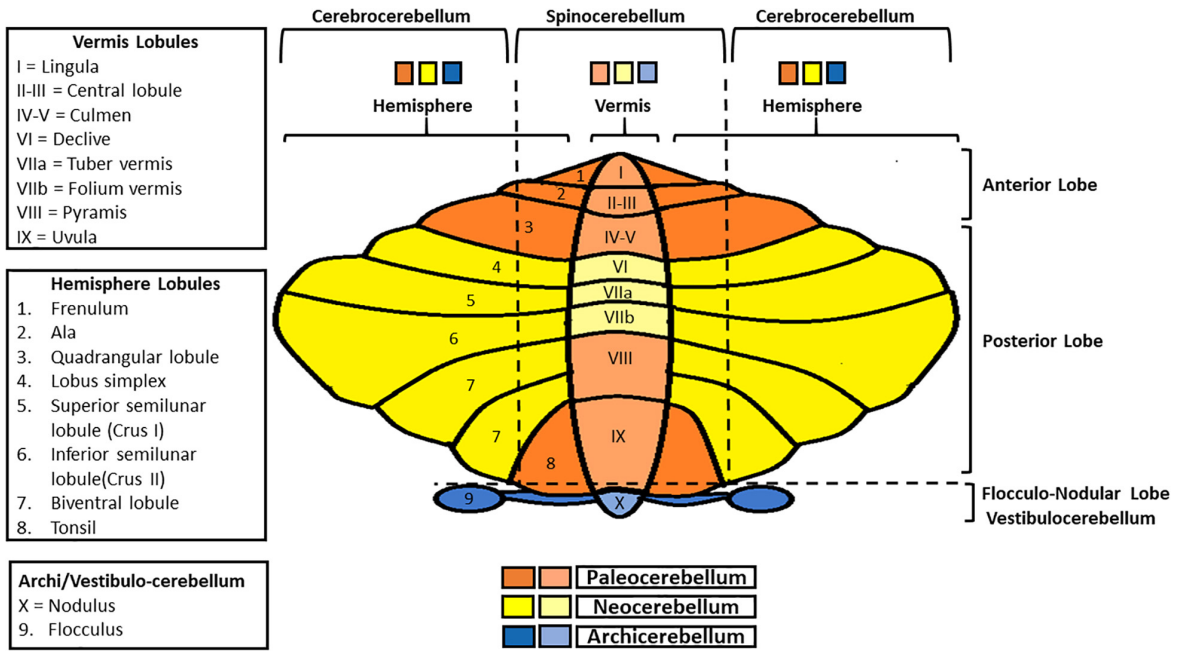

FIGURE 1 | Schematic representation of cerebellar gross anatomy. Anterior-posteriorly, the cerebellum presents three lobes (anterior, posterior, and flocculo-nodular), each one subdivided in lobules. Medio-laterally, it is composed of a central part (the vermis), and two lateral ones (cerebellar hemispheres). Vermis and paravermial zones form the spinocerebellum, so-called since it communicates with the spinal cord; the most lateral zones of the hemispheres constitute the cerebrocerebellum, in connection with the cerebral cortex. Finally, in regard to phylogenesis, the cerebellum can be divided into three parts: the archicerebellum (the most ancient one, corresponding to the vestibulocerebellum), paleocerebellum and neocerebellum.

systems, being in charge of the distal muscles of limbs and fingers. Overall, the outputs of these pathways are involved in postural control, balance, locomotion, and gaze direction (Manni and Petrosini, 2004; Kandel et al., 2013). Furthermore, they are also involved in adjusting motor outputs, integrating and comparing motor commands and sensorimotor feedback, and in the anticipatory control of posture and movements. The lateral zones receive from the cortex and send information, through the dentate nucleus, to motor, premotor and prefrontal cortices, being involved in motor planning and various cognitive tasks (Kandel et al., 2013). Nowadays, it is common knowledge that cerebellar dysfunctions may lead to the so-called "cerebellar cognitive affective syndrome" (CCAS), comprehensive of a wide variety of neurologic and psychiatric signs and symptoms, such as impaired executive functions, abnormal visuospatial cognition, language deficits, personality, and behavioral disorders (Schmahmann and Sherman, 1998).

Cerebellar Microanatomy and Circuitry

The cerebellum presents an outer gray matter layer (namely the cerebellar cortex), a deeper cerebellar white matter (the so-called arbor vitae), and, within this latter, the deep cerebellar nuclei (dentate, globose, emboliform, and fastigial nuclei; Voogd, 2003).

The cerebellar cortex is composed of three layers (from the deepest to the most superficial: the granular layer, the Purkinje layer, and the molecular layer), four inhibitory cell types [stellate cells, basket cells, Purkinje cells (PCs), and Golgi cells], two excitatory cell populations [granule cells and unipolar brush cells (UBCs)], and glial cells (among which Bergman glia; **Figures 2**, **3**; Buffo and Rossi, 2013; Kandel et al., 2013; Roostaei et al., 2014).

The granular layer contains a large number of granular cells (excitatory). Each of them presents few descending dendrites, and a single ascending axon reaches the molecular layer, where it splits in a T-shaped way, generating the parallel fibers. This layer also contains interneurons, such as the UBCs and the Golgi cells, whose descending dendrites, together with the granule cells dendrites, and the mossy fibers (a major afferent cerebellar pathway originating from the brainstem nuclei, the spinal cord, and the reticular formation) form the synaptic structure known as "glomerulus" (Voogd and Glickstein, 1998; Mugnaini et al., 2011). Specifically, UBCs present one short dendrite whose brush engages in synaptic contact with a single mossy fiber terminal (the term brush indicates the fact that the tip of the UBC dendrite forms a paint brush-like tuft of dendrioles); while their axons branch locally within the granular layer, making contact with the granule cells (Mugnaini et al., 2011). Finally, the axons of the PCs (whose main body is located in the homonym middle layer, surrounded by multiple Bergman glia cells that, in turn, modulate their activity) cross this layer to reach the deep cerebellar nuclei, thus generating the cerebellar efferences (Buffo and Rossi, 2013). Conversely, the PCs send their dendrites to the molecular layer [wherein Bergmann glia (BG) fibers extend], forming a "dendritic tree," making synapses both with the parallel fibers, and with the axons of the outer stellate cells (Voogd and Glickstein, 1998). These inhibitory interneurons are placed in the upper part of the molecular layer, as opposed

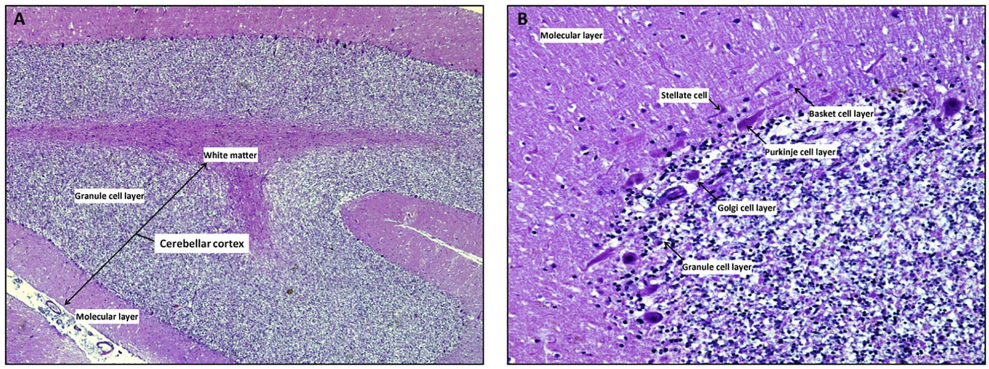

FIGURE 2 | The cerebellar cortex. Mid-sagittal section reveals the three layers in cerebellar folia: the superficial molecular layer, the deepest called granular and the Purkinje cells layer at the interface between the granular and molecular layers Note the inner white core of white matter (**A**, x4 hematoxylin/eosin stain). At higher magnification, the molecular layer contains superficially located stellate cells, basket cells which are scattered among dendritic ramifications and numerous thin axons that run parallel to the long axis of the folia. Ganglionic or Purkinje cell layer is formed of a single row of Purkinje cells with large pear-shaped bodies; while the granular layer is composed by small granule cells with dark-staining nuclei/scanty cytoplasm and Golgi type II cells (**B**, x20 hematoxylin/eosin stain).

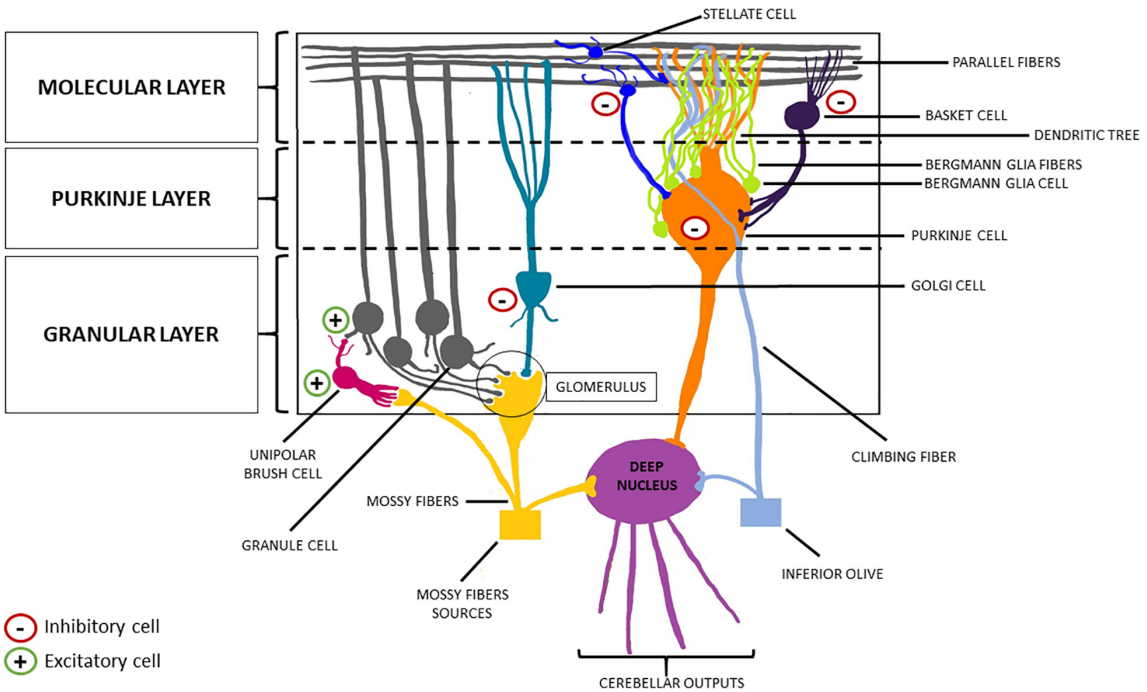

FIGURE 3 | Schematic representation of the cerebellar cortex. From the innermost part to the outermost one, the cerebellar cortex can be divided into three layers: the granular layer, the Purkinje layer, and the molecular layer. The former welcomes the granule cells (excitatory neurons) and the Golgi cells (inhibitory interneurons). The descending dendrites of these two cellular types together with the ascending mossy fibers (originating from the brainstem nuclei, the spinal cord and the reticular formation) make synapsis in this area, forming the so-called "glomerulus". Purkinje cells (inhibitory neurons) are located in the middle layer, from which they send their axon to the deep nuclei, crossing the granular layer, and their dendrites to the molecular layer, forming a "dendritic tree." Finally, basket cells and stellate cells are the two inhibitory interneurons of the molecular layer, making synapsis with the parallel fibers (originating from the T-split of the ascending axons of the granule cells).

to the internal stellate cells, which are below them and send an axon in the middle layer, making synapsis with the PCs (Sudarov et al., 2011; De Luca et al., 2016). Lastly, the molecular layer hosts the basket cells, another inhibitory interneuron type, and the climbing fibers. These latter represent the other major afferent pathway of the cerebellum, generating from the contralateral inferior olivary complex and making synapsis with the dendrites of PCs (Buffo and Rossi, 2013; Cattaneo, 2013; Roostaei et al., 2014).

Connecting the cerebellar cortex to the deep nuclei, there is the cerebellar white matter, namely the "arbor vitae," so called for its tree-like branching pattern. It contains afferent and efferent fibers conveying sensorimotor information to/from the cerebellum (Cattaneo, 2013).

Finally, the deep nuclei constitute the cerebellar outputs, through which the fibers get to their targets after crossing the superior and inferior peduncles (the middle one is only crossed by afferents from the basilar pontine nuclei; Machold and Fishell, 2005; Wang et al., 2005). Nevertheless, it is worth recalling that the efferences going from the archicerebellum to the vestibular nuclei are the only ones that bypass the deep nuclei (Cattaneo, 2013; Roostaei et al., 2014).

Cerebellar circuitry appears to be a complex network of excitatory and inhibitory inputs and outputs with recurrent and interconnected loops involving the cerebellum and different brain regions. Notably, evidence deriving from anatomical, clinical, and neuroimaging data allowed us to point out the mutual connection between the cerebellum and basal ganglia, multiple cerebral cortex areas (particularly primary and associative ones), as well as thalamus and hypothalamus (Bostan et al., 2013; Benagiano et al., 2018).

This evidence showed that the cerebellum is not exclusively a motor structure, but it is part of somatotopically organized sensorimotor and cognitive networks, playing a significative role also in non-motor processes, such as cognition, visuospatial reasoning, associative learning, emotion, behavior, and, specifically in regard to basal-ganglia dense interconnections, reward-related learning (Schmahmann, 1998; O'Doherty et al., 2003; Stoodley et al., 2012).

Accordingly, patients with cerebrocerebellar damage are also showing specific cognitive disorders involving ideation (e.g., impairment of planning of daily activity), attention (e.g., impairment of shifting focus of attention), and sensory-perceptions (e.g., auditory or visuospatial neglect, sensory aphasia, dyslexia, and agnosia). Moreover, cerebrocerebellar damages have been detected in some patients affected by mood disorders or other psychiatric diseases (Benagiano et al., 2018).

EMBRYOLOGY

To better perceive the cerebellar functions' complexity, it is crucial to understand its morphogenesis and how its connections with other CNS structures are established. Cerebellar development is a process that starts early during the first trimester of pregnancy (30 days post- conception) and lasts until 2 years of postnatal age (van Essen et al., 2020). There are very few literature data regarding human cerebellar development before the 8th gestational week (Haldipur et al., 2018) and most of our knowledge about cellular and molecular maturation is derived from animal-based studies on fish, birds and rodents, especially mice. In view of the preservation of cerebellar ontogenesis and circuitry across evolution in these species, the analysis of these vertebrate models is crucial to understand the complexity of cerebellar development in the early stage of life (Haldipur et al., 2018, 2019). Even the correlation between volumes of the cerebellum and the total brain is consistent across species, though foliation is more variable in the hemispheres rather than the vermis (Leto et al., 2016).

The cerebellum originates from the dorsal portion of the hindbrain and its development can be summarized in four steps: organization of the cerebellar territory, establishment of cerebellar progenitors (GABAergic and glutamatergic ones), migration of the granule cells, and formation of the cerebellar nuclei and circuitry (ten Donkelaar et al., 2003).

Studies on chick, quail and mice embryos demonstrated that, at neural plate stage, the first segmental division is determined by the expression of the transcription factors Otx2 and Gbx2: the former defines the forebrain and midbrain territory, while the latter is expressed by the hindbrain, so their juxtaposition delineate the midbrain-hindbrain boundary (Marin and Puelles, 1994; Liu et al., 1999).

The isthmic organizer (IsO) is a patterning center that arises from this limit and expresses a protein of the fibroblasts growth factor family (FGF8), which is essential to the development and differentiation of cerebellum (Sato and Joyner, 2009). Other important products of the neural tube, such as WNT1, sonic hedgehog (SHH), bone morphogenetic protein, and transforming growth factor-ß, interact with the IsO to determine the anterior-posterior axis and the rhombomere segmentation (De Luca et al., 2016; van Essen et al., 2020).

In the upper part of the hindbrain, the rhombomere 1, the expression of the basic-helix-loop-helix proteins ATOH1 and PTF1a marks the rhombic lip (RL) and the ventricular zone (VZ), respectively, Hoshino et al. (2005), Machold and Fishell (2005), and Wang et al. (2005). In the lower portion of the RL, the most dorsal part develops into the roof plate, a transient pseudostratified epithelium constituted by a population of cells expressing the protein WNT1. This layer covers the fourth ventricle roof and originates the choroid plexus cells (Awatramani et al., 2003; Hunter and Dymecki, 2007). The choroid plexus is responsible for the production of the cerebrospinal fluid (CSF) and its proper function is essential for brain development: a reduction of CSF volume is implicated in cerebral growth impairment (Desmond and Jacobson, 1977; Andescavage et al., 2016), while its increase can determine hydrocephalus (McAllister, 2012). Moreover, an excess of CSF in the subarachnoid space has been proposed as an early marker of autism spectrum disorder (ASD; Shen et al., 2013). Interestingly, despite the cerebellum and the choroid plexus share a common genesis, Chizhikov et al. (2006) performed genetic fate mapping studies demonstrating that the roof plate does not originate from cerebellar cells.

Cerebellar nuclei cells are the first to be born, the glutamatergic ones originating from the RL and the GABAergic ones descending from the VZ and becoming interneurons (Haldipur et al., 2019). Development of the cerebellar nuclei starts with a "nuclear transitory zone" in a marginal position. The glutamatergic neurons follow a tangential pattern of migration and establish the GABAergic interneurons further maturation. The lateral nuclei develop early and project to thalamus and midbrain, while the medial group appears later and make connections to the hindbrain (Green and Wingate, 2014). Derivatives of the hindbrain that will form extra-cerebellar structures of the CNS also arise from the RL, like the pontine nuclei. A strict interconnection occurs between brainstem nuclei and cerebellum as the brainstem delivers proprioceptive/vestibular/auditory sensations and cortical

information to the cerebellum (Machold and Fishell, 2005; Wang et al., 2005). In the developing murine brain, the protein semaphorin 3A acts as a guidance for the pontocerebellar axons that will reach the cerebellar granule layer and form the mossy fibers (Solowska et al., 2002).

Rhombic lip produces all the remaining cerebellar glutamatergic interneurons and neurons. The excitatory interneurons are the UBCs, especially represented in the flocculonodular lobe (Munoz, 1990; Víg et al., 2005). The granule layer cells are the glutamatergic neurons and spring up from granule cell progenitors (G). This population migrates tangentially to form the external granule layer (EGL) and, following FGF8 and SHH signaling, goes through clonal expansion during the late pregnancy period, determining the formation of a six-eight cells layer (Sato and Joyner, 2009). This process produces an amount of granule neurons so large that it overcomes the cerebral cortex ones (Roostaei et al., 2014; Leto et al., 2016). Later, GCPs differentiate and move inward into the cerebellar anlage to form the internal granule layer (IGL). During the postnatal age, the RL continues to produce granule cells and the EGL progressively disappears during the second year (Rakic and Sidman, 1970; Haldipur et al., 2018; van Essen et al., 2020).

The VZ originates the GABAergic neurons (PCs) and interneurons of the cerebellum. Two groups of PCs leave the VZ to form the so-called "Purkinje cell plate" (Goffinet, 1983): early PCs, born in the posterior VZ, migrate tangentially, then change orientation toward the EGL under the influence of the protein reelin secreted by the GCPs; on the contrary, late PCs, born in the anterior VZ, move following a radial pattern, guided by Bergmann glial fibers signaling (Yamada and Watanabe, 2002). Subsequently, the PCs plate reorganizes itself to form a monolayer of PCs, beneath which the IGL will locate (Ben-Arie et al., 1997; van Essen et al., 2020). The granule cells produce trophic factors necessary to develop the PCs dendritic trees. At 20th gestational week, the human cerebellum presents a transient cellular region called "lamina dissecans," between the PCs layer and the IGL. Its function in the cerebellar development is yet unknown and it disappears by the 32nd gestational week (Rakic and Sidman, 1970; Haldipur et al., 2018). All inhibitory interneurons come from a common progenitor expressing a protein called PAX2 and, during the third trimester of pregnancy, differentiate in Golgi cells, that will establish in the granule layer, and stellate and basket cells, that will take place in the molecular layer (Sudarov et al., 2011).

Cerebellar astrocytes, BG and a small number of oligodendrocytes expressing Olig2 domain originate from the VZ (Seto et al., 2014), while the majority of oligodendrocytes derive from extracerebellar regions of the CNS (Lee et al., 2005). Glial cells are involved in numerous processes of the cerebellar development: cellular migration (especially the PCs), synapse organization, production of neurotrophic factors, and formation of the blood-brain barrier (Araujo et al., 2019).

In mice, the exponential proliferation of the GCPs occurs after birth, while, in humans, it starts at 24th gestational week and continues during postnatal age, achieving a peak at the 32nd gestational week (Dobbing and Sands, 1973; Volpe, 2009). This process provokes an increase in the cerebellar mass that exceeds the volume of the posterior fossa, determining a series of folding along the anterior/posterior axis and allowing the expansion of the cerebellar surface (Sudarov and Joyner, 2007). This foliation starts with the organization of the "anchoring centers" and the appearance of scissures that form the folia and separate the lobes. In this process equally participate EGL, PCs, and BG (Sudarov and Joyner, 2007).

CEREBELLAR NEUROIMAGING

Neuroimaging studies on the cerebellum have provided important insights into its role both in adulthood and developing age. Continuous spreading and implementation of non-invasive neuroimaging tools have led us to: (1) monitoring the structural and functional state of the cerebellum, (2) detecting eventual abnormalities, (3) making diagnosis, (4) assessing prognosis, and (5) suggesting and monitoring therapies (Manto and Habas, 2016).

Magnetic resonance imaging (MRI), performed through both conventional (such as T1, T2, proton density, FLAIR, and DWI) and unconventional methods (such as functional MRI techniques), represents the most supportive diagnostic tool (Currie et al., 2013).

The recent advances in prenatal diagnosis allowed to monitor the development of the cerebellum during fetal life and early detect several malformations (Plaisier et al., 2015; D'Antonio et al., 2016). Furthermore, thanks to the recent developed complementary tools, structural or anatomical abnormalities may be detected and metabolic and functional ones (D'Antonio et al., 2016).

Functional MRI Techniques

Among the functional MRI techniques available, it is worth mentioning blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI), resting-state functional connectivity, MR spectroscopy and diffusion tensor imaging (DTI; Manto and Habas, 2016).

Blood oxygenation level-dependent functional magnetic resonance imaging is a technique that specifically exploits the differences in blood flow among the brain regions to compose functional images based on the increased activity of a specific site during a task (Glover, 2011). Structural and/or functional damages of certain areas of the CNS, therefore, of the cerebellum, may generate abnormal signals, contributing to giving important information about cerebellar diseases (Manto and Habas, 2016). Jayakumar et al. (2008) performed a BOLD-fMRI on SCA1 patients and healthy patients during the execution of the hands' supination-pronation movements, detecting an activation of cerebellum network during this movement and a malfunctioning of cortico-cerebellar loops in the former. Another study carried out by Duarte et al. (2016) used BOLD-fMRI to compare SCA3 patients versus a control group while performing a motor task (finger tapping). The authors demonstrated the cerebellum's abnormal response signals and other cerebral regions, such as the somatosensory and prefrontal cortices and subcortical areas (putamen, globus pallidus, and thalamus). According to their

work, this technique may allow not only to discriminate between SCA3 patients and controls executing the motor task at 5 Hz, but also to monitor the disease progression through performance-level-dependent differences.

Resting-state fMRI methods are based on the assumption that different brain regions, sharing a temporal correlated activity in terms of spontaneous BOLD signal, form functional networks that can be analyzed in healthy subjects and pathological conditions. They appear to be promising techniques in detecting the brain's functional alterations, such as in ataxias, and, interestingly, in psychiatric disorders too (Woodward and Cascio, 2015). This is even more intriguing in the light of the fact that this particular tool, compared to other fMRI techniques, does not require the patient's active participation (Woodward and Cascio, 2015). Khan et al. (2015) exploited this peculiar technique to assess functional cortico-cerebellar connectivity in autistic children and adolescents, detecting an atypical predominant cortico-cerebellar overconnectivity, majorly in sensori-motor networks, and a concurrent underconnectivity in supramodal ones. A later study carried out by Ramos et al. (2019) on a vast cohort of autistic patients provided further data, detecting a reduced intrinsic connectivity between the cerebellum and various cortical regions involved in ASD, i.e., right fusiform gyrus, right superior temporal gyrus, and left middle temporal gyrus. MinlanYuan, Meng et al. (2017) used resting-state fMRI to demonstrate the relationship between social anxiety disorder and specific cerebellar neural circuits, revealing lower levels of connectivity in certain cerebellar regions of patients than controls. Furthermore, this study allowed to correlate higher levels of anxiety to lower connectivity and to predict clinical improvement after cognitive-behavioral therapy in those patients with stronger circuits levels at baseline. Though the relatively small cohort of patients, this study is consistent with the aforementioned concept that functional neuroimaging is slowly becoming more crucial in clinical practice (MinlanYuan, Meng et al., 2017).

H-magnetic resonance spectroscopy is used to measure quantitatively and qualitatively numerous neurometabolites, among which *N*-acetyl-aspartate, Choline, Creatine, Myo-inositol, Lactate, Glutamate, Glutamine, and Gamma-aminobutyric acid (GABA), possibly contributing to various brain diseases and widely implicated in neuronal and axonal health, membrane turnover, energetic metabolism, and neurotransmission (Zhu and Barker, 2011).

Concerning cerebellar disorders, this technique seems particularly useful when it comes to tumors, infections, strokes, metabolic disorders, or white-matter diseases, as well as in the assessment of the metabolism of other organs, such as heart and muscle, often compromised in cerebellar ataxias (Lodi et al., 2001; Nachbauer et al., 2013; Manto and Huisman, 2018).

Diffusion tensor imaging is a non-invasive MRI technique based on the analysis of diffusion of water in different tissues, allowing a three-dimensional (3D) graphic reconstruction of the areas investigated, permitting, and a 3D analysis of white matter. In this latter case, the method is also referred to as tractography (Habas and Manto, 2018). This technique is particularly interesting when it comes to cerebellar disorders, since it provides important information on its anatomy and its connections (afferents and efferences), even during the phase of the development. In this regard, Bruckert et al. (2019) retrospectively analyzed the MRI tractography scans of a vast cohort of patients (aged 1 day to 17 years) showing age-related changes of the cerebellar white matter throughout the development, and reporting, an increase of mean tract fractional anisotropy and a concomitant decrease of mean tract mean diffusivity in all peduncles, with particularly rapid changes both in diffusion measures during the first 24 months of life, followed by more gradual change later in life. Despite the limitations of the study, e.g., the small sample of subjects and the interindividual differences among them, this work offers new interesting data that may contribute to identifying sensitive biomarkers of cerebellar abnormalities and better characterize cerebellar circuitry in clinical populations (Bruckert et al., 2019).

Moreover, as recently reviewed by Crippa et al. (2016), different studies showed a decrease of fractional anisotropy, measure of white matter integrity, in the white matter of individuals with ASD, hence, suggesting a weaker structural connectivity of their cerebro-cerebellar circuits, and strengthening the currently accepted notion of ASD as a connectivity disorder.

In conclusion, tractography can be used to study cerebellar development since fetal life, particularly in preterm brain injuries and neurodevelopmental disorders in which the cerebellum is notably often involved. Habas and Manto (2018) recently reviewed previous reports showing the different tractography applications in cerebellar diseases, such as cerebellar malformations, autosomal-recessive ataxias, neoplastic or degenerative disorders, and traumatic injuries, throughout the different phases of life.

Other Neuroimaging Techniques

A separate mention should be made for other neuroimaging techniques, such as nuclear medicine and ultrasonography.

Single-photon emission computed tomography and positron emission tomography (PET) must be cited, though their application to the pediatric field remains limited due to the use of dangerous radiation (Manto and Huisman, 2018). Nevertheless, Szyszko et al. (2015) have recently described a potential role of F-fluorodeoxyglucose PET/computed tomography in the assessment of certain pediatric dystonia, such as neurodegeneration with brain iron accumulation, in which an overactivity of the putamen and an underactivity of the cerebellum were detected.

Cranial Ultrasound Scan (cUS) is a common diagnostic tool, safe and feasible, allowing bed-sided serial investigations in newborns (Ecury-Goossen et al., 2015). cUS appears particularly useful for the evaluation of the neonatal brain, especially for the identification of those at high risk of neurodevelopmental impairment, such as the preterm ones (Plaisier et al., 2015; Steggerda et al., 2015). cUS has two main limits: it is highly related to the rater's skills, and, it is applicable only until the acoustic windows are available (approximately 6 months of age; Steggerda and van Wezel-Meijler, 2016). The best acoustic window to study the posterior fossa is usually represented by the mastoid

fontanel (MF; Buckley et al., 1997; Luna and Goldstein, 2000; Steggerda et al., 2015). However, a recent study carried out by Muehlbacher et al. (2020) encouraged the approach through the Foramen occipital magnum (FOM) in very low birth weight infants. The FOM window allows to examine both hemispheres at the same time and easily detect even small cerebellar damages. Therefore, this approach must be considered, especially in very preterm infants (Muehlbacher et al., 2020). Particularly in this specific population, different studies proved that cUS, though unable to detect cerebellar microhemorrhages, plays an important role in revealing massive cerebellar ones, severe conditions potentially leading to cerebellar disruption and eventual atrophy, with subsequent long-term pervasive neurodevelopmental impairments, involving cognitive, learning, and behavioral areas (Limperopoulos et al., 2005, 2007; Parodi et al., 2015). Finally, it may be concluded that recent developments in the ultrasonography field, such as contrast-enhanced ultrasonography, microvessel imaging, or elastography, are significantly enriching the neonatal care field (Manto and Huisman, 2018).

OVERVIEW OF THE CEREBELLAR FUNCTIONS: FROM MOTOR TUNING TO COGNITION

Originally, the cerebellum was thought to be merely implicated in motor functions, as it is involved in maintaining balance and in executive control of movements (synergy), almost functioning as a "real-time movement tuner." Therefore, a lesion of the cerebellum usually presents with gait and balance disorders (namely ataxia and astasia, respectively) and abnormal coordination of opposite muscle groups (asynergia), leading to an impaired coordination of the limbs (dysmetria), difficulties in articulation of speech (dysarthria), and excessive movements of the eyes with inadequate focus stability (nystagmus; Mutani et al., 2012; Schmahmann, 2019).

Since the attention to cerebellar malfunction shifted from the motor disorders to the cognitive and behavioral impairments, we discovered the numerous non-motor roles of this complex organ, especially memory, executive functions, and language (Sathyanesan et al., 2019). This is consistent with the data suggesting that most of the cerebellum is connected with associative areas of the cerebral cortex (Bostan et al., 2013).

Several cerebellar functions proposed during the last few decades included: motor and sequence learning, biological timer, prediction of results and movement assessment, automatization, long-term depression supporting memory, body dynamics storage and sensory inputs integration (Schmahmann et al., 2019). Schmahmann proposed a theory based on the repetitiveness of the cerebellar microanatomical structure, the universal cerebellar transform (UCT). The UCT acts as an unconscious regulator of movement and behavior, combining external and internal stimuli adjusting the response to the circumstances. According with this assumption, deficits of non-motor functions are described as "Dysmetria of thought" (Schmahmann, 1998). This hypothesis is also interesting in the perspective of the cerebellum, seen as a fundamental organ engaged in the development and specialization of cognitive regions of the cerebral cortex (Molinari et al., 2018).

As previously discussed, the cerebellum has been divided into three functional areas: the anterior lobe, formed by lobules I–V, is mostly implicated in sensorimotor connections and in determining posture, tone e movements; the posterior lobe, represented by lobules VI–IX, is involved in cognitive, social and behavioral tasks; the flocculonodular lobe, constituted by lobule X, is responsible for equilibrium, eye movements and adjusting reflexes (Stoodley and Schmahmann, 2018). These findings have been confirmed by numerous anatomic, clinical and functional neuroimaging studies, demonstrating no overlap between motor and cognitive/affective areas except for tasks that include both motor and non-motor characteristics, such as language and social processing (Sathyanesan et al., 2019; Schmahmann et al., 2019).

Among the cognitive functions fulfilled by the cerebellum, there are visuomotor sequence learning (the ability to recognize events and organize them as a sequence) and other executive functions, such as visual and auditory sequential memory, strategy planning, visuo-spatial ability, and attention (Molinari et al., 1997; Riva, 1998). These functions are implicated in writing and reading; therefore, a lesion of posterior regions can determine learning disabilities and other neurodevelopmental disorders (Vicari et al., 2005). Also, the behavior is affected by cerebellar lesions, indicating an involvement in its regulation, and ataxic patients can present with an excess or reduction of response to internal and external stimuli (Molinari et al., 2018).

Language is one of the most important functions in which the cerebellum is implicated. Considering the initial belief of a mere involvement in the motor control of speech, to date, a more complex role of the cerebellum, including non-motor aspects of language, has emerged (Mariën et al., 2014). An involvement of the right lateral region of the cerebellum, contralateral to the Broca's area, has been widely demonstrated in language impairments through anatomical and functional neuroimaging studies (Mariën and Borgatti, 2018). In detail, a lesion in the right cerebellum may, in its turn, determine a functional depression of supratentorial language areas due to reduced inputs crossing the cerebello-cortical pathways (cerebello-cerebral diaschisis; Mariën et al., 2009). Conversely, a cerebro-cerebellar diaschisis, namely a supratentorial lesion causing a loss of function in cerebellar regions, has been associated with language deficits (Abe et al., 1997). Furthermore, today there is new evidence of a more intricate connection between both cerebellar hemispheres and dominant language cortex, supporting a possible left cerebellar hemisphere contribution to linguistic processes *via* ipsilateral cerebellar-basal ganglia-cortical pathways, hence claiming a role of ipsilateral cerebello-cerebral diaschisis in language impairments (Murdoch and Whelan, 2007).

The cerebellum's association with language function is determined by the specific cortico-cerebellar connectivity to the right cerebellum from the left cortical hemisphere, and supported by structural and functional connectivity analyses that revealed projections from higher-order association areas, including the prefrontal, posterior parietal, and superior temporal cortices, known to be involved in language function, to posterior cerebellar

lobules VI, Crus I, Crus II, and VIIb (**Figure 1**). Further studies are needed to well-assess these complex projections and establish a functional topographic map (especially to lead specific targets for rehabilitation; Vias and Dick, 2017).

There are many signs and symptoms related to speech in children, including deficits in fluency and verbal initiative, anomia, grammar, and pragmatical difficulties, or even total absence of language (Salman and Tsai, 2016). An interesting entity is the cerebellar mutism syndrome (CMS), consisting of a temporary total absence of speech, except for vocal phenomena such as whining and crying, due to various cerebellar damages, such as after surgical rescission of cerebellar tumors (Catsman-Berrevoets, 2017).

Still, in the posterior lobe, social functions are localized in the vermis zone, especially the ability to process emotion, i.e., pain, thanks to its connections to the limbic lobe. On the contrary, more complex social skills, as empathy, theory of mind, abstraction and mentalization are thought to be localized in the paravermial lobules (Leggio and Olivito, 2018).

Furthermore, recent functional neuroimaging findings comparing subjects with typical and atypical development (autism spectrum disorder) revealed an abnormal connectivity between the cerebellum and specific cortical areas in charge of functions usually compromised in autism, therefore strictly linked to autistic traits and symptoms, such as abnormal social processing (fusiform gyrus and lateral temporal cortex), motor impairments and stereotyped behaviors (frontocerebellar pathways; Just et al., 2012; Floris et al., 2016; Ramos et al., 2019). In this regard, Rogers et al. (2013) emphasized the association between abnormalities of cerebellar functions in autism and deficits in cognitive, motor behavior, and social reward. Moreover, though much more has yet to be unraveled, Right Crus I (RCrusI; **Figure 1**) dysfunctions have been reported both in mice models and humans with autism. In fact, this region is considered functionally related to circuits implicated in autism; hence a dysfunction of RCrusI may determine autistic symptoms, particularly in terms of social impairments and repetitive behaviors. Nevertheless, further data are needed to clearly assess its exact contribution to ASD and its eventual causal relationship with potential coexistent motor deficits (Stoodley et al., 2017). In conclusion, it is worth mentioning that cerebellar neuroanatomical alterations are the most replicated findings in postmortem brain samples of patients with autism (Wegiel et al., 2014).

CEREBELLAR NEUROLOGICAL FINDINGS

Several clinical signs can be evaluated when trying to assess cerebellar functioning. In this section we will therefore analyze detailed neurological findings according to an age-related assessment, thus retracing cerebellar physiological functions and development.

Abnormal eye movements are very common in cerebellar lesions. Nystagmus and inappropriate saccades are consistent findings of the so-called ocular instability. Five types of nystagmus have been described in the cerebellar oculomotor syndrome: (1) the downbeat nystagmus (upward slow phase and downward fast-phase of nystagmus); (2) gaze-evoked nystagmus (when the fast-phase corresponds to the direction of gaze); (3) periodic alternating nystagmus (a spontaneous horizontal nystagmus with periodic alternation of direction); (4) positioning nystagmus (which changes in relation to different head positions); and (5) spontaneous and head-shaking nystagmus (which follows head oscillations; Bodranghien et al., 2016). Inappropriate saccades usually consist of hypometric or hypermetric saccadic eye movements, meaning that the patient may under-, or overshoot the fixation target (Ataullah and Naqvi, 2020). Nevertheless, other deficits in saccades may be detected in cerebellar patients, as well as further ocular impairments, such as ocular misalignment and impaired vestibulo-ocular reflex (Bodranghien et al., 2016). Overall, even if not always anatomically specific, the above-mentioned oculomotor deficits can represent the only evident cerebellar abnormality in the early age of life (Weiss et al., 2009; Lee et al., 2016).

As cerebellar is involved in tone regulation (tonic function), hypotonia is usually encountered in hemispheric cerebellar lesions. Cerebellar patients often have pendular reflexes resulting in oscillations of the limb at the percussion and abnormal "dampening." This is due to the impaired calibration of muscular contraction (Mutani et al., 2012; Ataullah and Naqvi, 2020). Conversely, patients with chronic cerebellar syndromes usually show hypertonia, probably due to other brain systems' involvement. Cerebellar ataxic gait is typically characterized by a widened base, unsteadiness and clumsiness, with poor coordination of the legs and feet (usually excessively raised at each step), and lateral veering, and it is often referred to as "drunken" gait (Mochizuki and Ugawa, 2010; Ataullah and Naqvi, 2020). To assess the steadiness of gait, it may be interesting to test tandem gait too, asking the patient to walk ideally in a straight line, in such a way that the heel of the front foot touches the toes of the back one at each step. Usually, cerebellar ataxic patients are not able to do so. Furthermore, in a recent metanalysis, Buckley et al. (2018) have summarized the main differences between gait of cerebellar ataxic patients and healthy controls. It appears that the former group, in comparison to the latter one, presents a reduction of walking speed, cadence, step length, stride length and swing phase and an increase of base width, stride time, step time, stance phase and double limb support phase, as well as a higher variability of step length, stride length and stride time (Buckley et al., 2018). The above-mentioned peculiar characteristics are consistent with the typical walking style of ataxic patients previously mentioned (Mochizuki and Ugawa, 2010; Ataullah and Naqvi, 2020).

In regard to balance, besides the tandem gait, the Romberg test should be performed too. This test is considered positive when the patient, with the eyes closed, loses his balance, oscillating or falling. It is noteworthy mentioning that cerebellar ataxic patients usually present with a negative Romberg test. However, this peculiar maneuver is useful for a differential diagnosis, allowing to detect sensory ataxia (positive Romberg test), hence indicating the need to investigate the presence of myelopathies (Forbes and Cronovich, 2020). Cerebellar ataxia, due to vermian lesions,

is usually characterized by continuous oscillation of the body, retropulsion and attempts to correct muscular contractions, both with eyes open and closed (Mutani et al., 2012).

Vertigo and dizziness (presenting with an acute onset, or as recurrent attacks, or as chronic/permanent signs) are usually associated with imbalance and may be due to lesions of the cerebellar ocular motor systems or the pathway related to the vestibulocerebellum (Bodranghien et al., 2016).

To assess the presence of asynergia, the rebound phenomenon must be tested. This is useful to assess the inability of the malfunctioning cerebellum to regulate the action of opposing muscle groups. The examiner applies a certain pressure against the resistance exerted by the arm of the patient (outstretched or flexed with a closed fist), releasing it suddenly. Normally, a fleeting oscillation and a rapid return to the original position is expected. However, in cerebellar dysfunctions, a strong, inappropriate, rapid and opposite muscular force generates when the tested arm is released (Ataullah and Naqvi, 2020).

Cerebellar asynergia can be also evaluated by the finger-nose test and the heel-shin one. These tests may reveal other important cerebellar signs, such as hypermetria (when too much strength is used to reach the targets, namely nose, or shin) or dysmetria (when the finger/heel overshoots the target). Furthermore, cerebellar patients usually tend to decompose every single movement in its subparts and, when asked to alternate opposite movements rapidly, they are unable to do it (dysdiadochokinesia; Mutani et al., 2012; Ataullah and Naqvi, 2020).

Another important neurological sign of motor dysfunction due to cerebellar lesions is "intention tremor" or "action tremor" which starts and progressively increases in amplitude during the terminal phase of voluntary movement, disappearing during rest (Mutani et al., 2012; Ataullah and Naqvi, 2020). Even though not always tested, reaching and grasping movements are often compromised in cerebellar patients.

This may be secondary to other cerebellar signs and symptoms (such as tremor, decomposition of movements, dysmetria, and abnormal eye-movements), or directly related to a specific cerebellar damage (such as atrophy). Finally, language, cognitive and affective functions should also be assessed since they may be compromised in cerebellar damages, thus determining the previously mentioned CCAS (Bodranghien et al., 2016).

Cerebellar patients may present executive function deficits (with inability to plan and organize, poor problem-solving capacity, and concrete thinking), impairments of short-term memory, and visual-spatial deficits (Bodranghien et al., 2016).

Expressive language is often abnormal. "Slurred staccato speech," also known as "scanning speech," is a common finding in cerebellar disorders (Ataullah and Naqvi, 2020). This type of language is characterized by reduced verbal fluency, with words pronounced as broken in syllables and with long pauses between them. Moreover, reluctance to engage in conversation, difficulty in finding words, abnormal syntax and impaired metalinguistic ability may occur (Bodranghien et al., 2016). Recently, mutism of cerebellar origin (namely the aforementioned CMS) has been reported too (Catsman-Berrevoets, 2017).

Finally, with respect to the affective aspects, cerebellar damage may determine a wide variety of impairments, with regard to mood and emotional regulation, personality style, behavioral modulation, and social skills.

Moreover, nowadays, cerebellar lesions may correlate with neurodevelopmental and psychiatric disorders, such as autism, psychosis, mood disorders, panic disorder, dyslexia, attention deficit disorder, and many others (Bodranghien et al., 2016; MinlanYuan, Meng et al., 2017).

Overall, lesions of the anterior lobe appear to cause sensorimotor impairments, whereas lesions of the posterior lobe are associated with CCAS (Schmahmann et al., 2019).

AGE-RELATED CEREBELLAR EXAMINATION

The cerebellum in childhood may subserve several age-dependent functions that can be affected in a variety of CNS pathologies. An age-related assessment in such patients may address early diagnosis and proper intervention since the first months of life (Haldipur and Millen, 2019).

In newborns and infants, the neurological examination may be conducted using standardized methods, such as the Hammersmith Neurological examination, both in its Neonatal and Infant version (HNNE and HINE, respectively; Di Rosa et al., 2016). To the best of our knowledge, although correlations between HINE and HNNE specific items and cerebellar development have not been reported yet, hypotonia, developmental delay, abnormal reflexes, and abnormal eye movements are frequently observed in newborns and infants with cerebellar malformations (Romani et al., 2013). Feeding difficulties and failure to thrive are commonly related to hypotonia or uncoordinated oro-motor function in these children and sometimes require nasogastric feeding tubes or gastrostomy placement to prevent aspiration and provide adequate caloric intake. Abnormal ocular movements (oculomotor apraxia, nystagmus, and strabismus) can be early onset features associated with cerebellar malformations and

TABLE 1 | Age related signs and symptoms in cerebellar malformations.

Age-onset	Hypotonia	Ocular symptoms	Coordination disorders	Oro-motor apraxia	Balance disturbances	Ataxia	Other cerebellar signs
Neonatal	+++	++	+++	+ –	/	/	/
Infantile	++	+++	+++	+++	/	+–	/
Prescholar	+–	+++	++	++	+–	+++	++
School-age	+–	+++	+–	+–	+++	+++	+++

Signs or symptoms severity: / = not valuable; +–: not always valuable; + = mild severity; ++ = moderate severity; and +++: severe.

potentially represent the most suggestive "cerebellar" findings in newborns or infants. Fine-motor skills are commonly affected in children with cerebellar dysfunctions, with subsequent age-related impairment in reaching, grasping, visuomotor manual skills, drafting and writing across infancy and early childhood. Indeed, clinical evaluation of balance and gait, cannot be easily performed before 18 months of age, when independent standing and walking have already appeared in the majority of children (Scharf et al., 2016).

Tam et al. (2019) recently reported the constellation of neurological findings in a cohort of preterm infants with cerebellar hypoplasia. Hypotonia was the most common finding at 18 months' corrected age, associated with hyperreflexia and postural instability on standing, likely related to smaller cerebellar volume (Tam et al., 2019). Oculomotor apraxia is a highly suggestive symptom of cerebellar malformation also in toddlers and older children. Saccadic initiation failure is the most common eye movement abnormality, being saccades hypometric or absent (Tusa and Hove, 1999; Salman and Chodirker, 2015). Furthermore, more complex abilities, such as tandem gait or finger-nose and heel-shin tests, cannot be examined before 4 years of age or according to the cooperation skills of the child. As a rule, in children aged between 4 and 8 years, specific cerebellar tests (particularly those exploring fine-coordination skills) may be physiologically affected by the degree of cerebellar maturation, as well as the cooperation of the patient. After 8 years of age, a complete neurological examination may be performed as well as in the adult age. The most common motor symptoms of cerebellar dysfunction in school-aged children include dyssynergia, dysmetria, dysdiadochokinesia, and ataxia. Expressive language impairment with scanning speech due to oral-motor dyspraxia can be easily disclosed in preschool and school-aged children. The neurological signs of cerebellar dysfunctions across developing age are summarized in **Table 1**.

DISCUSSION

The cerebellum remains a fascinating and still relatively unexplored part of the CNS involved in several neurocognitive functions. From the initial mere involvement in motor coordination up to a central role in cognition, social behavior, and communication, we were led to revalue the developmental role of the cerebellum. Age-dependent neurological findings need to be taken into account in clinical practice to assess cerebellar functioning even in early childhood properly. Even though the main evidence of cerebellar involvement comes from the observation of the pathological counterpart, fewer insights have been provided by longitudinal studies in typically developing children. Further studies in wide populations may provide details on clinical developmental trajectories of cerebellar functions and address early detection of pathological conditions.

AUTHOR CONTRIBUTIONS

AN and GD conceived, planned, and supervised the study. GA and GS wrote the first draft of the manuscript. GA and AI designed the figures. LV and GQ helped supervise the project. All authors contributed to manuscript revision, read, and approved the submitted version.

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frontiers in Systems Neuroscience

REVIEW
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The Forward Model: A Unifying Theory for the Role of the Cerebellum in Motor Control and Sense of Agency

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For more than two decades, there has been converging evidence for an essential role of the cerebellum in non-motor functions. The cerebellum is not only important in learning and sensorimotor processes, some growing evidences show its implication in conditional learning and reward, which allows building our expectations about behavioral outcomes. More recent work has demonstrated that the cerebellum is also required for the sense of agency, a cognitive process that allows recognizing an action as our own, suggesting that the cerebellum might serve as an interface between sensorimotor function and cognition. A unifying model that would explain the role of the cerebellum across these processes has not been fully established. Nonetheless, an important heritage was given by the field of motor control: the forward model theory. This theory stipulates that movements are controlled based on the constant interactions between our organism and its environment through feedforward and feedback loops. Feedforward loops predict what is going to happen, while feedback loops confront the prediction with what happened so that we can react accordingly. From an anatomical point of view, the cerebellum is at an ideal location at the interface between the motor and sensory systems, as it is connected to cerebral, striatal, and spinal entities *via* parallel loops, so that it can link sensory and motor systems with cognitive processes. Recent findings showing that the cerebellum participates in building the sense of agency as a predictive and comparator system will be reviewed together with past work on motor control within the context of the forward model theory.

Keywords: prediction error, sensory mismatch, neuroimaging, motor control, movement disorders

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INTRODUCTION

Over the past decades, there has been accumulating evidence suggesting that the role of the cerebellum goes far beyond motor control and involves a variety of cognitive tasks (Strick et al., 2009). The unique architecture of the cerebellum could explain its involvement in such a diverse range of functions. The connectivity between the cerebellum and the cerebral cortex is organized in parallel loops: different regions of the cerebellum receive inputs from a large set of cerebral regions

(not only from motor regions, but also from associative areas) through the pontine nuclei (PN), and in return, the deep cerebellar nuclei send projections back to the same cerebral regions through the thalamus, thus forming a Cerebro-Ponto-cerebello-dentato-thalamocortical pathway (Ito, 2006; Sokolov et al., 2017; Diedrichsen et al., 2019; Cabaraux et al., 2020; Tanaka et al., 2020). Contrary to the neocortex, the local circuitry of the cerebellum is highly uniform across its different regions, suggesting that the diversity of cerebellar functions could rely on a single cerebellar computation that would be embedded in parallel cerebro-cerebellar loops (Diedrichsen et al., 2019). Among the proposals for this single cerebellar algorithm, the "forward model" is of particular interest (Sokolov et al., 2017; Diedrichsen et al., 2019; Tanaka et al., 2020).

The forward model is a computational model of voluntary motor control that emphasizes the critical role of the comparison between the intentional content of our actions and their outcomes. It was first proposed as a model to control arms and eye-movement systems (Sperry, 1950), but has now reached recognition to apply to a larger repertoire of human actions (Imamizu and Kawato, 2012). The forward model evaluates the input-output function of body segments involved in the movements and relies on two core functions: prediction and error processing (Sokolov et al., 2017). According to this model, a copy of the motor command, the "efference copy" representing the motor intention, is generated during the preparation of voluntary movements to predict the sensory consequence of the forthcoming action. This efference copy is sent to brain areas named "comparators" that monitor the congruence between the efference copy and the actual sensory feedback generated by the movement (Miall et al., 1993; Wolpert et al., 1995; Blakemore and Sirigu, 2003; Haggard and Whitford, 2004; Haggard, 2008; Jeannerod, 2009; Waszak et al., 2012; Dogge et al., 2019; Seghezzi et al., 2019; Tanaka et al., 2020). In particular, this model predicts an increased activation in the *comparator* areas in case of a sensory prediction error, i.e., when there is a mismatch between the motor command and the sensory feedback. Mismatch detection and the forward model are involved in different aspects of motor execution: in motor control (for rapid online movement adaptation, for sensory attenuation), in motor learning (sensorimotor adaptation), but also for the sense of agency (Miall et al., 1993; Wolpert et al., 1998; Desmurget and Grafton, 2000; Blakemore and Sirigu, 2003; Jeannerod, 2009; Haggard, 2017; Dogge et al., 2019; Seghezzi et al., 2019). The sense of agency can be defined as the "experience of controlling our own actions, and through them, events in the outside world" (Haggard, 2017). The sense of agency is an important cognitive process underlying action execution, as it links motor control and the feeling of being the author of our own actions. The forward model plays a crucial role in two mechanisms that occur during action execution: it ensures proper motor control and contributes to the sense of agency (Haggard, 2017). It is thus possible that the brain regions underlying motor control through a forward model could also contribute to the sense of agency. Among these areas, the cerebellum is of particular interest and could be a *comparator* considering its unique architecture and connectivity (Miall et al., 1993; Wolpert et al., 1998; Desmurget and Grafton, 2000; Blakemore and Sirigu, 2003; Ito, 2006, 2008; Jeannerod, 2009; Tanaka et al., 2020; **Figure 1**).

In the first part, we will define self-agency and the underlying brain network to show how motor control and the forward model are related to this concept. In the second part, we will describe the functional neuroanatomy of the cerebellum and emphasize

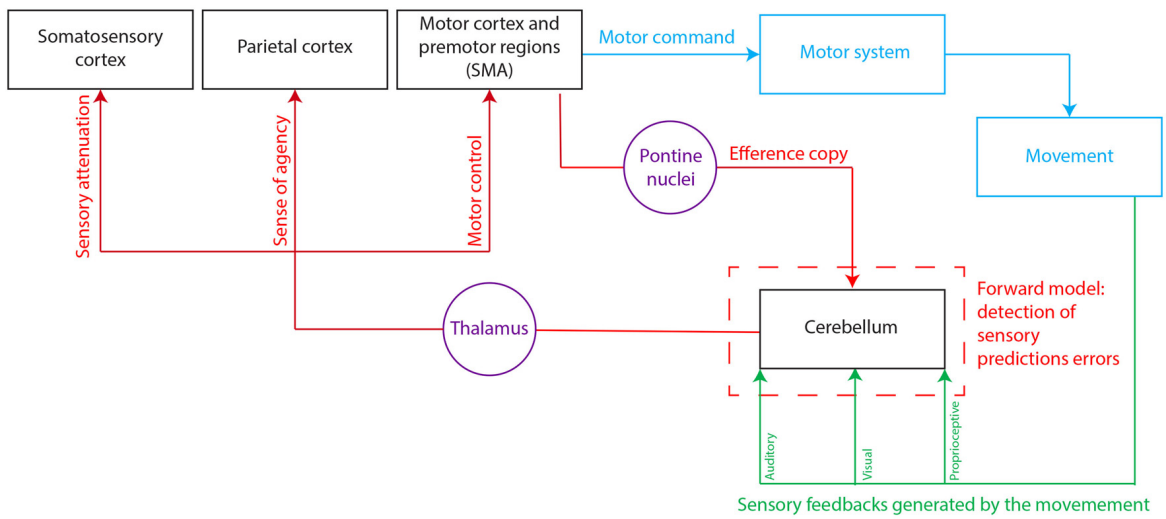

FIGURE 1 | Hypothetical model for the cerebro-cerebellar loops involved in the forward model. The cerebellum is thought to integrate the efference copy—a copy of the motor command that originates from the motor and premotor areas and represents the intentional content of the action—and the actual sensory feedback generated by the movement. The existence of a discrepancy between the predicted and actual motor outcome (or sensory prediction error) would be detected at the level of the cerebellum. This signal error would then be sent to different cortical areas to serve different functions: motor control, sensory attenuation, and sense of agency. SMA, supplementary motor area.

how its singular organization is relevant regarding the forward model theory and self-agency. In a third part, we will review the functional evidence supporting the role of the cerebellum as a *predictor* and a *comparator*, in particular the fact that this region is sensitive to a sensory prediction error, i.e., to a mismatch between the intentional content of the action and its outcome, that are key processes for self-agency. We will also review the role of the cerebellum in the different functions related to motor control and learning that have been associated with the forward model and that can influence the prediction system important to self-agency. In a fourth part, we will review recent evidence linking the cerebellum to the sense of agency and we will discuss how the cerebellum could be a node of the self-agency network as a comparator and mismatch detection system.

THE SENSE OF AGENCY AND THE FORWARD MODEL

Framework

In the present work, we will use an operational definition of self-agency, "the experience of controlling our own actions, and through them, events in the outside world" (Haggard, 2017). Because it is a subjective feeling, the sense of agency has been mainly studied in humans, although some pieces of evidence are suggesting that non-human primates also have a sense of agency (Kaneko and Tomonaga, 2011; Couchman, 2012). Fitting with this conception introduced by Patrick Haggard, we will consider the sense of agency as the experience that occurs before, during, and after the actual movements. In daily life, we do not often question whether we are the agent of our actions. It rather comes as an element of surprise, when unexpectedly, we detect an incongruence between our intention and the action outcome. This occurs for instance when you are fully focused on a skilled motor task (writing between two tiny lines, playing "Tretris" on your smartphone), and a neighboring person collides with you and disturbs your neat movement. This induces a discrepancy between what you planned on doing and the actual results of the action, and the feeling that you are not responsible for the action results. This example underlines that certain conditions are necessary for the sense of agency to occur. First, it requires a voluntary movement, which we refer to as an action that is purposefully initiated by the subject, by opposition to involuntary movements such as reflexes or movements caused by external devices (Haggard, 2017). Second, the expected and actual results of the action need to be compared, so that sense of agency is related to the action goals. Overall, the feeling of self-agency depends on all the steps of voluntary action and links the intention to the movement outcome. Volition and agency are two concepts that are linked (Hallett, 2010; Haggard, 2017): the first is the sense of willing a movement, the second is the sense that the willed movement has occurred. An involuntary movement could disrupt or decrease the sense of agency by inducing a discrepancy between the predictions and the actual results of the action. The neuroanatomical bases of what makes the difference between involuntary and voluntary movements are not clear cut (Hallett, 2010), especially in pathologies when both occur at the same time. The interpretation of voluntariness seems to arise from a feed-forward neural signal, a corollary discharge. The comparator that processes predictions signals from the corollary discharge and the actual movement results would help to then give rise to the sense of agency.

The sense of agency is usually divided into two distinct steps. The first one is referring to the low-level, non-conceptual, implicit feeling of control over an action, without a relationship to any conscious thought, and is known as implicit agency, feeling of agency, or instrumental agency (Synofzik et al., 2008b; Haggard, 2017). The second is referring to the explicit judgment of being the source of the action-outcome, also known as "judgment of agency" or explicit agency (Synofzik et al., 2008b). The explicit judgment of agency requires one to attribute sensory events to one's intentional action, and is influenced by cognitive biases (such as positive outcomes); on the contrary, implicit measures capture an instinctive feeling without the need to explicitly think about agency or control, and thus are less prone to cognitive biases (Haggard, 2017). The feeling of agency and judgment of agency are two distinct processes that both contribute to the sense of agency.

Asking a subject whether he thinks he was the author of a given action is an easy way to assess the judgment of agency. By contrast, the measure of the implicit feeling of agency requires a specific experimental set-up. One implicit measure of self-agency is intentional binding. It focuses on time perception, which is influenced by the processes involved in voluntary movement. Intentional binding is the instinctive compression of the perceived time interval between an action and its outcome. In other words, the perceived time of voluntary action is shifted towards the subsequent outcomes (a sensory event following the action, such as a tone), and the perceived time of the outcomes themselves (in this example, the tone) are perceived shifted towards the voluntary actions that caused them (Haggard, 2017). As a result, intentional binding refers to the degree of control that we have over our actions (Beck et al., 2017). Sensory attenuation is an important factor influencing self-agency (Blakemore et al., 1998; Beck et al., 2017). Sensory attenuation refers to the fact that the sensory consequences of our actions are perceived differently from identical sensory input when it is externally generated: for instance, a self-produced tactile stimulus is perceived as less ticklish than the same stimulus generated externally (Blakemore et al., 1998). According to the forward model theory, sensory attenuation results from a comparison between the anticipation of movement outcome (through the efferent copy) and the actual consequence of the movement. This comparison allows us to distinguish sensory events produced by our own actions from those produced by external events, which is an important process to establish the sense of agency (Haggard, 2017). It was suggested that sensory attenuation (when stimuli are self-administrated compared to externally administrated) and outcome binding may track a common underlying process related to the sense of agency. Alternatively, perceived stimulus intensity and intentional binding could be linked by a domain-general mechanism such as multisensory cue integration (Beck et al., 2017). Last, one way of evaluating

the implicit feeling of agency is to manipulate the sensory feedback (by the introduction of a delay between an action and its outcome or by the distortion of visual feedback for instance) in order to induce a mismatch with the subject actual movement. This results in a "non-agency" or "disrupted-agency" feeling, as opposed to the "positive agency" (when the predicted and actual movement outcome match).

Networks Involved in the Sense of Agency

Over the last two decades, the use of neuroimaging techniques has led to the identification of the cerebral networks involved in the sense of agency. As stressed in the previous paragraph, the different measures of the sense of agency (explicit judgment of the agency, "non-agency" and intentional binding) have been associated with different brain regions, that have been recently reviewed in meta-analyzes (Sperduti et al., 2011; Seghezzi et al., 2019; Zito et al., 2020). The judgment of agency has been linked with activation in the anterior prefrontal cortex, the orbitofrontal cortex, the fronto-median cortex (Spengler et al., 2009; Miele et al., 2011; Zito et al., 2020), indicating that this process requires high-order, conceptual mechanisms. The network that is activated when the agency is disrupted consistently involves the temporo-parietal junction (TPJ) or inferior parietal lobule (IPL), the dorsomedial prefrontal cortex, the precuneus, the pre-supplementary motor area (preSMA), the superior and middle temporal gyrus, the angular gyrus (Sperduti et al., 2011; Seghezzi et al., 2019; Zito et al., 2020). By contrast, the "positive" self-agency has been associated with the insula, the primary somatosensory cortex, the premotor cortex, the SMA, the calcarine sulcus, the cerebellum (Sperduti et al., 2011; Seghezzi et al., 2019). Thus, it appears that the neurological substrate underlying the "two steps" of agency—the feeling of agency and the judgment of agency—is organized according to a rostrocaudal gradient in the human brain. While the feeling of agency, which has mainly been explored through the "non-agency" paradigm, seems to primarily rely on the posterior parietal cortex, the higher-order, conceptual step of the judgment of agency is implemented in prefrontal areas.

What Is the Link Between the Sense of Agency and the Forward Model Theory?

The "comparator model" of agency suggests that the low-order, sensorimotor process underlying the implicit feeling of agency relies on a forward model (Synofzik et al., 2008b; Jeannerod, 2009; Haggard, 2017). This model relies on the prediction of the sensory consequences of actions based on the original motor commands. The comparison between the prediction of the sensory consequences of the action to the actual movement feedback is used to produce a "prediction error". In the case of "positive" self-agency, the actual feedback fits exactly to the prediction, and the result of the comparison is zero when the event is caused by one's action (the internal predictive model is correct in that case); otherwise, in case of a mismatch between the anticipated and the actual outcome of the movement, the result is a negative prediction error (Haggard, 2017). However, the comparator model is not sufficient to explain the higher-order level of the judgment of agency: the prediction error would then be transmitted to higher-order associative areas in the prefrontal cortex, where it would be integrated along with contextual knowledge and belief reasoning to give rise to the judgment of agency (Synofzik et al., 2008b).

FUNCTIONAL NEUROANATOMY OF THE CEREBELLUM RELEVANT TO FORWARD THE MODEL THEORY

The cerebellum is a complex structure that is connected with the entire central nervous system (Stoodley and Schmahmann, 2018). The connectivity of the cerebellum is organized in a series of parallel loops with the cerebral cortex, the striatum, and the spinal cord, which makes the cerebellum a key sensorimotor interface: each region of the cerebellum receives inputs from a specific region of the central nervous system, and sends back projections to these same regions (Sokolov et al., 2017; Diedrichsen et al., 2019; Cabaraux et al., 2020; Tanaka et al., 2020; **Figure 2**). *Via* the **afferent** connections, it receives information from the cerebral cortex and processes sensory feedback from the peripheral system (muscles, joint position, auditory, visual, vestibular, and proprioceptive information; Baumann et al., 2015). The middle cerebellar peduncle (MCP) conveys inputs from a large set of brain regions (not only motor areas but also associative areas) and deep brain nuclei [striatum, subthalamic nucleus (STN)] that are relayed by the pontine nuclei (Bostan and Strick, 2010; Milardi et al., 2016; Cacciola et al., 2017; Bostan et al., 2018; Diedrichsen et al., 2019). The inferior cerebellar peduncle contains the afferent information from the spinal cord (spino-cerebellar tract and inputs from the inferior olivary nucleus), including the muscle spindles, joint receptors, and Golgi tendon organs (Cullen, 2011). Thus, the cerebellum is ideally located to integrate both the motor command (or efference copy), which originates from the motor cortex and the sensory feedback generated by the movement. This singular position makes it a good candidate to be a "comparator" in the framework of the forward model, that could detect a mismatch between the motor command and the sensory feedback (Miall et al., 1993; Ito, 2006, 2008; Sokolov et al., 2017; Diedrichsen et al., 2019; Tanaka et al., 2020). This error signal would then be sent back to the cortical brain areas and spinal cord *via* the **efferent** connections, to adapt the motor output to the constant changes of our environment. The cerebellar outputs are conveyed by the deep cerebellar nuclei: the superior cerebellar peduncle (SCP) contains all the efferent white matter fibers toward the cerebral cortex that are relayed by the red nucleus (RN) and thalamic nuclei, while the inferior cerebellar peduncle contains the outputs to the spinal cord that target motoneurons and body muscles *via* the vestibular nuclei and reticular formation (Cullen, 2011).

This connectivity pattern is remarkably conserved across the different cerebellar regions. From a macroscopic point of view, the cerebellum is divided into two lobes (anterior and posterior)

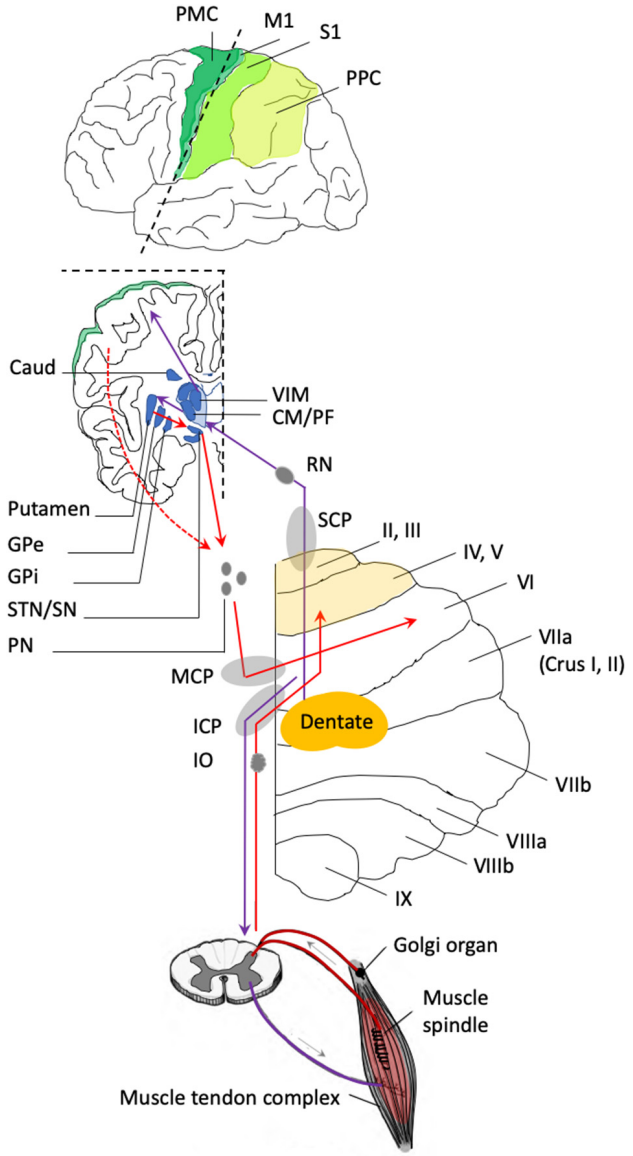

FIGURE 2 | Anatomical connections of the cerebellum relevant to the forward model. The anterior lobe of the cerebellum is represented in light yellow and includes the lobules labeled from I to V. The posterior lobe of the cerebellum includes the lobules labeled from VI to IX. The functional connectivity of the cerebellum is organized in a series of loops, where the cerebellum receives inputs from the cerebral cortex, the striatum, and the spinal cord, and in return, the deep cerebellar nuclei send projections back to these same regions. **Incoming pathways** to the cerebellum are represented in red. The middle cerebellar peduncle (MCP) contains the fibers that project from the cerebral cortex and the striatum (caudate (caud) and putamen) to the posterior lobe of the cerebellum through a relay in the pontine nuclei (PN). The cerebellum receives input from a large number of cortical areas, including regions associated with motor preparation and execution (represented in green; PMC, premotor cortex; M1, primary motor cortex; S1, primary somatosensory cortex; PPC, posterior parietal cortex). The cerebellum also receives inputs from the basal ganglia (represented in blue). The subthalamic nucleus (STN) is an additional relay between the striatal output [globus pallidum pars interna (GPi) and pars externa (GPe)] and the pontine nuclei. Also, the anterior cerebellum receives sensory (proprioceptive)

(*Continued*)

FIGURE 2 | Continued

inputs from the spinal cord and the inferior olive that pass through the inferior cerebellar peduncles (ICP). **Outgoing pathways** from the cerebellum are represented in purple. The superior cerebellar peduncle (SCP) contains the fibers that project to the red nucleus (RN) and to the thalamic nuclei that relay the information to the cerebral cortex and the striatum. The thalamic nuclei include the ventral intermediate nucleus (VIM), which is the relay between the cerebellum and cortical brain areas; the centro-medial (CM) nucleus and the parafascicular (PF) nucleus, which are the relay between the cerebellum and the striatum. The inferior cerebellar peduncle (ICP) contains fibers that project from the cerebellum to the spinal cord.

that are separated by the primary fissure. Each of them is further parcellated in different lobules (labeled from I to IX) that are associated with various functions, ranging from sensorimotor, cognitive, and emotional processes (Schmahmann et al., 2019). The microstructural organization of each cerebellar lobule is identical, consisting of cerebellar modules (Ito, 2006, 2008). The Purkinje cells receive excitatory inputs from the axons of granule cells (the parallel fibers) that relay the mossy fibers. In humans, there is a striking expansion of the information, as approximately 250 million mossy fibers contact 50 billion granule cells, followed by compression through 15 million Purkinje cells (Sanger et al., 2020). The Purkinje cells also receive excitatory inputs from the climbing fibers that originate in the inferior olivary. Also, the mossy fibers and climbing fibers provide excitatory inputs to the deep cerebellar nuclei. The Purkinje cells are the sole output of the cerebellar cortex and provide an inhibitory signal to their target neurons in the deep cerebellar nuclei. This specific architecture of the cerebellar modules allows a single Purkinje cell to integrate both the efference copy from the motor cortex and sensory feedback from the periphery, thus forming an adequate anatomical and functional substrate for a forward model (Cabaraux et al., 2020). In particular, learning in the cerebellum is driven by error signals (Doya, 2000; Hikosaka et al., 2002). These signals would be conveyed by climbing fibers originating from the inferior olive that encode sensorimotor information (Kitazawa et al., 1998), then integrated into Purkinje cells (Wang et al., 2000), and transmitted to the cerebral cortex *via* dentate-thalamic relays. Conceptually, motor commands originating from the cerebral cortex are optimized in terms of their sensorimotor accuracy, by going through the cerebellar loop circuits, this process being critical for motor skill learning.

Overall, the cellular microcircuitry and macroscopic connectivity pattern of the cerebellum provide the critical neural substrates of its putative role in the forward model, and thus for the feeling of agency.

THE CEREBELLUM AS A PREDICTOR AND COMPARATOR

A forward model relies on two core processes: prediction and detection/processing of prediction errors (Tanaka et al., 2020). In the following section, we will review the evidence supporting the role of the cerebellum in prediction and in the detection of sensory prediction errors that are key processes involved in determining self-agency. Last, we will report evidence showing that the cerebellum is also involved in anticipating self-generated

movements, resulting in sensory attenuation that is linked to self-agency.

Anticipatory Responses

Cerebellar activity is observed during the period preceding movement onset. For instance, a bilateral cerebellar activity was shown during the preparatory period of sequential finger movements (Cui et al., 2000). Pre-movement potentials were recorded in the VIM nucleus (a relay of the cerebello-cortical pathway) targeted during deep brain stimulation surgery in tremor patients (Paradiso et al., 2004; Purzner et al., 2007). When confronted with predictable perturbation, cerebellar activity in monkeys is modulated during the period preceding adaptive hand responses (Dugas and Smith, 1992; Monzée and Smith, 2004). Studies of patients with cerebellar lesions suggest that the cerebellum is involved in updating the prediction of the sensory consequences of movements to inform the perception of self-actions (Synofzik et al., 2008a; Roth et al., 2013). When dropping a ball with one hand and catching it with the other hand, the EMG pattern of the receiving hand in healthy subjects shows an anticipation process. This is not the case in cerebellar patients, suggesting that the cerebellum is involved in predicting the consequences of self-generated movements (Nowak et al., 2007). Specifically, the cerebellum might contribute to the action preparatory activity by facilitating the transitions between cortical activity states, thus contributing to adaptable and timely appropriate response (Li and Mrsic-Flogel, 2020).

Electrophysiological studies in non-human primates explored the relationship between the activity of Purkinje cells and different behavioral parameters (movement kinematics and dynamics) to precise the role of the cerebellum as an internal model (Tanaka et al., 2020). The underlying assumption was the following: a correlation between the Purkinje cells firing rate and the movement kinematics (the trajectory of the hand for instance) would be in favor of the forward model. By contrast, a correlation of the Purkinje cells activity and the movement dynamic (muscle activity) would suggest that the cerebellum functions as an inverse model that transforms the desired goal into a motor command. These experiences raised contradictory results, showing that Purkinje cells firing rates correlated either with the movement kinematics or with the movement dynamics (Pasalar et al., 2006; Yamamoto et al., 2007; Tanaka et al., 2020). A recent study clarified these controversial results by showing that the dentate nuclei cells firing rates could predict the future inputs to the cerebellum, strongly supporting the forward model (Tanaka et al., 2019). At the cellular level, this model postulates that the sensory feedback is conveyed by mossy fibers, that the prediction is computed by the Purkinje cells, and that the comparison between the sensory feedback and the prediction is operated at the level of the deep cerebellar nuclei (Tanaka et al., 2020).

Detection of Sensory Prediction Errors

The cerebellum has been repeatedly associated with mismatch detection, a process that is essential for the feeling of agency. First, activity in the cerebellum is increased during motor errors (Diedrichsen et al., 2005; Schlerf et al., 2012). Second, activity in the cerebellum is modulated when the sensory feedback (visual, auditory, or tactile) generated by the subject's movement is manipulated. This manipulation induces a discrepancy between the initial motor intention and the prediction of the movement outcome on the one hand, and the actual sensory consequences of the movement on the other hand. In particular, when introducing a variable and unexpected delay between the subject's movement and its sensory consequences (tactile or visual), the activity in the cerebellum positively correlated with this delay (Blakemore et al., 2001; van Kemenade et al., 2019). In another study, the subjects were instructed to make hand movements while receiving real-time visual feedback of a simulated hand. The simulated hand was either visually synchronous with the subject's movements, or not with a varying degree of mismatch. This procedure induced a loss of control of the hand based on the manipulated visual feedback and was associated with increased activation in the cerebellum among other regions (Nahab et al., 2011).

It thus appears that the cerebellum computes sensory prediction errors (sPE), which relate to the error between the sensory outcome and its prediction (Wolpert and Flanagan, 2001). Two mechanisms could be at play: the cerebellum may process errors as unexpected sensory events or may signal both the occurrence of unexpected stimuli and the omission of expected stimuli (Schlerf et al., 2012). In a study involving somatosensory stimulation in absence of movement, oscillations in the cerebellum measured with MEG were enhanced after the distortion of predicted somatosensory feedback (Tesche and Karhu, 2000). The cerebellar response was modulated as a function of expectancy and attention. Is this result a question of timing or sensory expectation? In his comment of this result, Richard Ivry considered the cerebellar response "to be best characterized as a detector of change or deviation in the sequence of sensory events, [. . .] yet the cerebellar response is not strictly sensory in that it does not require the delivery of an actual stimulus" (Ivry, 2000). This suggests that the "expected" aspect of the presence or absence of sensory feedback is the key factor for a cerebellar anticipatory response (Chabrol et al., 2019). In this sense, the cerebellum has the functional and anatomical properties to predict and anticipate events.

Sensory Attenuation

The sensory feedback that is generated by our voluntary actions elicits smaller cortical responses as compared to externally generates sensory signals. This phenomenon is known as "sensory attenuation" and is thought to rely on the forward model (Blakemore et al., 2000). As stipulated earlier, an efference copy of the motor command sent to the muscles would be used by the forward model to predict the sensory consequences of the command. The predicted consequences are compared to somatosensory feedback: if these match perfectly, cortical perceptual systems may not fully process the afferent signal, as it adds no information to the prediction (Haggard and Whitford, 2004). It has thus been proposed that sensory attenuation could be a process associated with the feeling of agency, as it allows us to distinguish self-produced as opposed to externally generated sensory stimuli (Blakemore et al., 1998, 2000).

The cerebellum could play a particular role in sensory attenuation, by evaluating the degree of matching between the predictions with the actual feedback. In agreement with this view, cerebellar activity is decreased in response to self-generated movements associated with tactile stimulation, while this activity is increased by external tactile stimulation (Blakemore et al., 1998). A recent study showed that disrupting cerebellar activity with TMS interfered with the cortical sensory attenuation of self-initiated sounds (Cao et al., 2017). In keeping with this, electrophysiological recordings of the cerebellum in non-human primates demonstrated that cerebellar neurons can cancel the reafferent sensory effects produced by self-generated movements (Brooks and Cullen, 2013).

Cerebellum and Forward Model During Motor Control and Learning

In this part, we will present the pieces of evidence supporting the role of the cerebellum in different motor processes that rely on the forward model: on-line correction of movement, visuomotor adaptation, and conditional learning. Indeed, the ability to control our movement and to predict the movement outcome are two key processes for self-agency. Showing the involvement of the cerebellum in these processes would bring further arguments to explain its involvement in the sense of agency.

Online Motor Control and Rapid Corrections

There is an apparent contradiction between the rapidity of fast-tracking hand movements and the duration of sensory feedback processing. The latter appears to be too long to directly influence hand trajectory during fast movements (Desmurget and Grafton, 2000). In other words, because it takes time for sensory afferences to be processed, there is always a lag between the actual state of the motor effectors and how this state is perceived by the central nervous system. It has thus been proposed that on-line motor control relies on a forward model. The forward model integrates both the efference copy of the motor command and the sensory feedback to produce a prediction of the sensory consequences of the motor command. These predictions are directly compared with the sensory feedback generated by the movement and thus provide an optimal estimate of the state of the effector; any discrepancy would be used to correct the on-going movement (Miall et al., 1993; Wolpert et al., 1998; Desmurget and Grafton, 2000; Tanaka et al., 2020). On-line motor correction using the forward model would be faster than the processing time of using the sensory feedback alone. Empirical observations in healthy subjects of online motor corrections are consistent with the timing estimated with the forward model (Miall et al., 1993; Wolpert et al., 1998; Desmurget and Grafton, 2000). Patients with cerebellar lesions are impaired for on-line movement correction: overshooting or undershooting the target (dysmetria) and oscillatory corrections (intention tremor) are the hallmarks of cerebellar ataxia, which can be broadly defined as inaccuracy and incoordination in limb movements and instability in posture, gait and ocular saccades (Holmes, 1939; Cabaraux et al., 2020). Disrupting the lateral cerebellum with transcranial magnetic stimulation in healthy subjects alters on-line control of the ongoing movement (Miall et al., 2007). The cerebellum was thus proposed to act as a forward model during on-line motor control (Miall et al., 1993, 2007; Wolpert et al., 1998; Desmurget and Grafton, 2000). In particular, it was shown that cerebellar patients rely more importantly on visual feedback as compared to healthy controls as if they were missing an internal forward model (Day et al., 1998; Bhanpuri et al., 2013; Kakei et al., 2019; Tanaka et al., 2020; Zimmet et al., 2020). Reciprocally, an erroneous forward model recapitulates the tracking deficits observed in cerebellar ataxia (Miall et al., 1993). Altogether, this suggests that some of the deficits observed in cerebellar patients could be explained by an impaired forward model resulting in increased dependence on delayed visual feedback (Kakei et al., 2019; Cabaraux et al., 2020; Tanaka et al., 2020; Zimmet et al., 2020).

The role of the cerebellum in the forward model during rapid motor corrections seems to depend on the nature of sensory information that is relevant during movement execution. Proprioceptive feedback present two advantages compared to visual feedback: they are not easily deceived since they are directly related to the movement's results in healthy individuals, and they are more rapidly processed by the central nervous system as compared to other sensory modalities. Optimal multisensory integration and feedback control in real-time rely more importantly on proprioceptive information (Crevecoeur et al., 2016). Once again, findings in pathophysiological models involving patients with cerebellar impairment allow narrowing this question. Cerebellar patients have an active proprioceptive deficit consistent with disrupted movement prediction rather than an inability to enhance peripheral proprioceptive signals during the action (Bhanpuri et al., 2013). Besides, cerebellar patients can also show a reduced feedback gain in situations where responses are driven by proprioception more than vision (Kurtzer et al., 2013). When the responses are driven by enhanced visual feedback, cerebellar patients rely on time-delayed cursor feedback of their hand position and appear unable to generate predictions of their hand position (Zimmet et al., 2020). Altogether, these results suggest that a fundamental property of the cerebellum in the forward model is the integration of proprioceptive information during the control of body movements.

Visuomotor Adaptation

Visuomotor rotation tasks induce a discrepancy between the movement of the limb and the visual feedback. In such tasks, the repetition of trials results in a gradual reduction of the error, known as visuomotor adaptation. Visuomotor adaptation of reaching movement is a form of implicit motor learning that relies on the updating of a forward model through sensory prediction error (sPE). This forward model tends to minimize the discrepancy between the anticipated motor outcome and the actual sensory feedback to optimize the motor performance trials after trials (Mazzoni and Krakauer, 2006; Krakauer, 2009). Several lines of evidence suggest that the cerebellum is involved in updating the forward model during sensorimotor adaptation. First, patients with cerebellar

lesions are impaired in visuomotor rotation tasks (Weiner et al., 1983; Martin et al., 1996; Smith and Shadmehr, 2005; Tseng et al., 2007; Rabe et al., 2009; Werner et al., 2010; Schlerf et al., 2013; Bernard and Seidler, 2013; Burciu et al., 2014). Second, neuroimaging studies repeatedly confirmed that cerebellar activity is increased during visuomotor adaptation in healthy subjects (Bernard and Seidler, 2013; Küper et al., 2014; Tzvi et al., 2020). Last, different modalities of cerebellar stimulation with transracial direct current stimulation (tDCS) in healthy volunteers can lead to improved or impaired visuomotor adaptation (Galea et al., 2011; Herzfeld et al., 2014; Yavari et al., 2016), strongly suggesting that the cerebellum is a key area for the forward model.

The cerebellum is not the only brain region required for on-line motor correction and motor learning, and the involvement of the striatum in this process has been reported (Graybiel, 2008; Doyon et al., 2009; Seidler et al., 2013). Interestingly, both cerebellar patients and patients with striatal degeneration (Huntington's disease) are impaired at on-line movement correction. However, while Huntington's patients were able to adapt to an external perturbation and improved their motor performance from trial to trial, cerebellar patients did not. This is consistent with the model of motor learning proposed by Doyon et al. (2009), which distinguishes motor sequence learning (incremental acquisition of a sequential movement) from motor adaptation (compensation for environmental changes). During the early encoding phase, motor sequence learning and motor adaptation recruit the same cerebral structures, involving the striatum and the cerebellum. The interaction between these two structures is thought to be critical for establishing new motor routines (Hoshi et al., 2005; Doyon et al., 2009). It is only later that these two types of learning are distributed over distinct cerebral structures: while motor adaptation relies more on the cerebellum, motor sequence learning and habit formation rather rely on the striatum (Graybiel, 2008; Doyon et al., 2009). Indeed, patients with basal ganglia disorders are not impaired during motor adaptation tasks (Seidler et al., 2013). The mechanisms underlying motor control and learning in the striatum and the cerebellum are thus different: while the cerebellum seems to provide a substrate for motor adaptation through the updating of a forward model, it is not the case for the striatum (Smith and Shadmehr, 2005; Graybiel, 2008; Seidler et al., 2013).

Instrumental Conditional Learning

Instrumental conditional learning, also called operant conditioning, refers to the mechanism of creating the relationship between the stimulus and motor response to obtain a reward and to avoid punishment. Cerebellar Purkinje cells generate conditioned response and through the connections with the inferior olive, regulate the signal from the unconditional stimulus (Rasmussen and Hesslow, 2014). A growing body of evidence suggests that the cerebellum is also involved in reward processing and that the cerebellum learns to select the correct action *before motor execution*. Tracing and optogenetic activation of cerebellar projections in mice show that the cerebellum sends an excitatory efferent signal to the ventral tegmental area (VTA; Carta et al., 2019). The VTA is one of the regions sending brain-wide dopaminergic projections that represent the major pathways by which the brain controls reward and motivational behaviors. The existence of such a pathway would explain how repeated stimulation of the cerebellum increases dopamine in the mouse medial prefrontal cortex (Rogers et al., 2011). Second, the activity pattern of cerebellar cells is consistent with its active contribution during conditional learning tasks. Recent animal studies show that some cells located in sensorimotor areas of the cerebellar cortex modulate their activity in response to the reward, this modulation being stronger when the reward is unexpected (Heffley et al., 2018). Also, these cells fire in anticipation of the reward, when forelimb movements are correctly executed. This activity pattern resembles reward prediction error (rPE) signals recorded in the ventral striatum or the prefrontal cortex. Contrary to the striatal and prefrontal responses, cerebellar responses would be related to reward expectation, regardless of its valence (Kostadinov et al., 2019). Altogether, it seems that in addition to the error-related signal, the cerebellum is involved in selecting correct movements by processing reward-related signals to reinforce motor responses and to associate them with the dopaminergic release. Thus, the cerebellum can participate in motor selection by considering the probability of motor outcomes to be correct and rewarding, which would be important information to consider for the involvement of the cerebellum in the sense of agency.

DISCUSSION: CEREBELLUM AND THE SENSE OF AGENCY

Although the validity of the forward model has been questioned regarding the role of the cerebellum in cognitive processes (Sokolov et al., 2017; Diedrichsen et al., 2019), there is a growing body of evidence suggesting the role of the cerebellum in the sense of agency. Indeed, regardless of the forward model, the specific role of the cerebellum in the self-agency is poorly understood, but the cerebellum has been related to several aspects of actions goal-directness and self-attribution, which are the fundamental feature of intentional actions (Haggard, 2008). In line with our previous sections, we link motor control and the feeling of agency in a twofold manner. First, proper motor control is necessary for establishing a sense of agency. Second, these two processes might be supported by the same computation: the forward model. Here, we will also present some examples of movement disorders which could illustrate the role of the cerebellum in disrupted agency.

In the comparator model of agency, which is derived from the forward model of motor control (Synofzik et al., 2008b; Haggard, 2017), the implicit feeling of agency results from a match between the intentional content of the action and the actual sensory feedback generated by the movement. According to this model, a discrepancy in this comparison would result in a reduced or absent sense of agency (Haggard, 2017). A forward model is necessary for the feeling of agency, although it is not sufficient to explain the explicit judgment of agency (Synofzik et al., 2008b). The sense of

agency thus seems to rely only partially on a forward model. Several arguments support the role of the cerebellum in the comparator model of agency. First, the cerebellum is a major region contributing to the sense of body ownership, described as "a feeling of mineness" that we experience toward our body parts (Tsakiris, 2010). Several empirical and experimental studies pointed to the strong interaction between the sense of body ownership and sense of agency, which usually mutually strengthened each other if they co-occur (Braun et al., 2018). It has thus been proposed that body ownership might rely on a forward model (Grechuta et al., 2019), and patients with cerebellar ataxias, a group of disorders characterized by cerebellar degeneration, showed an abnormally reduced sense of body ownership, evaluated by the rubber hand illusion experience (Fiorio et al., 2014). Second, as shown in the previous section, the cerebellum is involved in detecting a mismatch between the expected and actual sensory feedback, leading to a feeling of disrupted agency (Blakemore et al., 2001; Nahab et al., 2011; Seghezzi et al., 2019). For instance, in conversion tremor, patients exhibit involuntary postural tremor, leading to a mismatch between the intended movement and the actual movement results. In this case, aberrant motor symptoms critically use voluntary motor pathways, but patients experience the movements as involuntary, despite the absence of neurological causes for these symptoms. In conversion tremor patients, a task eliciting conversion tremor (posture specific) was compared to a task involving a voluntary mimic of the tremor (Voon et al., 2010). The authors found that a network involving the temporo-parietal junction and the cerebellum had decreased connectivity during conversion tremor. They suggested that this finding may reflect the lack of an appropriate sensory prediction signal, which would lead to the perception that the conversion movement is not self-generated.

In some of the experimental paradigms testing disrupted agency, the conditions artificially induced a mismatch by deceiving the participant with the manipulation of one modality of sensory feedback (introducing a delay between the movement and the production of an auditory tone or distorting the visual feedback for instance). As a result, brain activation during such tasks could be attributed to the realization of this deception and to a "simple mismatch" without agency disruption. This is especially true for healthy participants who do not have impaired motor control and who can rely on proprioceptive feedback. In other words, the increased cerebellar activity in these studies could be related to the detection of an inter-sensory mismatch between the proprioceptive feedback generated by the movement and the erroneous visual or auditory feedback. Alternatively, the increased cerebellar activity could be associated with the detection of a mismatch between the anticipation of the movement outcome and the actual sensory feedback, as postulated by the forward model. To disentangle these two possibilities, a recent study manipulated the visual feedback produced by hand movements during active and passive movements (van Kemenade et al., 2019). The authors introduced a temporal delay between the actual movement and the displayed image of that movement. They did so in two different conditions: in the active condition, the movement was initiated by the subject, whereas in the passive condition, the hand movement was generated by an external device. In both situations, the proprioceptive feedback generated by the hand movement was identical, but according to the forward model, the comparison between the efference copy and the sensory feedback generated by the movement should occur only in the active condition. Accordingly, the cerebellar activity was positively correlated to the delay between the movement and the visual feedback, specifically in the active condition, confirming its role as a *comparator* in the framework of the forward model. By contrast, other brain regions such as the temporo-parietal junction were sensitive to a mismatch in both active and passive conditions, suggesting a more general role in detecting inter-sensory mismatch (van Kemenade et al., 2019). These results strongly suggest that the cerebellum contributes directly to the implicit feeling of agency by comparing the anticipation of the movement outcome with the actual sensory feedback. This hypothesis is further supported by a recent study on the neural correlates of intentional binding (Zapparoli et al., 2020b). Compared to previous studies that explored the network underlying disrupted agency, this recent work used a more "physiological" approach by identifying the neural substrate of intentional binding, an implicit measure of self-agency (see "The Sense of Agency and the Forward Model" section). They showed that among other brain regions, the cerebellum activity positively correlated with the measure of intentional binding, providing strong evidence of its involvement in the feeling of agency (Zapparoli et al., 2020b).

As discussed in "The Sense of Agency and the Forward Model" section, the sense of agency is thought to rely on two distinct processes: the low-level, implicit, sensorimotor feeling of agency which relies on a forward model, and the higher-order, conceptual, and explicit judgment of agency (Synofzik et al., 2008b). We reviewed an accumulating body of evidence supporting the role of the cerebellum in the implicit feeling of agency: (i) the cerebellum presents the anatomical and functional properties required for a forward model; (ii) the cerebellum is involved in detecting a mismatch between the anticipated and actual sensory consequences of the movement; and (iii) activity in the cerebellum is correlated to the measure of the intentional binding, an implicit measure of the feeling of agency. The role of the cerebellum in the feeling of agency makes it necessary, but not sufficient, to establish the sense of agency. Indeed, although the feeling of agency and the judgment of agency both contribute to the sense of agency, they rely on distinct mechanisms. For instance, an explicit judgment of agency is possible despite a "non-agency" feeling (Synofzik et al., 2008b). Also, patients with lesions in the parietal lobe—which is a key region involved in detecting a mismatch between the intended movement and the movement's results (Synofzik et al., 2008b; Haggard, 2017)—still have an agency judgment (Sirigu et al., 1999). By contrast, patients with prefrontal lesions can adapt to spatial sensorimotor discrepancies, yet they are unable to consciously detect these

TABLE 1 | Cerebellar functional anatomy related to functions associated with the forward model and the sense of agency.

Function	Article	Experimental design	Cerebellar region involved
	Diedrichsen et al. (2005)	fMRI correlate of target error (unpredictable change in target location)	Lobules V, VI, VIII and dentate nucleus
Detection of sensory prediction errors		fMRI correlate of target error (unpredictable change in target location) fMRI correlate of execution error (alteration of visual feedback)	Lobules V, VI, VIII and dentate nucleus
	Schlerf et al. (2012)	Error detection	Lobules V and VI
	Blakemore et al. (2001)	Correlation of cerebellar activity with the abnormal delay of sensory feedbacks	Border of lobule VI and crus II
	van Kemenade et al. (2019)	Correlation of cerebellar activity with the abnormal delay of sensory feedbacks	Lobule V
	Nahab et al. (2011)	Correlation with the loss of control	Left cerebellar tonsil, left cerebellar pyramid
On-line motor control	Miall et al. (2007)	Cerebellar stimulation with TMS impairs on-line motor control	Lateral cerebellum
Sensory attenuation	Blakemore et al. (1998)	Decreased cerebellar activation in response to self-generated tactile stimulus	Right anterior cerebellar cortex
	Brooks and Cullen (2013)	Electrophysiological recordings in the cerebellum of non-human primates suggest a role in the cancellation of self-produced afferences	
	Cao et al. (2017)	Cerebellar stimulation with TMS alters the cortical sensory attenuation of self-generated sounds	Lateral cerebellum
Visuomotor adaptation	Bernard and Seidler (2013)	A Meta-analysis of fMRI and PET study exploring visuomotor adaptation	Lobule IV
	Küper et al. (2014)	fMRI study of visuomotor adaptation	Lobule VIII and caudal dentate nucleus
	Tzvi et al. (2020)	fMRI study of visuomotor adaptation	Lobule VIII, crus II, lobule VI, crus I
	Galea et al. (2011)	tDCS over the cerebellum causes faster adaptation during visuomotor adaptation	Right cerebellar cortex
	Yavari et al. (2016)	tDCS over the cerebellum alters localization of the hand after a movement without visual feedback	Right cerebellar cortex
Conditional learning	Carta et al. (2019)	In mice, cerebellar nuclei send projections to the VTA and modulate the reward pathway	Deep cerebellar nuclei
	Rogers et al. (2011)	In mice, stimulation of the cerebellar nuclei triggers. Dopamine release in the medial prefrontal cortex	Dentate nucleus
	Heffley et al. (2018)	In mice, climbing fibers responses in the lateral cerebellum encode reward prediction	Lateral cerebellum
	Kostadinov et al. (2019)	In mice, the cerebellum encodes reward prediction	Lobule simplex
Anticipation	Tesche and Karhu (2000)	MEG study exploring the event-related potential during sensory ommission	Lateral cerebellum + vermis
	Cui et al. (2000)	Event-related during a delayed sequential finger movement task	Cerebellum lobules VI
Sense of agency	Seghezzi et al. (2019)	A Meta-analysis of fMRI study exploring the sense of agency	Right cerebellum lobule VI
	Zapparoli et al. (2020b)	fMRI study of the cerebral regions which activity correlates with the intentional binding	Cerebellum lobules IV and V

Anatomical specifications of the different cerebellar structures involved in the references listed in the manuscript.

mismatches (Slachevsky et al., 2001). A recent example may illustrate the fact that the cerebellum is needed to properly detect mismatch, and that this mismatch information would then be used by associative areas to evaluate the explicit measure of the sense of agency. Delorme et al. (2016) used an explicit agency task in which participants had to catch targets with a cursor by moving a computer's mouse. The control over the cursor could be disrupted by adding a spatial or a temporal discrepancy between the mouse and the cursor's movements. The authors measured the level of the perceived discrepancies by the participants, who reflect them in metacognitive judgments of agency on an analogic scale. This task was performed by patients with cervical dystonia and healthy controls. Noteworthy, cerebellar dysfunction has an important if not a major contribution to dystonia (Neychev et al., 2008), including cervical dystonia (Popa et al., 2018). Dystonic patients explicitly reported being more in control in the temporal discrepancy condition than healthy participants, suggesting that they failed to detect any mismatch between their intended movements and the perceived feedback of the timing of their action. The implication of the cerebellum could only be hypothesized, because of the absence of neurophysiological

data that could be associated with the observed behavior. Patients with Gilles de la Tourette's syndrome (GTS), a hyperkinetic movement disorder with tics, also showed a "disturbed" agency in explicit and implicit agency tasks (Delorme et al., 2016; Zapparoli et al., 2020a). Specifically, in this patient population, weaker level of intentional binding was associated with disease severity as well as a silencing of the cerebello-parieto-premotor network (Zapparoli et al., 2020a) usually related to intentional binding (Zapparoli et al., 2020b). This suggests that the cerebellum is an element of the agency network and that this network can be affected by the unreliability of the motor output due to involuntary movements present in various movement disorders. In some movement disorders, voluntary movements are always accompanied by an involuntary one. In severe forms of essential tremor involving cerebellar pathways, patients might not feel in full control of their actions during voluntary movements due to systematic action tremors. If the involuntary movement is systematic, patients can anticipate that their movement is going to be disrupted. To our knowledge, implicit or explicit measures of the agency were never investigated in pathologies in which involuntary and voluntary movements co-occur.

We hypothesize that the cerebellum, together with the posterior parietal cortex, is part of a neural network that is involved in comparing the predicted movement outcome (through the integration of the efference copy) with the actual sensory feedback generated by the movement. This first step would be involved in the implicit feeling of agency, and the result of this comparison would then be transmitted to higher-order associative areas in the prefrontal cortex, where it would be integrated along with contextual knowledge and belief reasoning to give rise to the judgment of agency (Synofzik et al., 2008b). At the level of the cerebellar module, the deep cerebellar nuclei may integrate both the efference copy and the sensory feedback through the inputs of the Purkinje cells and the mossy fibers, as is the case for motor control (Tanaka et al., 2020). The sensory prediction error would then be transmitted to different cortical regions through parallel loops: to the parietal cortex to establish the feeling of agency, and to the motor regions to serve motor control (**Figure 1**).

CONCLUSION

The sense of agency depends upon a set of mechanisms involving the processing of specific neural signals, from sensory as well as from central origin. The first one, the implicit feeling of agency, would relate to the action monitoring and predictive processes; the second one, the explicit judgment of the agency, would relate to the high-order mechanism. The first level provides an immediate signal for controlling and adapting actions to their goal during action execution and is thought to rely on the principle of congruence of the action-related signals through the forward model. In contrast, the second level provides information about the intentions, plans, and desires of the author of these actions. These two levels are interdependent and together contribute to elaborate the sense of agency along the action execution. Here, we brought a conceptual analysis of empirical data that lead us to consider the role of the cerebellum in the implicit feeling of agency. In support of this view, **Table 1** illustrates the functional involvement of parts of the cerebellum in the references cited in the different sections. As such, the cerebellum is necessary, but not sufficient, to establish a sense of agency. Indeed, direct proof of the involvement of the cerebellum in the explicit judgment of agency is still missing and we could only infer some working hypotheses that need a demonstration.

We consider that the role of the cerebellum in the feeling of agency is twofold: first, the cerebellum ensures the quality control of movements, which is a necessary condition for the establishment of the sense of agency; second, recent evidence suggests that the cerebellum is directly involved in the sense of agency by comparing the intentional content of our actions with their outcomes, a process that is thought to rely on a forward model.

AUTHOR CONTRIBUTIONS

QW, YW, and CG conceived of and wrote the article. All authors contributed to the article and approved the submitted version.

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frontiers in Systems Neuroscience

REVIEW
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Cerebellum and Prematurity: A Complex Interplay Between Disruptive and Dysmaturational Events

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The cerebellum plays a critical regulatory role in motor coordination, cognition, behavior, language, memory, and learning, hence overseeing a multiplicity of functions. Cerebellar development begins during early embryonic development, lasting until the first postnatal years. Particularly, the greatest increase of its volume occurs during the third trimester of pregnancy, which represents a critical period for cerebellar maturation. Preterm birth and all the related prenatal and perinatal contingencies may determine both dysmaturative and lesional events, potentially involving the developing cerebellum, and contributing to the constellation of the neuropsychiatric outcomes with several implications in setting-up clinical follow-up and early intervention.

Keywords: cerebellar hemorrhage, cerebellar infarction, cerebellar underdevelopment, cerebellum and neurodevelopment, early intervention, prematurity

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INTRODUCTION

In the last few decades, increasing evidence has driven attention to the cerebellar role in motor coordination as initially believed, and in cognition, behavior, language, memory, and learning (Salman and Tsai, 2016). Although adult cerebellar morphology and basic circuitry have been described for more than 100 years, the molecular and cellular mechanisms which drive cerebellar development have more recently begun to be elucidated (Haldipur et al., 2018). Human cerebellar development occurs late in gestation and is hindered by preterm birth. Moreover, longitudinal studies investigating cerebellar maturational trajectories from birth through childhood in preterm infants have revealed smaller volumes and reduced cerebellum growth both at short- and long-term observation. Beyond gestational age, several perinatal factors have been associated with smaller cerebellar volumes and growth (Pieterman et al., 2018). Encephalopathy of the preterm encompasses a constellation of neuropathological and clinical signs originating from both dysmaturative and lesional events occurring during prenatal and perinatal life, obviously including cerebellar development (Matthews et al., 2018). Indeed, it is reported that multiple perinatal risk factors, including exposure to invasive procedures in Neonatal Intensive Care Units (NICUs), may influence the central nervous system (CNS) maturation, leading to poor neurodevelopmental outcomes (Valeri et al., 2015; Montirosso et al., 2016). Here we reviewed the main morphological

and neurodevelopmental features of cerebellar dysfunctions associated with preterm birth and their implications in setting-up clinical follow-up and early intervention.

CEREBELLAR DEVELOPMENT AND PREMATURITY

The human cerebellum develops over a long time, extending from early embryonic period until the first postnatal years. To date, it is commonly accepted that the first cerebellar anlage starts to form in the first month of gestation, and lasts until the second postnatal year (van Essen et al., 2020). However, most of its volume increases during the last trimester of pregnancy, which is considered a critical period for cerebellar development (Volpe, 2009).

The cerebellar anlage takes origin from the hindbrain due to the interaction of multiple embryonic structures (ten Donkelaar et al., 2003). The first step of this process consists in the expression of the transcription factors Otx2 and Gbx2 that allow the organization of the forebrain/midbrain and hindbrain territories, respectively, determining a boundary structure called Isthmic organizer (Marin and Puelles, 1994; Liu et al., 1999). This is a patterning center essential for the establishment of the anterior-posterior axis and the rhombomere segmentation (De Luca et al., 2016; van Essen et al., 2020), and a disruption of its organization in the earliest period of cerebellar development may result in cerebellar hypoplasia (CH) with disproportionally hypoplastic vermis (Basson and Wingate, 2013).

Later, in rhombomere 1, the proteins Atoh1 and Ptf1a identify the rhombic lip and the ventricular zone, respectively, the areas including the cerebellar progenitors: the rhombic lip will originate the glutamatergic cells, while the ventricular zone will produce GABAergic cells (Hoshino et al., 2005; Machold and Fishell, 2005; Wang et al., 2005). The granule layer cells are glutamatergic neurons originating from the granule cell progenitors (GCPs), a population that migrates tangentially to form the external granule layer during the last months of pregnancy and undergoes a cloning expansion, eventually giving rise to 95% of all cerebellar neurons.

Being the most represented cell type in the cerebellum, a disorder in this fast and massive proliferation might determine a severe hypoplasia (Basson and Wingate, 2013). This overgrowth process is mediated by the expression of Sonic Hedgehog (SHH), a protein produced by mature Purkinje cells, Bergmann glia, and choroid plexus cells (De Luca et al., 2016; Cheng et al., 2018). Therefore, a defect in the SHH signaling pathway may cause a reduction in the entire cerebellar volume, inducing a more homogeneous hypoplasia (Basson and Wingate, 2013).

During the third trimester of pregnancy, the Purkinje cells (the GABAergic neurons deriving from the ventricular zone) are organized in a single layer and begin to make connections in the molecular layer with the parallel fibers and the stellate cells (Leto et al., 2016). This maturation occurs between the 24th and the 40th gestational week, determining overall a fivefold dimensional enlargement of the cerebellum and its subsequent foliation to accommodate in the posterior fossa (Volpe, 2009).

The last few months of gestation are also the time during which the cerebellar nuclei start to form their major afferents and efferences from/to the cerebral cortices and subcortical structures, i.e., thalamus, and this development will continue during the first years after birth, inducing the expansion of the cerebellar anlage (Pierson and Al Sufiani, 2016; Sathyanesan et al., 2019).

The principal afferent pathways of the cerebellum are the mossy fibers and the climbing fibers. The former originates from the brainstem nuclei, the spinal cord and the reticular formation, and the latter from the inferior olivary complex (Roostaei et al., 2014). Conversely, the deep nuclei represent the cerebellum's outputs, through which the efferences deriving from the vermis and the hemispheres get to their targets (Kandel et al., 2013). The archicerebellum's efferences (corresponding to the flocculonodular lobe) constitute an exception since they reach their target (vestibular nuclei), bypassing the deep nuclei (Roostaei et al., 2014). In detail, the vermis receives visual, auditory and vestibular inputs and, together with the intermediate zones of the hemispheres (paravermis), welcomes sensorimotor information.

The efferences coming from these two zones (globally known as spinocerebellum) mainly target the medial vestigial and interposed nuclei, giving origin to the descending motor system. The lateral zones of the hemispheres (cerebrocerebellum) are reciprocally connected to the cerebral cortex, and their outputs target the dentate nucleus (Basson and Wingate, 2013; Roostaei et al., 2014). On the whole, it is reasonable to state that "for the majority of the cerebellum, the targeting of output of each nucleus determines the functional output of the overlying cerebellar cortex" (Basson and Wingate, 2013), acknowledging a correspondence between the anatomical and functional organization.

Nowadays, numerous studies have clearly established the cerebellar connections with the contralateral cerebral cortices and particularly with the dorsolateral prefrontal cortex, the parietal and superior temporal lobes (Dijkshoorn et al., 2020). An interruption of this well-formed circuit between areas of the CNS may determine a diaschisis, meaning a functional impairment of the region linked to the one subject of a structural lesion (Catsman-Berrevoets, 2017). Therefore, it may be clearly assumed that damage of CNS territories correlated to the forming cerebellum may also alter its morphological architecture due to a trans-synaptic degeneration (Volpe, 2009).

The disruption of the cerebral and cerebellar white matter due to prematurity and its complications, in association with supratentorial injuries or even in their absence, has been investigated by relatively new neuroimaging techniques, such as tractography. In that regard, Hasegawa et al. (2018) showed a reduction of the fractional anisotropy in the superior cerebellar peduncle (through which the efferences are sent from the cerebellum to the cerebral cortex), and in the medial one (through which the cerebellum receives auditory, visual, vestibular, and somesthetic afferences); whereas, Brossard-Racine et al. (2017) revealed an increase of the fractional anisotropy in the dentate nuclei. Moreover, a lower mean diffusivity in the vermis has been

reported and correlated to the severity of supratentorial injuries (Brossard-Racine et al., 2017).

CEREBELLAR NEUROPATHOLOGY

Cerebellar injury in preterms has been a subject of interest for many years. Indeed, preterm cerebellar lesions can be divided into two main groups: (1) cerebellar underdevelopment (namely cerebellar atrophy/hypoplasia, which may be regional or global); and (2) destructive cerebellar lesions (which are primary and focal injury, manifesting as hemorrhage or infarction) (Volpe, 2009; Tam, 2018).

Cerebellar Underdevelopment

To date, cerebellar underdevelopment (hence atrophy and hypoplasia) is one of the most common complications in preterm infants associated with poor neurodevelopmental outcome (Gano and Barkovich, 2019). In particular, hypoplasia refers to a structure exhibiting incomplete development or underdevelopment, often due to a developmental arrest, whereas atrophy is due to degeneration of previously existing cells in a formed structure that results in decreased organ or tissue size. Since both of these manifestations lead to a decreased cerebellar volume, it is difficult to discriminate between these two entities; hence in literature, they are usually referred to as a unique condition (Pierson and Al Sufiani, 2016; Poretti and Boltshauser, 2015).

Cerebellar hypoplasia after prematurity has been reported for the first time in a study carried out by Allin et al. (2001), who detected a reduction in cerebellar volume in a group of adolescents born before the 33rd week of gestation, compared to a control group. It is noteworthy mentioning that CH may globally involve the cerebellum (affecting equally the hemispheres and the vermis) or, in contrast, may present with a volume loss of both the hemispheres with or without vermis abnormalities (Tam, 2018). In this regard, a recent study carried out by Wu et al. (2020) compared preterm babies and healthy controls, demonstrating that prematures show not only smaller volumes (global and regional), but also different shapes both of cerebellum and brainstem, even when a structural injury of these areas fails to be detected by MRI scans. Even if numerous lesional patterns have been reported, the most typically observed includes bilateral and symmetric involvement of the two cerebellar hemispheres, associated with smaller pons, and supratentorial injuries (Pierson and Al Sufiani, 2016). However, it is also necessary to remember that 25% of CH coexisting cases with pontine hypoplasia are ascribable to genetic causes (Poretti et al., 2014). These conditions must be taken into account during the assessment and the differential diagnosis of CH. Nevertheless, they will not be discussed in this review, as they may determine *per se* CH, regardless of preterm birth's potential coexistence.

Currently, many factors are known to be potential causes of cerebellar underdevelopment in preterm babies. Among these, the most significant include blood products (hemosiderin), perinatal glucocorticoid exposure, opioids and pain, inadequate nutrition, infections, inflammations, hypoxic-ischemic insults, cerebral brain injuries, and socioeconomic status (Volpe, 2009; Tam, 2018).

Blood Products (Hemosiderin)

Blood products derive from different types of hemorrhages, either directly involving the cerebellum (intraparenchymal hemorrhages) or adjacent structures (intraventricular and subarachnoid hemorrhages). Whilst it is true that cerebellar hemorrhages (CBHs) may result in a destructive lesion (which will be later discussed), blood products *per se*, particularly hemosiderin, may determine CH. This may be due to hemosiderin's direct effect, which reaches the surface of the cerebellum and the brainstem, traveling inside the cerebrospinal fluid and generating reactive oxygen species (ROS) (Volpe, 2009; Gano and Barkovich, 2019). The GCPs of the external granular layer appear to be highly susceptible to ROS-mediated damage and, once struck, may lead to cerebellar underdevelopment (Volpe, 2009; Gano and Barkovich, 2019). As a consequence, obstructive hydrocephalus may occur, which, in its turn, could lead to further mechanical injuries to the CNS (Tam, 2018). Another proposed mechanism through which hemosiderin may lead to CH implies a dysfunction of the FOXC1 pathway, usually responsible for the embryonic cerebellar growth *via* mesenchymal-dependent signaling (Haldipur et al., 2014). Moreover, another potential mechanism, though to the best of our knowledge not yet demonstrated, may involve the SHH pathway, known for its proliferative effect on the external GCPs. Usually, an alteration of this specific pathway is described in literature regarding glucocorticoid exposure (Heine and Rowitch, 2009). Therefore, further investigation on this potential correlation might be of interest for future research.

Glucocorticoid Exposure

Perinatal exposure to glucocorticoids may have adverse effects on the developing CNS, potentially leading to poor neurodevelopmental outcomes. However, there are a wide variety of conditions requiring glucocorticoid administration, both in the prenatal and postnatal periods. Antenatally, betamethasone or dexamethasone are the most used glucocorticoids in the mother at high risk of preterm delivery to promote lung maturation. Postnatally, dexamethasone is used to avoid or treat chronic bronchopulmonary diseases, while hydrocortisone is commonly employed in managing refractory hypotension in premature newborns (Tam, 2018). A recent case-series emphasized the use of hydrocortisone to treat refractory neonatal seizures (Di Rosa et al., 2020). In particular, a clear model of long-term effect on the brain volume played by glucocorticoids can be provided by the adrenocorticotropic hormone, the gold standard treatment for infantile spasms. In this case, the brain volume loss appeared to be proportional to brain's immaturity (Salpietro et al., 2014). According to these assumptions, the fetal age, during which the cerebellum is notably still growing, can be considered the most "at-risk." Moreover, the highest concentrations of glucocorticoid receptors in the brain have been reported in prenatal and early postnatal life (Pavlík and Buresová, 1984). Experimental studies showed that glucocorticoids might interfere with normal neurodevelopment through mechanisms

that involve transcription factors and protease enzymes (Aden et al., 2008; Noguchi et al., 2008; Bhatt et al., 2013; Austdal et al., 2016). This way, the proliferation of the progenitor brain cells (namely the GCPs in the cerebellum) may be impaired, resulting in apoptosis and loss of neural function. The glucocorticoids-mediated inhibition of Sonic-Hedgehog-Smoothened signaling, notably involved in the proliferation of the GCPs (Heine and Rowitch, 2009) has been thought to underlie cerebellar dysfunction. Conversely, the interplay between SHH and glucocorticoids has been further supported by the fact that the Smoothened-Hedgehog agonist (SAG) has been shown to play a potential neuroprotective effect mediating the activation of the 11ß-hydroxysteroid dehydrogenase type 2 pathway (11ßHSD2). 11ßHSD2, is a NAD-dependent high-affinity enzyme highly expressed in the placenta and the developing CNS (particularly in the GCPs) mainly involved in the local metabolic inactivation of endogenous glucocorticoids, such as prednisolone and corticosterone (Heine et al., 2011; Nguyen et al., 2018).

Pain and Opioids

Preterm infants often experience pain during diagnostic and therapeutic procedures in NICU. Therefore, the use of opioids is quite common in these infants. Recent data have established a correlation between pain, cerebellar underdevelopment, and opioids. Ranger et al. (2015) revealed a significant reduction in the posterior VIIIA and VIIIB lobules of the cerebellum in brain MRI scans of a group of 56 very preterm children at school age who had suffered neonatal procedural pain. Moreover, decreased cerebellar volume has been reported in a cohort of preterm infants treated with morphine (Zwicker et al., 2016). A higher rate of cerebellar injuries and lower cerebellar diameters emerged in another study on preterm infants exposed to fentanyl (McPherson et al., 2015). Furthermore, animal models emphasized the potential detrimental effect of opioids on neurodevelopment. A study carried out by Sabir et al. (2018) showed fentanyl induced apoptosis of the Granule cells of the internal layer in 13 healthy newborn pigs. Aboulhoda and Hassan (2018) detected a relationship between tramadol administration during pregnancy, oxidative stress, and structural abnormalities on the post-natal cerebellar cortex in a group of rats. Finally, another study demonstrated the possible effects of opioids administered during the developmental period on the NMDA receptor (NMDAR) expression and function, exploiting animal models. In particular, it showed how rat cerebella continuously exposed to opioids during the prenatal age may present an opioid-induced reduction of the NMDAR subunit GluN2B (the subunit primarily expressed prenatally in rodents) during the first 3 weeks after birth. This finding supports the idea that NMDAR might be an important target of opioids, especially during neurodevelopment, being potentially involved in their neurotoxic effects and long-term detrimental consequences (Fjelldal et al., 2019).

Inadequate Nutrition

Nutrition plays an important role in general growing processes, and CNS structures development, such as the cerebellum. Although infant nutrition is often taken into account among the variables influencing neurodevelopment, especially in preterm infants, a limited number of studies have addressed this issue so far. Limperopoulos et al. (2005) demonstrated a significant correlation between decreased cerebellar volumes in prematures and clinical parameters such as head circumference and weight. This finding indirectly supports the importance of an appropriate nutrition of the baby for cerebellum development, especially in the early postnatal period (when the premature cerebellum is still in the midst of its development). Similar conclusions have been recently described by Coviello et al. (2018), who reported in a cohort of 131 infants, born under the 31st week of gestation and investigated at term equivalent age, a significant correlation between a balanced and normocaloric diet of the baby and larger volumes of CNS structures, including the cerebellum. They also demonstrated a positive correlation between infant nutrition, white matter maturation at term equivalent age, and better neurodevelopmental outcomes at 2 years' corrected age. Accordingly, Choudhri et al. (2014) demonstrated smaller brains, including cerebellum, and an impaired neurodevelopment in preterm pigs fed via parenteral nutrition. Finally, inadequate maternal nutrition during the gestational age has been linked to an abnormal expression of the enzyme regulating the metabolism of maternal cortisol, namely the placental steroid dehydrogenase, resulting in an excessive cortisol exposure for the fetus (Volpe, 2009). This data appears particularly interesting in the light of the previously mentioned effects of glucocorticoids on the preterm cerebellum. Interestingly, Koning et al. (2017) carried out an observational study highlighting an association between higher maternal BMI and decreased cerebellar growth trajectories, probably due to various mechanisms (i.e., dietary intake, nutritional status, chronic inflammation and oxidative stress). In conclusion, though the exact mechanisms through which nutrition affects brain development remain largely unexplained, it appears that an adequate intake of macronutrients and calories for the mother (during pregnancy), as well as for the infant (since the first moments of postnatal life), play an important role in brain development, certainly worthy of further investigation (Volpe, 2009).

Infection/Inflammation and Hypoxia-Ischemia

Prenatal and perinatal infection/inflammation may play a central role in the etiopathogenesis of CH. Evidences of congenital cytomegalovirus infections and poor neurodevelopmental outcomes have been commonly reported, often in the presence of structural CNS lesions, including CH (Smithers-Sheedy et al., 2014; Nishida et al., 2020). Lee et al. (2014) retrospectively studied a cohort of 155 preterm babies, detecting a significant correlation between the presence of necrotizing enterocolitis with sepsis and decreased transcerebellar diameters. Ranger et al. (2015) demonstrated that other factors, including infections, may generate CH in preterm infants beyond neonatal procedural pain. A direct link between animal parvovirus infections and extensive injuries of the cerebellum, including CH, has been documented in numerous species (Aeffner et al., 2006; Marusak et al., 2010; Wünschmann et al., 2020), while little is known when it comes to humans. Grant et al. (2009) showed human parvovirus in the human cerebellum, suggesting a possible

role in cerebellar injuries. Moreover, Sanapo et al. (2017) have recently described a case of congenital parvovirus infection associated with bilateral cerebellar hemispheres and inferior vermis hypoplasia, further suggesting a possible involvement of parvovirus in brain pathology. Indeed, the relationship between immune-inflammatory reactions and CNS dysfunctions has been increasingly reported due to the detrimental action of free radicals, cytokines, and several neurotoxic factors. In this regard, systemic inflammation in fetal sheep has been demonstrated to cause disruptive lesions of the cerebellum, throughout different mechanisms, such as an abnormal activation of microglia and apoptosis of Purkinje cells (Hutton et al., 2014). Hypoxia-ischemia plays a potential role in cerebellar underdevelopment mediated by the effects of mechanical ventilation, patent ductus arteriosus, early intubation, and catecholamine treatment, leading to decreased cerebellar volumes in prematures (Volpe, 2009; Gano and Barkovich, 2019). Specifically, GCPs seems to be a potential target of hypoxia-ischemia (Volpe, 2009).

Cerebral Brain Injuries (Crossed Cerebrocerebellar Diaschisis)

The experienced use of cranial ultrasound and early brain MRI scans allowed to identify supratentorial injuries causally related to CH in those infants presenting without direct cerebellar lesions (Gano and Barkovich, 2019). Overall, it appears that brain injuries, such as non-cystic periventricular leukomalacia, periventricular hemorrhagic infarction, and posthemorrhagic hydrocephalus, may be responsible for a crossed cerebro-cerebellar diaschisis (Volpe, 2009). In other words, the damage involving supratentorial regions may indirectly induce the impairment of the development of the downstream pathways with consequent dysfunction in neural networks also located at distance, such as the contralateral cerebellum (Patay, 2015). Conversely, it is of interest that a primary lesion of the cerebellum has been demonstrated to impact the brain's development or functioning. This is the case, for example, in cerebellar mutism, occurring after postoperative posterior fossa syndrome. This particular condition appears to be a reverse form of diaschisis, namely cerebello-cerebral diaschisis, in which damage, primarily involving the cerebellum and its efferent networks, eventually results in a global supratentorial cortical dysfunction (Mariën et al., 2009). Specifically, cerebellar mutism seems to be strictly related to a trans-synaptic cerebral cortical dysfunction presenting with supratentorial hypoperfusion, mostly in the frontal regions, due to postsurgical damage to efferent cerebellar pathways (Patay, 2015). Although this syndrome's pathophysiology and anatomic basis are not completely known, an impairment of the dentato-thalamo-cortical pathway is thought to play a central role (Morris et al., 2009). Moreover, vasospasm of vessels supplying the deep cerebellar nuclei and the cerebello-thalamic fibers, due to different perioperative factors, has been suggested as a potential cause of reversible hypoperfusion and ischemia (Catsman-Berrevoets, 2017). Furthermore, numerous neuroimaging findings support the correlation between abnormal supratentorial perfusion patterns and cerebellar mutism syndrome, strongly supporting the current accepted notion of cerebello-cerebro diaschisis as the underlying pathomechanism for this peculiar clinical entity (Miller et al., 2010; Patay, 2015). The demonstration represents well another worthwhile example of cerebello-cerebral diaschisis, that large hemorrhages of the cerebellum not only result in a focal atrophy, but they may also correlate to a decreased volume of contralateral cerebral regions (Limperopoulos et al., 2014). On the whole, though much more has yet to be unraveled on the topic, remote trophic transneuronal signaling likely underlies these mechanisms (Volpe, 2009).

Overall, the etiology of cerebellar underdevelopment can be traced back to two groups of mechanisms, that are (1) direct effects and (2) remote effects, which may act alone or concomitantly (Volpe, 2009), potentially resulting in greater damage on the developing cerebellum (**Figure 1**). This is the case of CH generated by a crossed cerebro-cerebellar diaschisis from loss of contralateral connections, in which further damage is produced by a concomitant ventricular hemorrhage (Tam, 2018). As a rule, blood products accumulation, glucocorticoids, opioids, inadequate nutrition, infections/inflammations, and hypoxia-ischemia may directly cause a detrimental effect on the growing cerebellum. Conversely, cerebral injuries (crossed cerebro-cerebellum diaschisis) act *via* an indirect remote effect, disrupting trans-synaptic interconnections, even at distance (Volpe, 2009; Pierson and Al Sufiani, 2016).

Socioeconomic Status

Besides the aforementioned risk factors, it is noteworthy mentioning that cerebellar normal development has been related to socioeconomic status (Tam, 2018). The literature suggests an association between poor socioeconomic conditions and higher inflammatory and cardiometabolic risks, and poor neurocognitive outcomes. Interestingly, Cavanagh et al. (2013) carried out a study on a group of healthy males with a deprived socioeconomic status, detecting lower cerebellar gray-matter volumes. Even though these findings do not directly refer to prematurity, socioeconomic status could represent an additional risk factor likely offering new investigation fields.

Destructive Cerebellar Lesions

Focal or diffuse brain injuries in preterm infants have long been widely described as potential causative factors of subsequent neurodevelopmental impairment. Awfully, despite the reduction of the occurrence of the worst patterns of lesions, a correspondent decrease in preterm neurodevelopmental disabilities has not been shown (Gano and Barkovich, 2019). Given these assumptions and the raised interest in the cerebellum involvement in motor and non-motor functions, such as cognitive, affective, and behavioral ones, a correlation between destructive cerebellar lesions and their consequences has been extensively studied. This is particularly true in the light of the improved care in NICU of the at-risk newborns leading to the increased survival rate of preterm infants (Tam, 2018).

Cerebellar focal injuries are commonly considered as premature birth complications and they generally consist of hemorrhages and infarctions, though a clear distinction between them is hard to be made since they frequently coexist in the same patient. These lesions are usually observed in the inferior

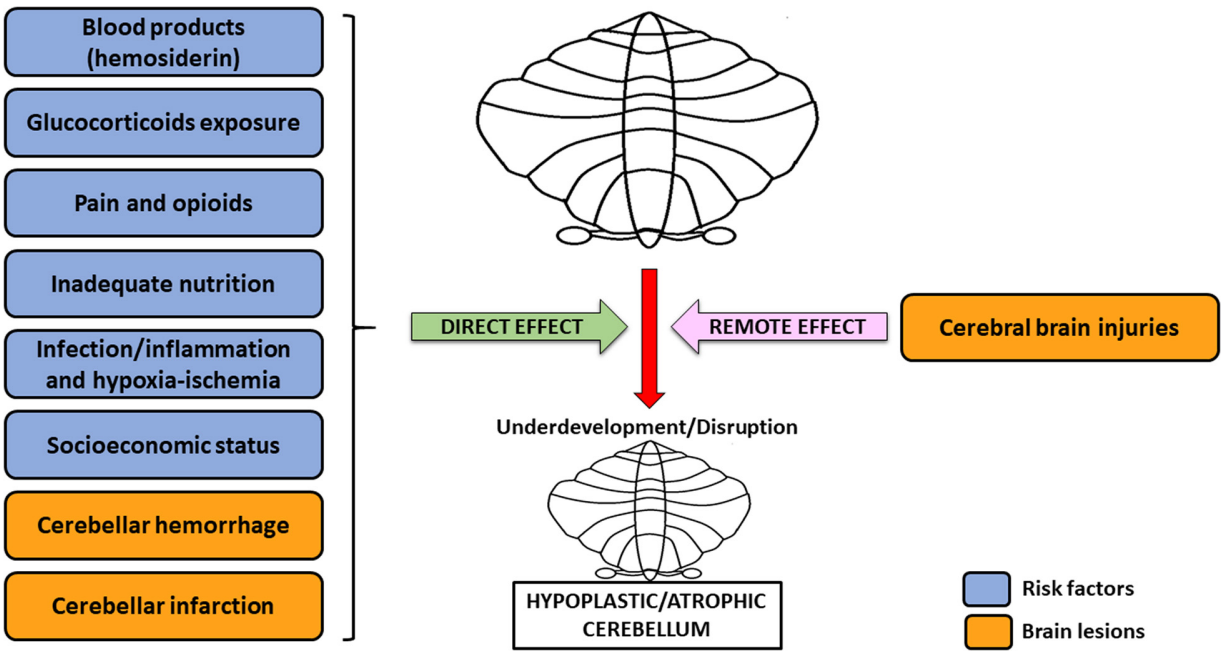

FIGURE 1 | Risk factors and brain lesions leading to cerebellar underdevelopment/disruption. The risk factors nowadays acknowledged for cerebellar underdevelopment/disruption are: blood products (hemosiderin), glucocorticoids exposure, pain and opioids, inadequate nutrition, infection/inflammation, and hypoxia-ischemia. All of these, together with cerebellar hemorrhage and infarction (possible injuries affecting the cerebellum), usually act through a direct effect, potentially leading to cerebellar hypoplasia/atrophy. However, this latter condition may also be the result of cerebral brain injuries, which cause dysfunction in a distant, though neurally connected area of the brain, i.e., the contralateral cerebellum (remote effect) (Volpe, 2009; Pierson and Al Sufiani, 2016).

lobes of the cerebellum, an area supplied by the posterior inferior cerebellar artery, leading to the speculation that an immature development of this vessel might be the origin of both damages (Pierson and Al Sufiani, 2016).

Cerebellar Hemorrhage

Cerebellar hemorrhage is the most explored injury affecting the cerebellum in preterm newborns with incidence ranging from 2.2 to 37% (Boswinkel et al., 2019; Gano and Barkovich, 2019). The wide range of incidence across the studies may rely on the different employed diagnostic tools: cranial ultrasound is feasible and reliable in routine preterm care in NICU, and frequently used to evaluate the posterior fossa serially, but it mainly detects wider lesions. In contrast, brain MRI is sensible to catch spot injuries smaller than 4 mm, though its application is often limited to cases presenting with evident neurological signs, with heterogeneous protocols from center to center (Boswinkel et al., 2019). In regards to cranial ultrasound, different acoustic windows can be explored, from the anterior fontanel to the posterior one, although the mastoid fontanel is commonly considered the best option to visualize cerebellar and brainstem lesions (Snyder et al., 2018). Recently, a suboccipital access through the foramen occipital magnum has been considered for its higher resolution of the cerebellar parenchyma, allowing to detect smaller lesions and the possibility to compare both hemispheres at the same time (Muehlbacher et al., 2020).

Cerebellar hemorrhage is a well-known complication of premature birth with a higher risk of incidence in children born before 28 weeks of gestational age and a birthweight inferior to 750 g. This is even truer in premature newborns with worse adaptation to extrauterine life (Volpe, 2009; Dijkshoorn et al., 2020). Other noteworthy risk factors include preeclampsia, traumatic delivery, sepsis, prolonged mechanical ventilation, patent ductus arteriosus, and hemodynamically significant hypotension (Boswinkel et al., 2019; Gano and Barkovich, 2019; Garfinkle et al., 2020).

Although CBH is commonly associated with multifactorial etiology, cerebrovascular alterations have been mostly emphasized, suggesting the impaired autoregulation of the cerebral circulation and consequent treatment being the principal etiological factors (Tam, 2018; Boswinkel et al., 2019). This autoregulatory function develops progressively between the 23rd and the 33rd week of gestation (Rhee et al., 2016). Therefore, preterm infants may present with anatomically incomplete and underdeveloped cerebral vasculature, not yet fully able to autoregulate, determining an increased risk of brain injuries due to cerebral blood flow fluctuations (Rhee et al., 2018). From the microanatomic perspective, the cerebellar zone mostly involved in CBH is the external granule cells layer, since it is highly vascularized and contains overall the highest number of cells among the nervous system. CBH may be consequent to a vulnerability of the newly formed vessels in the external granule cells layer supplied by the posterior inferior cerebellar artery. Specifically, it appears that the fast angiogenesis taking place during the third trimester in the germinal matrix of the cerebellum (located in the roof of the

fourth ventricle and the external granule layer) may generate vessels that are still immature. These vascular structures cannot sustain these cerebral flow fluctuations; hence they may be more prone to insults (Volpe, 2009). Accordingly, Pierson and Al Sufiani (2016) stated that the recurrent association between CBH and intraventricular hemorrhage (IVH) relies on a shared pathogenetic mechanism, by which fluctuations of the blood pressure may increase hemorrhagic risk in both districts. The authors also proposed that CBH might result from a chronic process, with multiple hemorrhagic events occurring over time with single lesions merging into larger ones. Moreover, CBH location appears to be related to the origin of the bleeding, being the germinal matrix of the ventricular zone near the fourth ventricle mainly implicated in vermian hemorrhages, and the one located in the external granule layer more likely associated with focal unilateral CBH (Volpe, 2009).

Cerebellar bleeding may involve different parts of the cerebellum and, according to its extension, it has been classified as massive, medium, and punctate CBH (Boswinkel et al., 2019). Since it has a high mortality rate, larger CBH may be detected as an autoptic finding. It usually involves both cerebellar hemispheres and can be related to supratentorial lesions, as the IVH, leading to obstructive hydrocephalus (Tam, 2018). The outcome of the massive bleeding typically includes generalized atrophy with severe neurological sequelae, i.e., cerebral palsy. Vermis involvement is frequently associated with social and behavioral disorders, such as those typically detectable in the autism spectrum disorder (Limperopoulos et al., 2007). On the contrary, punctate hemorrhages, namely hemorrhages smaller than 4 mm, do not present with acute clinical signs and usually do not develop in cerebellar atrophy. It is commonly accepted that these lesions result in better neurodevelopmental outcomes, with minimal neurological abnormalities in tone, strength and reflexes, and cognitive level varying from normal to lower based on the cerebellar region injured (Boswinkel et al., 2019; Gano and Barkovich, 2019). CBHs involving only one-third of the cerebellar hemisphere are named medium or limited hemorrhages: they frequently involve only a lobe, developing into focal atrophy and leading to a milder neuropsychiatric outcome than the one caused by the massive CBH (Volpe, 2009; Boswinkel et al., 2019). Given the above and given the correlation between lower gestational age of birth and higher incidence of CBH and IVH reported by Zayek et al. (2012), it is presumable that preterms born at lower gestational ages may present with larger hemorrhages with worse outcomes (**Figure 2**).

Cerebellar Infarction

The cerebellar infarction is another type of direct lesion of the cerebellum in preterm infants and, as the CBH, it is considered a complication of extreme prematurity. Both the CBH and the infarction seem to be related to the same pathogenetic mechanism, underlying the vessel walls' immaturity due to the rapid angiogenesis (Volpe, 2009). As mentioned above, the newly formed vessels seem to be affected by fluctuations in cerebral blood flow, causing several brain injuries. This is even more interesting in the light of the fact that blood pressure is lower in preterm infants compared with term ones and, especially in prematures with hypotension, cardiac cycle changes can influence cerebral blood flow, often being absent during diastole (Rhee et al., 2018).

Additionally, neonatal respiratory distress syndrome, a common condition in premature babies, and its treatment through non-invasive respiratory support, may affect cerebral perfusion. A recent study on nasal continuous positive airway pressure (nCPAP), one of the most frequent ventilation methods used in NICU, analyzed the effects of high pressure on cerebral hemodynamics, stating that cerebral perfusion remains relatively stable when the pressure is set between 4 and 8 cmH_2O (Zhou et al., 2020).

As for CBH, the most affected area is the inferior cerebellum, supplied by the posterior inferior cerebellar artery, and an ischemic infarction possibly evolves into a hemorrhagic lesion (Mühlbacher et al., 2018). The hypoxic-ischemic insult determines a loss of neurons in the internal granule layer, resulting in a focal atrophy of the cerebellar parenchyma (Pierson and Al Sufiani, 2016). Even more than CBH, the cerebellar infarction is related to supratentorial white matter abnormalities, suggesting a common pathogenesis (Volpe, 2009; Suppiej et al., 2015).

NEURODEVELOPMENTAL OUTCOMES

According to the cerebellum's central role in sensorimotor control, posture and tone, executive functions, language, and behavioral regulation, it should not surprise that a significant correlation between cerebellar lesions and impairment of the neurodevelopmental outcome, especially in preterm infants (Brossard-Racine et al., 2015). As previously discussed, impaired cerebellar development, with its adverse consequences, may originate both from direct and indirect injuries, with or without a structural correlate.

Regarding direct injuries, many studies have focused on the neurodevelopmental outcomes deriving from hemorrhages. It appears that the larger is the hemorrhage, the worst are the effects on motricity, cognitivity, language, and behavior (Gano and Barkovich, 2019). Motor impairments are mainly encompassed by cerebral palsy, the severity of which appears to be related to procedures of shunt positioning, and, in a direct proportionate manner, to the grade of IVH, to the extent of white matter damage, and to the size of ventricles (Valdez Sandoval et al., 2019). A study conducted by Tam et al. (2011) reported alterations in muscle tone, strength, and reflexes in association with small CBHs, detectable only via MRI rather than cranial ultrasound. A various degree of motor delay has been previously reported in the literature (Gano and Barkovich, 2019) with more severity in preterm infants who present with cerebellar hemorrhagic injury concomitant to supratentorial parenchymal lesions (Limperopoulos et al., 2007). Rarely, CBH may also result in limited and specific motor dysfunctions. In this regard, a late preterm infant with a hemorrhagic lesion in the right cerebellar hemisphere and the vermis, with midline shift and intraventricular bleeding, presented with right peripheral facial

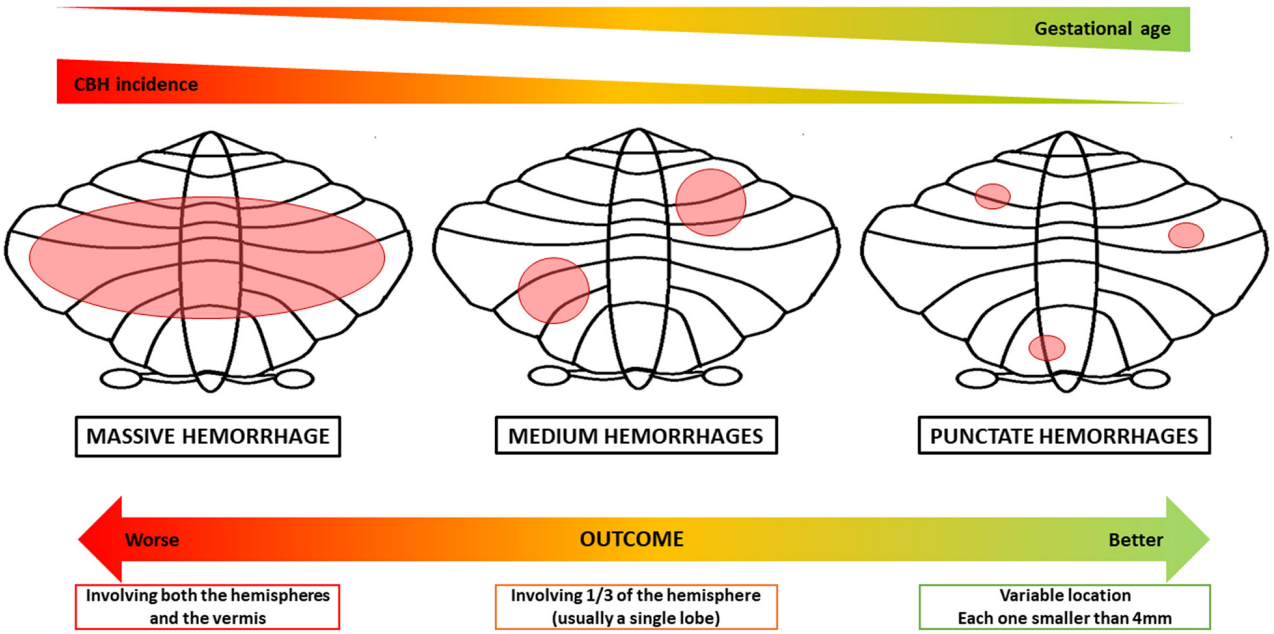

FIGURE 2 | Types of cerebellar hemorrhage in relation to possible timing and outcomes. The picture shows the possible correlation between lower gestational ages of birth and higher incidence of larger hemorrhages, concerning outcomes. Massive hemorrhage usually involves both the hemispheres and the vermis and can be related to supratentorial lesions, i.e., IVH. It has the worst outcome, leading to generalized cerebellar atrophy and to significant neurological sequelae, presenting the highest mortality rate. Medium hemorrhages involve only one-third of the cerebellar hemisphere, hence usually a single lobe (i.e., anterior or posterior lobe). It frequently evolves in focal atrophy and a variable neuropsychiatric outcome, typically milder than the massive one. Punctate hemorrhage is smaller than 4 mm. Generally, it does not lead to cerebellar hypoplasia and presents minimal neurological abnormalities, depending on the lesion site (Volpe, 2009; Zayek et al., 2012; Boswinkel et al., 2019; Gano and Barkovich, 2019).

palsy at 24 h of life (Coviello et al., 2020). About the non-motor domains, Limperopoulos et al. (2007) reported severe impairments in infants with isolated cerebellar hemorrhagic injuries, particularly involving communicative (in terms of both expressive and receptive language) and social-behavioral skills, including internalizing and externalizing problems as well as autistic features. A large study on 397 extremely preterm born children revealed pathological outcomes in social-emotional competences (26%) significantly related to the presence of cerebellar lesions on near-term MRI (Duncan et al., 2019).

Depending on the affected cerebellar region, infarction has also been related to various degree of neurodevelopmental sequelae, i.e., cerebral palsy, microcephaly, cognitive and language delay, ataxia and other sensorimotor abnormalities (Pierson and Al Sufiani, 2016; Mühlbacher et al., 2018). Patients with cerebellar underdevelopment, either with or without structural damages, have been shown to have several neurodevelopmental impairments. A significant correlation between CH with poor motor performances and cognitive defects has been reported, showing a lifespan course up to adulthood (Gano and Barkovich, 2019; Tam et al., 2019). Mixed spastic–ataxic–dyskinetic type of cerebral palsy with severe cognitive deficits have been reported in a case-control study carried out on prematures presenting with a disrupted cerebellar development (Messerschmidt et al., 2008). Ranger et al. (2015) demonstrated that a reduction of the posterior VIIIA and VIIIB lobules of preterm children exposed to opioids is significantly related to poorer outcomes in terms of cognition and motor/visual integration. Poor motor and cognitive outcomes at 18 months have been shown in the cohort of preterm patients exposed to morphine studied by Zwicker et al. (2016). Lind et al. (2011) showed in a cohort of 164 preterm patients a correlation between reduced total brain volume, including cerebellum, and larger ventricles, with poor neurological performance at 2 years of corrected age. Another study on a vast cohort of very preterm infants, evaluated at term equivalent age and at 7 years, demonstrated a correlation between CH and lower Intelligence Quotient (IQ), math computation and motor abilities (Anderson et al., 2017). Lower IQ was also related to persistent CH in preterm adolescents (Allin et al., 2001). In contrast, other studies failed to find significant correlations between motor and/or cognitive performances and cerebellar volume in prematures investigated at 2 and 5 years of age (Shah et al., 2006; Lind et al., 2010). Therefore, although during the last decade the role of cerebellar injuries in the neurodevelopmental outcome of preterm infants has been widely investigated, much more has yet to be unraveled on the topic, and further studies are needed.

A BRIEF OVERVIEW ON EARLY INTERVENTION

The recovery after cerebellar damage is usually slow, partial, and mostly depends on the lesions' site and size (Kelly and

Shanley, 2016). Despite several reports showing abnormal neurodevelopmental outcomes in preterm infants with both cerebellar dysmaturative and destructive lesions, less evidence is available for their early detection at long-term follow-up. Standardized neurological scales (i.e., Hammersmith Infant Neurological Examination) are extremely useful to assess neurological deficits during the first year of life. However, previous reports failed to show specific score range in patients with cerebellar malformations or injury who will later develop ataxia (Novak et al., 2017).

To date, no standardized protocols have been established to treat infants with cerebellar lesions specifically; therefore, more evidences on early neuromotor patterns are needed in order to provide targeted interventions. Kelly and Shanley (2016) proposed various rehabilitation strategies (such as strength and balance training, use of environmental cues, walking aids, compensatory head fixing, and retraining of specific abilities) targeting symptoms deriving from site-specific lesions of the cerebellum. In patients with cerebellar mutism syndrome, cognitive potentiation, physiotherapy, occupational, and language therapy are useful tools for an early recovery of motor and communicative functions (Catsman-Berrevoets, 2017). In the light of the frequent concomitant involvement of the supratentorial regions and given that a specific protocol of rehabilitation in cerebellar injuries has not been reported, appropriate treatment may also be chosen accordingly to previous evidences (Novak et al., 2017). Encouraging data are reported for constraint-induced movement therapy (CIMT), both prolonged and intermittent, as a feasible and effective treatment for hemiplegic cerebral palsy (Christmas et al., 2018). Conversely, CIMT has proved less efficacious than the same amount of upper limb therapy with no restraint (Chiu and Ada, 2016). Other types of interventions, such as gait and velocity trainings, electromyographic biofeedback training, and whole-body vibration, have been attempted to target the gait speed (Moreau et al., 2016). Slackline training has been reported as a useful tool to implement static postural control and motor skills (González et al., 2020). Moreover, the virtual reality training offers promising results in coordination and sensory-motor functions, and participation in daily living activities in multiple settings (Lopes et al., 2020). Patients with cerebellar damage may present impairments of some cranial nerve functions (i.e., swallowing and oculomotor coordination), based on which appropriate treatment can be addressed. Fucile et al. (2012) found that premature infants may benefit from oral, tactile/kinesthetic, and combined (oral plus tactile/kinesthetic) interventions, with better sucking skills and swallow-respiration coordination. Also, a multisensory early intervention program targeting visual functions may positively impact the neuro-visual outcome of preterm infants (Fontana et al., 2020).

DISCUSSION

During the last decades, more and more attention has been paid on the cerebellum. From the initial assumption of a mere role in motor coordination, new evidences have been continuously emerging on cerebellum involvement in a multiplicity of other functions (i.e., cognition, behavior, language, memory, and learning) (Salman and Tsai, 2016).

The human cerebellum develops over a long period of time; however, most of its volume increases during the last trimester of pregnancy. Therefore, this is considered a critical period for cerebellar maturation, even more when prematurity with all its contingencies occurs (Volpe, 2009; van Essen et al., 2020).

Here, we discussed the cerebellar neuropathology of preterm infants. Particularly, we retraced cerebellar development and analyzed the main factors entailed in the genesis of cerebellar underdevelopment and cerebellar destructive lesions in preterm infants, finally giving a brief overview of the potential neurodevelopmental outcomes and early intervention.

Even though the implications of encephalopathy of preterm have already been demonstrated, several undefined questions need to be answered.

First of all, the specific early clinical correlates of cerebellar prenatal and perinatal damages are yet to be well-defined by the most validated neurological examination scales in infancy. Second of all, few data on an early intervention for the preterm infants presenting with cerebellar injuries have been reported.

In light of this, we reckon that further studies specifically addressing these unsolved issues are needed. For instance, it would be of great interest and help for the clinical practice to analyze the correlation between clinical signs of suspect of cerebellar impairment, investigated through standardized neurological scales, and neuroimaging cerebellar abnormalities. This may help detect some red flags specifically related to cerebellar lesions, establish standardized tools of evaluation, and avoid the performing of useless and expensive examinations. More evidence on early neuromotor patterns would also be fundamental in providing targeted early intervention protocols and better assessing the prognosis. Finally, given the currently accepted notion that the cerebellum plays an important influence on non-motor functions (such as behavioral and social abilities), the follow up-programs of preterms with early cerebellar lesions should rightly include a systematical assessment of these skills.

Furthermore, other unsolved questions need to be answered regarding some of the above-mentioned causal factors of CH. For instance, as previously discussed, the molecular basis of glucocorticoids-induced brain injury has not been completely unraveled (Heine and Rowitch, 2009). A potential mechanism through which glucocorticoids may interfere with normal neurodevelopment appears to be via the inhibition of the Sonic-Hedhehog-Smoothened signaling, involved in the proliferation of the GCPs (Heine and Rowitch, 2009). Moreover, knowing the exact degree of causality and mechanisms through which molecules as glucocorticoids may actually act and cause CNS lesions in preterm would provide new insights on the topic and modify and improve the prenatal care protocols. The same goes for other modifiable factors previously mentioned, such as nutrition (both infant and maternal ones) or infections. More thorough and systematic research on the topic may unravel

the complex relationship between cerebellum and prematurity and help identify clear causality links, eventually allowing the modification of clinical and therapeutic protocols. Finally, comparative case-control studies may be of interest in detecting some protective factors too.

In conclusion, the complex relationship between cerebellar neuropathology and prematurity still gives rise to numerous and unsolved questions. Further studies on early detection, both clinically and neuroradiologically based, and on individually tailored intervention strategies or on the causality-link of numerous factors involved in cerebellar lesions need to be addressed in wide and gestational age-matched populations.

AUTHOR CONTRIBUTIONS

GD and AN designed and directed the project. GS and GA drafted the manuscript and designed the figures. LV, GQ, AC, and EG helped to supervise the project. All authors discussed the results and contributed to the final manuscript.

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Chronic Ethanol Exposure Enhances Facial Stimulation-Evoked Mossy Fiber–Granule Cell Synaptic Transmission *via* GluN2A Receptors in the Mouse Cerebellar Cortex

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Sensory information is transferred to the cerebellar cortex *via* the mossy fiber–granule cell (MF–GC) pathway, which participates in motor coordination and motor learning. We previously reported that chronic ethanol exposure from adolescence facilitated the sensory-evoked molecular layer interneuron–Purkinje cell synaptic transmission in adult mice *in vivo*. Herein, we investigated the effect of chronic ethanol exposure from adolescence on facial stimulation-evoked MF–GC synaptic transmission in the adult mouse cerebellar cortex using electrophysiological recording techniques and pharmacological methods. Chronic ethanol exposure from adolescence induced an enhancement of facial stimulation-evoked MF–GC synaptic transmission in the cerebellar cortex of adult mice. The application of an N-methyl-D-aspartate receptor (NMDAR) antagonist, D-APV (250 μM), induced stronger depression of facial stimulation-evoked MF–GC synaptic transmission in chronic ethanol-exposed mice compared with that in control mice. Chronic ethanol exposure-induced facilitation of facial stimulation evoked by MF–GC synaptic transmission was abolished by a selective GluN2A antagonist, PEAQX (10 μM), but was unaffected by the application of a selective GluN2B antagonist, TCN-237 (10 μM), or a type 1 metabotropic glutamate receptor blocker, JNJ16259685 (10 μM). These results indicate that chronic ethanol exposure from adolescence enhances facial stimulation-evoked MF–GC synaptic transmission *via* GluN2A, which suggests that chronic ethanol exposure from adolescence impairs the high-fidelity transmission capability of sensory information in the cerebellar cortex by enhancing the NMDAR-mediated components of MF–GC synaptic transmission in adult mice *in vivo*.

Keywords: cerebellar cortex, sensory stimulation, mossy fiber-granule cell synaptic transmission, *in vivo* electrophysiological recording, N-methyl-D-aspartate receptors, chronic ethanol exposure

INTRODUCTION

Ethanol is the most widely used and abused psychoactive substance and can cause damage to the central nervous system that leads to impairment of its function. The cerebellum is a major target of ethanol. Ethanol exposure causes alterations in behavior, motor coordination, speech, balance, and cognitive functions, which are considered to be induced by the impaired function of cerebellar neuronal circuits and synaptic transmission (Schmahmann and Sherman, 1997; Mameli et al., 2008; Luo, 2012).

In vitro, acute ethanol exposure was shown to increase the frequency of miniature and spontaneous inhibitory postsynaptic currents in cerebellar Purkinje cells (PCs) and molecular layer interneurons by enhancing γ-aminobutyric acid (GABA) release in rats (Mameli et al., 2008; Wadleigh and Valenzuela, 2012). *In vivo*, cerebellar surface application of ethanol was shown to modulate the facial stimulation evoked by γ-aminobutyric acid-ergic (GABAergic) responses in the mouse cerebellar molecular layer (Cui et al., 2014). Acute overdose ethanol exposure inhibited the facial stimulation-evoked outward current by activating cannabinoid receptor 1 *via* the protein kinase A signaling pathway in the mouse cerebellar cortex (Wu et al., 2016). In contrast, chronic ethanol exposure impairs neuronal function, reduces the number of neurons *via* activation of N-methyl-D-aspartate receptors (NMDARs) (Nagy, 2004), and significantly inhibits the simple spike and complex spike activities of PCs (Servais et al., 2005). Chronic intermittent ethanol exposure significantly reduces the abundance of myelin sheath proteins and enzymes in the cerebellum, the corpus callosum, and the spinal cord (Samantaray et al., 2015). Chronic ethanol exposure also impairs sensory stimulation-induced molecular layer interneuron–PC long-term depression *via* the activation of the nitric oxide signaling pathway (Li et al., 2019) and significantly facilitates sensory stimulation-evoked molecular layer interneuron–PC synaptic transmission *via* the nitric oxide signaling pathway in the mouse cerebellar cortex (Sun et al., 2020).

Cerebellar granule cells (GCs) are the main integrators and processors of input information in the cerebellar cortex (Hamann et al., 2002; Duguid et al., 2012) and are considered to decorrelate the information conveyed *via* convergent multimodal mossy fibers (MFs), increasing the use for learned associations (Billings et al., 2014; Cayco-Gajic et al., 2017). Sensory information is derived from MFs, which induce excitatory responses in cerebellar GCs and are involved in the modulation of the command output of PCs (Eccles et al., 1967; Jakab and Hámori, 1988). Passive movement of the forelimb without touching the receptive field can evoke spike firing in the GCs, which indicates that the sensory information is encoded by spike firing of GCs (Jörntell and Ekerot, 2006). GCs are relatively simple spike encoders that exhibit a relatively linear conversion of the depolarization level to spike firing frequency (D'Angelo et al., 1998; Jörntell and Ekerot, 2006). Cerebellar GCs comprise a low-noise, sparse coding system that can reliably relay sensory-evoked MF signals and filter out information not associated with sensory stimulation (Chadderton et al., 2004). The spike output of GCs could reflect the sensory information coding principal during the low-intensity rate-coded MF activation (Arenz et al., 2008). GCs exhibit high-frequency and high-fidelity properties in response to sensory stimulation, which ensures the transmission of accurate sensory information to PCs (van Beugen et al., 2013; Bing et al., 2015b). In addition, GCs activate Golgi cells *via* parallel fibers (Cesana et al., 2013), which inhibit GCs *via* Golgi axon branches (Mapelli et al., 2009). In the cerebellar granular layer (GL), ethanol mediates phase and tense GABAergic inhibition in GCs by activating Golgi cells (Botta et al., 2007) and inhibits sensory stimulation-evoked responses in cerebellar GCs by enhancing $GABA_A$ receptor activity (Wu et al., 2014). Chronic ethanol exposure causes a significant reduction in the number of GCs or in the total volume of the GL in adult rats (Tabbaa et al., 1999; Pentney et al., 2002). Adolescents are more sensitive to ethanol exposure than adults (Spear, 2016), especially in the cerebellum (Best and Miller, 2010). During the adolescent developmental period, chronic ethanol consumption leads to many adverse effects, such as impaired learning, attention and behavior (Maldonado-Devincci et al., 2021). Chronic ethanol exposure in adolescents has been shown to damage the cognitive flexibility of rats in adulthood (Semenova, 2012) and to impair the expression of long-term synaptic potentiation (Goodwani et al., 2017).

Cerebellar GCs exhibit high-frequency and high-fidelity properties during sensory information encoding and transfer to PCs, which are critical to motor regulation and motor learning behavior because of the modulation of the output of PCs. Chronic ethanol exposure from the adolescent stage could damage the cerebellar function by impairing the synaptic transmission of sensory information from MFs to GCs. Therefore, in this study, we studied the effects of chronic ethanol exposure in adolescence on facial stimulation-evoked MF–GC synaptic transmission in the cerebellar cortex of mice.

MATERIALS AND METHODS

Animals

A total of 96 (5-week-old) ICR mice were selected, and they were divided into the chronic ethanol exposure group (48 mice; 22 female, 26 male) and the control group (48 mice; 23 female, 25 male). The experimental procedures were approved by the Animal Care and Use Committee of the Yanbian University and were in accordance with the animal welfare guidelines of the United States National Institutes of Health. The permit number is SYXK (Ji) 2011-006. All animals were housed under a 12-h light/dark cycle with free access to food and water in a colony room kept under a constant temperature (23 ± 1°C) and humidity (50 ± 5%). Mice in the chronic ethanol group were given intraperitoneal (i.p.) injection of ethanol (0.8 g/kg; 15% in saline), while the mice in the control group were given i.p. injection of the same volume of saline. Ethanol (95%) was diluted in saline to a final concentration of 15%. The i.p. injection was performed 1 time/day during 8:00–9:00 a.m. for 28 days. The electrophysiological recordings were performed 1 day after the last injection of ethanol.

Anesthesia and Surgical Procedures

The anesthesia and surgical procedures have been described below (Chu et al., 2011a,b). The mice were anesthetized with urethane (1.3 g/kg body weight, i.p.) and were tracheotomized to avoid respiratory obstruction. On a custom-made stereotaxic frame, soft tissue was retracted to gain access to the dorsal portion of the occipital bone. A watertight chamber was created and a 1–1.5 mm craniotomy was drilled to expose the cerebellar surface corresponding to Crus II. The cerebellum surface was constantly superfused with oxygenated artificial cerebrospinal fluid (ACSF: 125 mM NaCl, 3 mM KCl, 1 mM $MgSO_4$, 2 mM $CaCl_2$, 1 mM NaH_2PO_4, 25 mM $NaHCO_3$, and 10 mM D-glucose) with a peristaltic pump (Gilson Minipulse 3; Villiers-le-Bel, France) at 0.5 ml/min. Rectal temperature was monitored and maintained at 37.0 ± 0.2°C.

Facial Stimulation and *in vivo* Electrophysiological Recording

Local field potential recordings from the GL were performed with an Axopatch-200B amplifier (Molecular Devices, Foster City, CA, United States). The potentials were acquired through a Digidata 1440 series analog-to-digital interface on a personal computer using Clampex 10.4 software (Molecular Devices). Recording pipettes were made with a puller (PB-10; Narishige, Tokyo, Japan) from a thick-walled borosilicate glass (GD-1.5; Narishige). Recording electrodes were filled with ACSF and with resistances of 3–5 MΩ. The recordings from the GL were performed at depths of 300–350 μm under the pia mater membrane.

Facial stimulation was performed by air-puff to the ipsilateral whisker pad through a 12-gauge stainless steel tube connected with a pressurized injection system (Picospritzer® III; Parker Hannifin Co., Pine Brook, NJ, United States). The air-puff stimuli were controlled by a personal computer, were synchronized with the electrophysiological recordings, and were delivered at 0.05 Hz *via* a Master 8 controller (A.M.P.I., Jerusalem, Israel) and Clampex 10.4 software. For isolating mossy fiber-granule cell (MF-GC) synaptic transmission, picrotoxin (100 μM) was added to ACSF during all recordings to prevent $GABA_A$ receptor-mediated inhibitory responses of Golgi cells. Single stimulation (60 ms, 60 psi) or stimuli train (20 Hz, 5-pulse, 10 ms, 60 psi) were used to evoke the MF-GC synaptic transmission in the absence of $GABA_A$ receptors activity.

Chemicals

Picrotoxin, (3,4-dihydro-2H-pyrano [2,3-b]quinolin-7-yl)-(cis-4-methoxy- cyclohexyl)-methanone [JNJ16259685 (JNJ)] and D-amino phosphono valeric acid (D-APV) were bought from Sigma-Aldrich (Shanghai, China). PEAQX and TCN 237 were purchased from Tocris (Bristol, United Kingdom). The drugs were dissolved in ACSF and applied directly onto the cerebellar surface by a peristaltic pump (0.5 ml/min).

Data Analysis

The electrophysiological data were analyzed using Clampfit 10.4 software (Molecular Devices, Foster City, CA, United States). All data are expressed as the mean ± SEM. A one-way ANOVA (the Turkey *post hoc* test) and a two-way ANOVA (SPSS software) were used to determine the level of statistical significance among the groups of data. *P*-values below 0.05 were considered as statistically significant.

RESULTS

Effect of Chronic Ethanol Exposure From Adolescence on the Facial Stimulation-Evoked Field Potential Response in Adult Mouse Cerebellar GL

To observe facial stimulation-evoked MF–GC synaptic transmission, we recorded the facial stimulation-evoked field potential response in the cerebellar GL in the presence of the $GABA_A$ receptor antagonist picrotoxin (100 μM), which blocks the inhibitory components of Golgi cells. Blockade of $GABA_A$ receptor activity and air-puff stimulation of the ipsilateral whisker pad (60 ms; 50–60 psi) evoked negative components N1 and N2 in the GL (**Figure 1A**), which were identified as components of facial stimulation-evoked MF–GC synaptic transmission (Bing et al., 2015a,b; Ma et al., 2019). To determine the effects of chronic ethanol exposure on facial stimulation-evoked MF–GC synaptic transmission, we compared the properties of the facial stimulation-evoked field potential response in the GL between chronic ethanol-exposed and non-ethanol-exposed (control) mice. Since there were no significant sex differences between the amplitudes of N1 and N2 in both control and ethanol-exposed mice, we pooled both the sexes for analysis. As shown in **Figure 1**, the N1 amplitude in the chronic ethanol-exposed group was 1.18 ± 0.12% mV (n = 10 mice), which was similar to that in the control group (1.13 ± 0.11% of the baseline value, n = 10 mice; F = 0.31, P = 0.67; **Figures 1A,B**). However, the area under the curve (AUC) of N1 was 138.2 ± 9.2% mV/ms (n = 10 mice) in the ethanol-exposed group, which was significantly larger than that in the control group (115.1 ± 7.9 mV/ms, n = 10 mice; F = 5.12, P = 0.016; **Figure 1C**). The N2 amplitude in the ethanol-exposed group was 0.42 ± 0.03 mV (n = 10 mice), which was significantly lower than that in the control group (0.25 ± 0.02 mV; n = 10 mice; F = 5.27, P = 0.003; **Figure 1D**). Moreover, the AUC of the N2 in the ethanol-exposed group was 6.85 ± 0.52 mV/ms (n = 10 mice), which was also significantly larger than that in the control group (4.56 ± 0.49 mV/ms; n = 10 mice; F = 4.41, P = 0.002; **Figure 1E**). These results indicate that the chronic ethanol exposure from adolescence induces a significant enhancement in the later components of facial stimulation-evoked MF–GC synaptic transmission in mice *in vivo*.

Chronic Ethanol Exposure From Adolescent Enhanced the Facial Stimulation-Evoked MF-GC Synaptic Transmission via NMDARs

Previous studies demonstrated that chronic ethanol exposure overdose impairs neuronal function *via* NMDARs (Nagy, 2004)

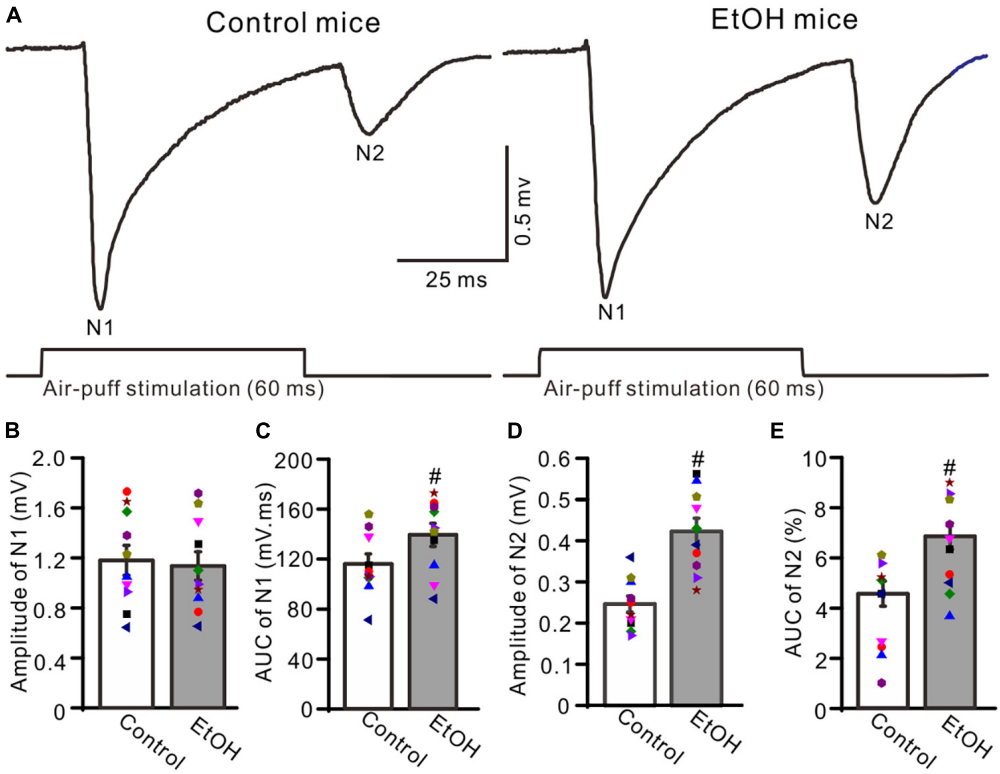

FIGURE 1 | Chronic ethanol exposure enhanced the facial stimulation-evoked mossy fiber-granule cell (MF–GC) synaptic transmission in the mouse cerebellar cortex. **(A)** Representative field potential recording traces showing the facial stimulation (60 ms, 50 psi)-evoked responses in the granular layer (GL) of control and ethanol-exposed mice. **(B)** The mean and individual data (Symbols of different colors) show the amplitude of N1 in control and ethanol-exposed (EtOH) mice. **(C)** A bar graph with individual data showing the area under the curve (AUC) of N1 in control and ethanol-exposed (EtOH) mice. **(D,E)** Bar graphs and individual data showing the amplitude **(D)** and AUC **(E)** of N2 in control and ethanol-exposed (EtOH) mice. n = 10 in each group. #$P < 0.05$ vs. control.

and that NMDARs contribute to the later components of facial stimulation evoked by MF–GC synaptic transmission in the mouse cerebellar GL (Zhang et al., 2020). We examined the effect of adolescent chronic ethanol exposure on the NMDARs-mediated components of facial stimulation-evoked MF–GC synaptic transmission. To activate NMDARs in the cerebellar GL during facial stimulation-evoked MF–GC synaptic transmission, we employed a facial stimuli train (20 Hz, five pulses) to evoke five field potential responses (N1–N5) in the cerebellar GL (Zhang et al., 2020). Application of the selective NMDAR antagonist D-APV (250 μM) did not significantly affect the amplitude of N1 but induced a decrease in the amplitudes of N2–N5 in both the control ($P < 0.05$ vs. ACSF; **Figures 2A,B**) and the chronic ethanol-exposed mice ($P < 0.05$ vs. ACSF; **Figures 2A,C**). Indeed, the amplitudes of N2–N5 in the ethanol group were significantly higher than those in the control group in the presence of ACSF ($P < 0.05$; n = 10; **Figure 2D**), but they were not significantly different in the presence of D-APV ($P > 0.05$; n = 10; **Figure 2E**).

To understand the changes in the D-APV-sensitive components in the control and the ethanol-exposed mice, we compared the normalized value of N2. In the presence of D-APV, the normalized amplitude of N2 was 76.7 ± 4.2% of the baseline value (F = 5.26, P = 0.003 vs. ACSF; n = 10 mice; **Figure 2F**) in the control group and 64.9 ± 3.8% of the baseline value (F = 5.17, P = 0.0006 vs. ACSF; n = 10 mice; **Figure 2F**) in the ethanol-exposed group. The mean value of the normalized amplitude of N2 for ethanol-exposed mice was significantly lower than that in the presence of ACSF (F = 4.31, P = 0.032 vs. control; n = 10; two-way ANOVA; **Figure 2F**). Moreover, the normalized AUC of N2 was 68.5 ± 4.6% of the baseline value (n = 10 mice; $P < 0.001$; **Figure 2G**) in the control group and 55.3 ± 4.9% of the baseline value (n = 10 mice; $P < 0.001$; **Figure 2G**) in the ethanol-exposed group. The mean value of the normalized AUC of N2 in the ethanol-exposed group was significantly lower than that in the control group (F = 4.54, P = 0.012; n = 10 mice; two-way ANOVA; **Figure 2G**). These results indicate that the chronic ethanol exposure from adolescence augments the facial stimulation-evoked MF–GC synaptic transmission *via* NMDARs in adult mice *in vivo*.

Chronic Ethanol Exposure From Adolescents Augmented the MF-GC Synaptic Transmission via GluN2A

GluN2A is expressed on the somas of GCs and the boutons of parallel fibers (Glitsch and Marty, 1999; Casado et al., 2000) and contributes to the facial stimulation-evoked MF–GC synaptic transmission in mice *in vivo* (Zhang et al., 2020). We

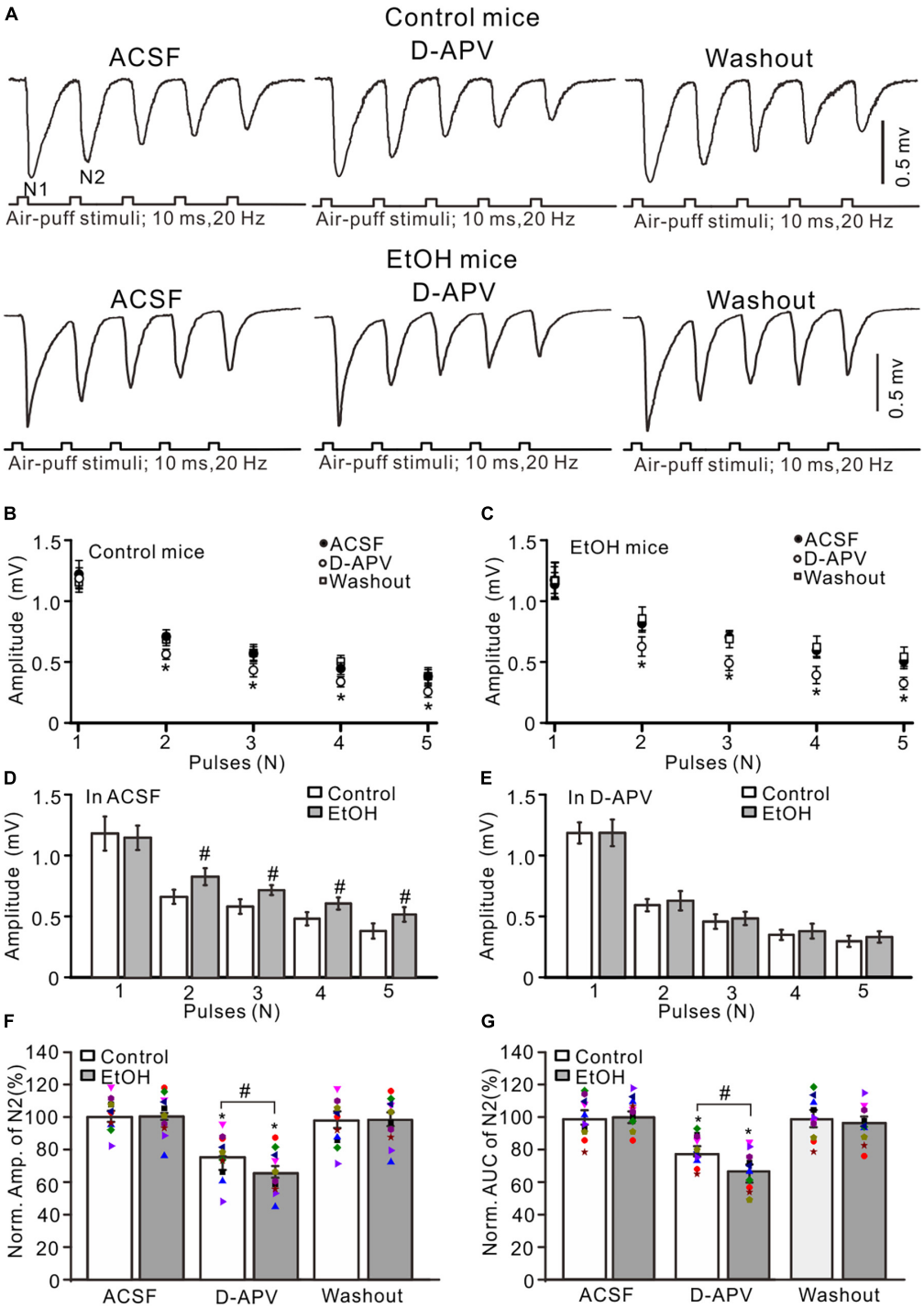

FIGURE 2 | Blockade of N-methyl-D-aspartate receptors (NMDARs) prevented the chronic ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. **(A)** Representative field potential traces showing that the air-puff stimuli (10 ms, 60 psi; 5 pulse, 20 Hz) on the ipsilateral whisker pad evoked field potential responses recorded from the GL of control **(upper)** and ethanol-exposed **(lower)** mice in treatments with artificial cerebrospinal fluid (ACSF), D-APV (250 μM), and recovery (washout). **(B)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, D-APV, and recovery (washout) in control mice. **(C)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, D-APV (250 μM), and recovery (washout) in ethanol-exposed mice. **(D)** A bar graph showing the mean amplitude of peaks recorded in the presence of ACSF in control and ethanol-exposed mice. **(E)** A bar graph showing the mean amplitude of peaks recorded in the presence of D-APV in control and ethanol-exposed mice. **(F)** A bar graph with individual data (Symbols of different colors) showing the normalized amplitude of N2 in control and ethanol-exposed (EtOH) mice in treatments with ACSF, D-APV, and recovery (washout). **(G)** A bar graphs with individual data (Symbols of different colors) showing the normalized AUC of N2 in control and ethanol-exposed (EtOH) mice in treatments with ACSF, D-APV, and recovery (washout). $n = 10$ in each group. $^*P < 0.05$ vs. ACSF; $\#P < 0.05$ vs. control.

observed the effect of a GluN2A blocker, PEAQX (10 μM), on the facial stimulation-evoked MF–GC synaptic transmission in the cerebellar GL of mice. Application of PEAQX did not significantly affect the amplitude of N1 but induced a significant decrease in the amplitude of N2–N5 in both the control ($P < 0.05$ vs. ACSF; **Figures 3A,B**) and ethanol-exposed mice ($P < 0.05$ vs. ACSF; **Figures 3A,C**). The amplitudes of N2–N5 in the ethanol-exposed group were significantly higher than those in the control group in the presence of ACSF ($P < 0.05$; $n = 8$ mice; **Figure 3D**) but were not significantly different in the presence of PEAQX ($P > 0.05$; $n = 8$; **Figure 3E**). In the presence of PEAQX, the normalized amplitude of N2 was 77.2 ± 3.9% of the baseline value ($F = 7.23$, $P = 0.0004$; $n = 8$ mice; **Figure 3F**) in the control group and 63.8 ± 3.5% of the baseline value ($F = 6.85$, $P = 0.0007$; $n = 8$ mice; **Figure 3F**) in the ethanol-exposed group. The mean normalized amplitude of N2 in the ethanol-exposed group was significantly higher than that in the control group ($F = 5.18$, $P = 0.036$; $n = 8$ mice two-way ANOVA; **Figure 3F**). Further, the normalized AUC of N2 was 68.6 ± 4.2% of the baseline value ($F = 7.32$, $P = 0.0006$; $n = 8$ mice; **Figure 3G**) in the control group and 56.5 ± 5.1% of the baseline value ($F = 7.08$, $P = 0.0003$; $n = 8$ mice; **Figure 3G**) in the ethanol-exposed group. The mean normalized AUC of N2 in the ethanol-exposed group was significantly larger than that in the control group ($F = 5.17$, $P = 0.016$; $n = 8$ mice; two-way ANOVA; **Figure 3G**).

Since PEAQX is not sufficiently selective to distinguish between GluN2A and GluN2B (Frizelle et al., 2006), we used a selective GluN2B antagonist, TCN-237, to determine whether GluN2B contributed to facial stimulation-evoked MF–GC synaptic transmission in the cerebellar GL (McCauley et al., 2004). Perfusion of TCN-237 (10 μM) did not significantly change the amplitude of N1–N5 in either the control ($P > 0.05$ vs. ACSF; **Figures 4A,B**) or the ethanol-exposed mice ($P > 0.05$ vs. ACSF; $n = 8$; **Figures 4A,C**). However, the amplitudes of N2–N5 in the ethanol-exposed group were significantly higher than those in the control group in the presence of ACSF ($P < 0.05$; $n = 8$; **Figure 4D**) as well in the presence of TCN-237 ($P < 0.05$; $n = 8$; **Figure 4E**). In the presence of TCN-237, the normalized amplitude of N2 was 98.3 ± 4.1% of the baseline value ($F = 0.19$, $P = 0.72$ vs. ACSF; $n = 8$ mice; **Figure 4F**) in the control group and 97.4 ± 5.1% of the baseline value ($F = 0.22$, $P = 0.65$; $n = 8$ mice; **Figure 4F**) in the ethanol-exposed group. The mean normalized amplitude of N2 in the ethanol-exposed group was similar to that in the control group ($F = 0.18$, $P = 0.67$; $n = 8$ mice two-way ANOVA; **Figure 4F**). Moreover, blockade of GluN2B did not significantly change the AUC of N2 in either the control or the ethanol-exposed mice. The normalized AUC of N2 was 97.7 ± 3.6% of the baseline value ($F = 0.18$, $P = 0.67$ vs. ACSF; $n = 8$ mice; **Figure 4C**) in the control group and 98.1 ± 5.7% of the baseline value ($F = 0.16$, $P = 0.71$ vs. ACSF; $n = 8$ mice; **Figure 4C**) in the ethanol-exposed group. The normalized AUC of N2 in the ethanol-exposed group was not significantly different from that in the control group ($F = 0.21$, $P = 0.62$; $n = 8$ mice two-way ANOVA; **Figure 4G**). These results indicate that chronic ethanol exposure from adolescence augments the NMDAR-sensitive components during the facial stimulation-evoked MF–GC synaptic transmission but not *via* GluN2B.

Blocking mGluR1 Failed to Prevent Chronic Ethanol-Induced Enhancement of Facial Stimulation-Evoked MF–GC Synaptic Transmission

Chronic ethanol exposure could enhance the expression and function of metabolic glutamate receptor 1 (mGluR1) in several regions of the brain (Cozzoli et al., 2014), and activation of mGluR1 may contribute to the chronic ethanol-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. Therefore, we examined whether mGluR1 contributed to the chronic ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. Administration of a selective mGluR1 receptor antagonist, JNJ16259685 (10 μM), did not induce a significant change in the amplitude of N1–N5 in the control (**Figures 5A,B**) and the ethanol-exposed mice (**Figures 5A,C**). In the presence of JNJ16259685, the normalized amplitude of N2 was 99.3 ± 5.3% of the baseline value ($F = 0.16$, $P = 0.65$; $n = 7$ mice; **Figure 5D**) in the control group and 98.4 ± 4.6% of the baseline value ($F = 0.23$, $P = 0.78$; $n = 7$ mice; **Figure 5D**) in the ethanol-exposed group. The mean normalized amplitude of N2 in the ethanol-exposed group was not significantly different from that in the control group ($F = 0.26$, $P = 0.63$; two-way ANOVA; $n = 7$ mice; **Figure 5D**). Moreover, the normalized AUC of N2 was 99.6 ± 5.8% of the baseline value ($F = 0.12$, $P = 0.76$; $n = 7$ mice; **Figure 5E**) in the control group and 97.7 ± 5.3% of the baseline value ($F = 0.13$, $P = 0.73$; $n = 7$ mice; **Figure 5E**) in the ethanol-exposed group. These results indicate that blockade of mGluR1 does not prevent the chronic ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission in mice *in vivo*.

DISCUSSION

In this study, we found that the chronic ethanol exposure from adolescence led to an enhancement in the facial stimulation-evoked MF–GC synaptic transmission, which was blocked by a selective NMDAR antagonist. The chronic ethanol exposure-induced enhancement of the facial stimulation-evoked MF–GC synaptic transmission was prevented by a selective GluN2A blocker but was not prevented by a selective GluN2B antagonist or a selective mGluR1 blocker. These results indicate that the chronic ethanol exposure from adolescence enhances facial stimulation-evoked MF–GC synaptic transmission *via* GluN2A, which suggests that chronic ethanol exposure from adolescence may impair high-fidelity properties during the sensory information processing in the cerebellar cortical GL.

Chronic ethanol exposure can affect neurotransmitter release, synaptic transmission, and neural circuit plasticity in multiple brain regions. The latter is related to tolerance and dependence in human (Tsai and Coyle, 1998; Koob, 2003; Heilig et al., 2010; Koob and Volkow, 2010, 2016; Wu et al., 2014; Li et al., 2019). Heavy chronic ethanol consumption from adolescence to adulthood was shown to significantly impair the motor performance in female rats, inducing spontaneous locomotor

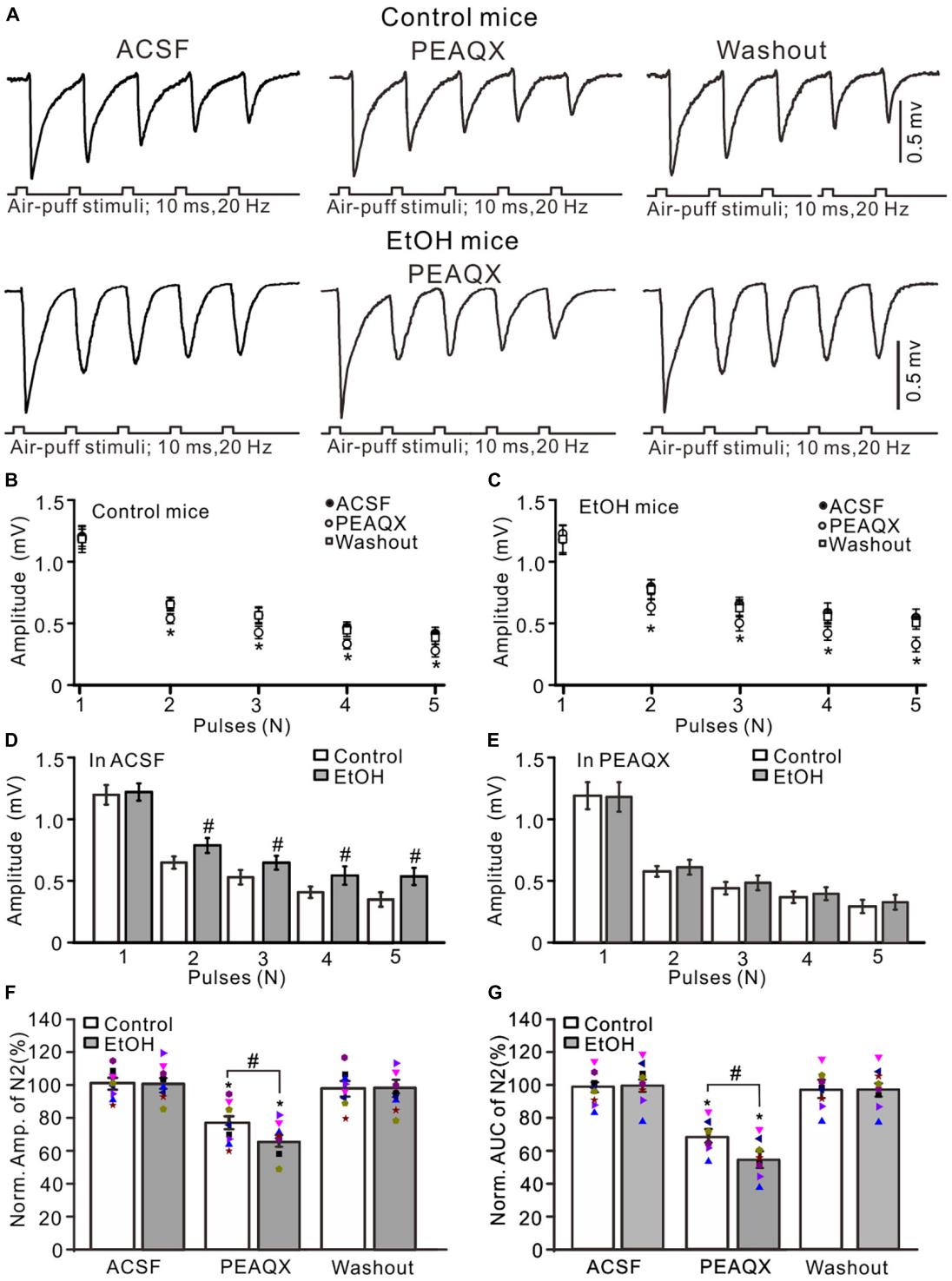

FIGURE 3 | Blockade of GluN2A abolished the chronic ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. **(A)** Representative field potential traces showing that the air-puff stimuli (10 ms, 60 psi; 5 pulse, 20 Hz) on the ipsilateral whisker pad evoked field potential responses, recorded from the GL of control **(upper)** and ethanol-exposed mice in treatments of ACSF, PEAQX (10 μM), and recovery (washout). **(B)** Summary of data showing the absolute (±SEM) amplitudes of N1–N5 in treatments with ACSF, PEAQX, and recovery (washout) in control mice. **(C)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, PEAQX, and recovery (washout) in ethanol-exposed mice. **(D)** Bar graph showing the mean amplitude of peaks recorded in the presence of ACSF in control and ethanol-exposed mice. **(E)** A bar graph showing the mean amplitude of peaks recorded in the presence of PEAQX in control and ethanol-exposed mice. **(F)** A bar graph with individual data (Symbols of different colors) showing the normalized amplitude of N2 in each treatment. **(G)** A bar graph with individual data (Symbols of different colors) showing the normalized AUC of N2 in treatments with ACSF, PEAQX, and recovery (washout). $n = 8$ in each group. $^*P < 0.05$ vs. ACSF; $\#P < 0.05$ vs. control.

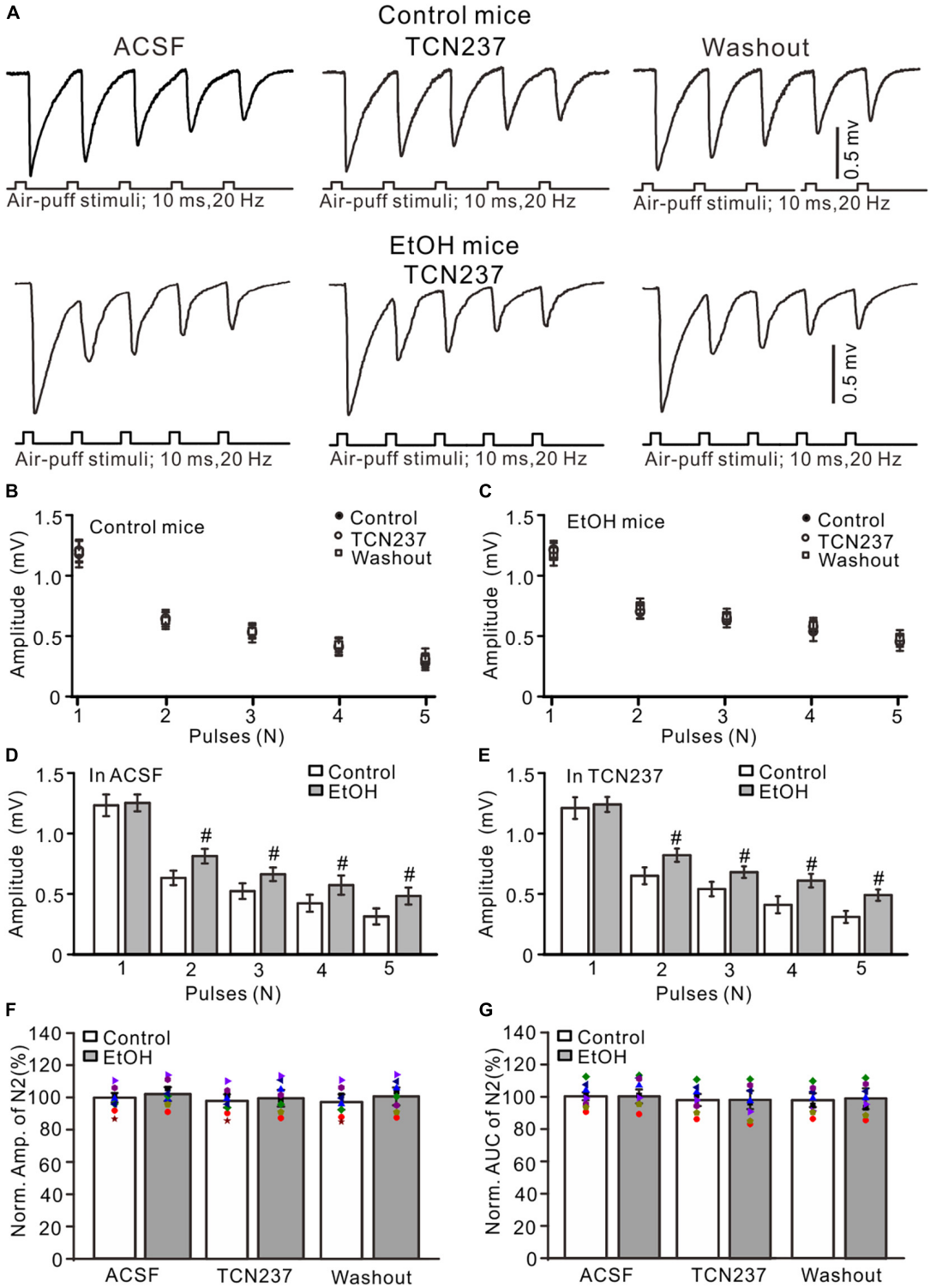

FIGURE 4 | GluN2B blockade failed to prevent the ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. **(A)** Representative field potential traces showing that the air-puff stimuli (10 ms, 60 psi; 5 pulse, 20 Hz) on the ipsilateral whisker pad evoked field potential responses, recorded from the GL of control **(upper)** and ethanol-exposed mice in treatments of ACSF, TCN (10 μM), and recovery (washout). **(B)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, TCN (10 μM), and recovery (washout) in control mice. **(C)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, TCN, and recovery (washout) in ethanol-exposed mice. **(D,E)** Bar graphs with individual data showing the normalized amplitude of N2 in ACSF **(D)** and in TCN237 mice. **(F,G)** Bar graphs with individual data (Symbols of different colors) showing the normalized amplitude **(F)** and AUC **(G)** of N2 in control and ethanol-exposed mice. $n = 8$ in each group. #$P < 0.05$ vs. control.

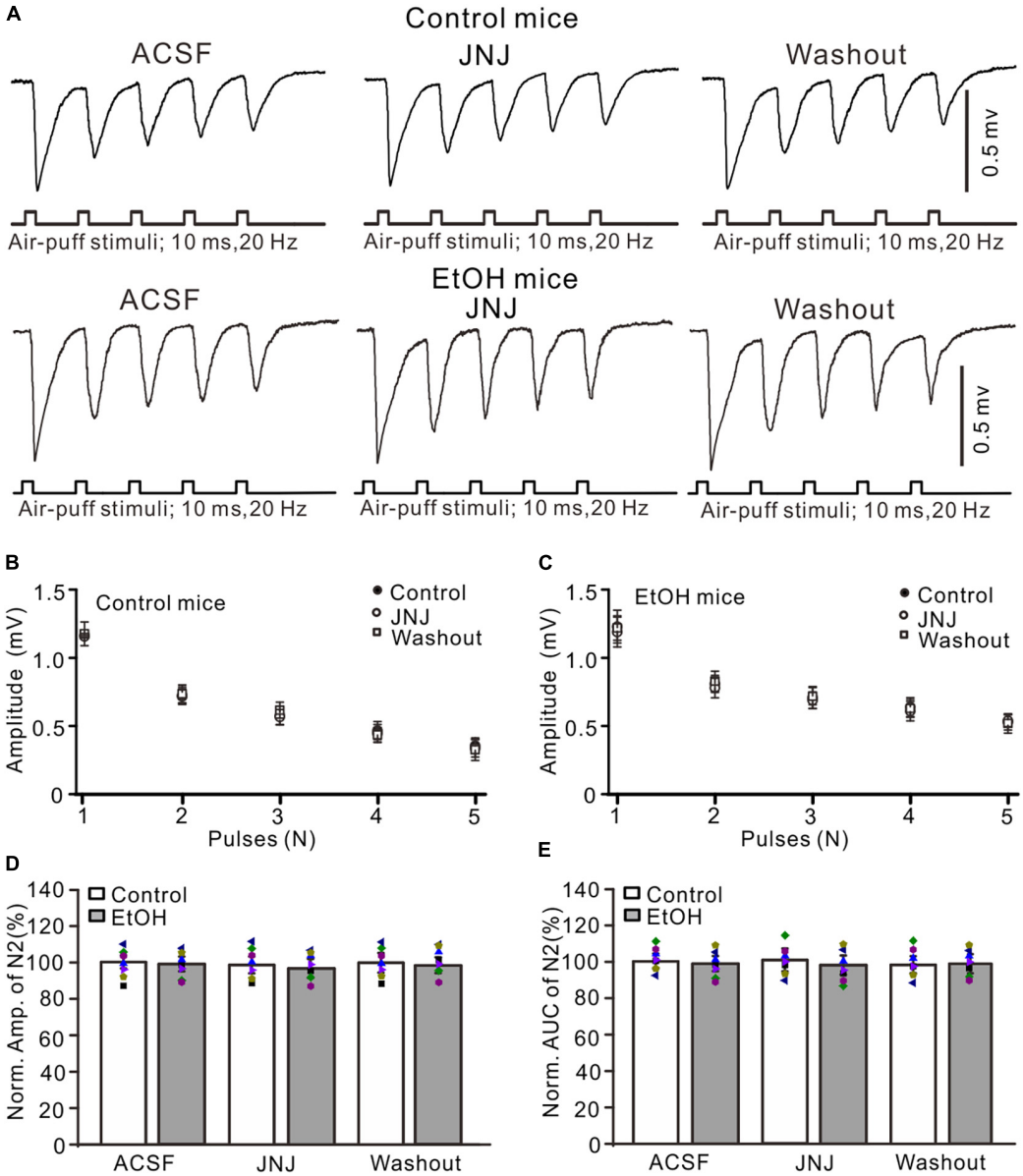

FIGURE 5 | Blockade of mGluR1 failed to prevent the ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission. **(A)** Representative field potential traces showing that the air-puff stimuli (10 ms, 60 psi; 5 pulse, 20 Hz) on the ipsilateral whisker pad evoked field potential responses, recorded from the GL of control and ethanol-exposed mice in treatments of ACSF, JNJ (10 μM), and recovery (washout). **(B)** Summary of data showing the absolute amplitudes of N1–N5 in treatments with ACSF, JNJ, and recovery (washout) in control mice. **(C)** Pooled data showing the absolute values of N1–N5 in treatments with ACSF, JNJ, and recovery (washout) in ethanol-exposed mice. **(D)** A bar graph with individual data (Symbols of different colors) showing the normalized amplitude of N2 in treatments with ACSF, JNJ, and recovery (washout). **(E)** A bar graph with individual data (Symbols of different colors) showing the normalized AUC of N2 for each treatment. $n = 7$ in each group.

activity deficits, bradykinesia, incoordination, motor learning disruption, and atrophy and neuronal loss in the cerebellum (Maldonado-Devincci et al., 2021). Behavioral studies have shown that adolescents and adults have different behavioral sensitivities to alcohol and that the cerebellum of adolescents is more sensitive to ethanol exposure (Best and Miller, 2010; Spear, 2016). Chronic ethanol exposure in adolescence could impair the expression of long-term synaptic potentiation in animals (Goodwani et al., 2017). The core of understanding the pathophysiology of ethanol dependence is describing the specific neural adaptations in glutamatergic and GABAergic synaptic transmissions caused by chronic ethanol exposure. The effects of chronic ethanol exposure on glutamatergic signal transduction are mainly concentrated on postsynaptic glutamate receptors (David and Marisa, 2013; Bliss et al., 2014), which affect ionic receptors and various metabotropic glutamate receptor subtypes.

In the cerebellar cortex, GCs receive and respond to sensory information conveyed by MFs (Huang et al., 2013; Ishikawa et al., 2015) and Golgi cells set the spiking threshold and therefore the number of different afferents required to drive GC firing by offering feed-forward inhibition (Marr, 1969; D'Angelo et al., 2013). To isolate the effect of chronic ethanol exposure on MF–GC excitatory synaptic transmission, we applied a GABAA receptor antagonist to the cerebellar surface to block Golgi cell–GC GABAergic transmission. The results showed that chronic ethanol exposure significantly enhanced facial stimulation-evoked MF–GC synaptic transmission in the absence of the GABAA receptor activity, which suggests that the chronic ethanol exposure modulates the MF–GC excitatory synaptic transmission in mice *in vivo*.

N-methyl-D-aspartate receptors are a crucial target of chronic ethanol exposure in the central nervous system and are involved in tolerance, dependence, withdrawal, craving, and relapse (Woodward, 2000; Pignataro et al., 2009). Acute ethanol exposure leads to inhibitory actions on the activity of NMDARs, which has been illustrated previously in the slices of several brain regions (Calton et al., 1999; Ronald et al., 2001; Yaka et al., 2003; Boikov et al., 2020). Chronic ethanol exposure in adult animals induces upregulation of the number and function of NMDARs and also increases the expression of NMDAR subunits (Chandler et al., 1993; Follesa and Ticku, 1995; Hoffman et al., 1996). Many studies found that chronic ethanol exposure could significantly enhance the function of NMDARs and its mediated glutamatergic synaptic transmission (Gulya et al., 1991; Smothers et al., 1997; Grover et al., 1998; Cebere et al., 1999; Lack et al., 2007) and that chronic ethanol exposure activates NMDARs to a greater extent than the other ionic glutamatergic receptors (Gulya et al., 1991; Chandler et al., 1997, 1999; Smothers et al., 1997). Chronic ethanol exposure was shown to produce a long-term increase in the activity of NR2B-containing NMDARs in the dorsomedial striatum of rats (Wang et al., 2007, 2010). Consistent with the findings of previous studies (Gulya et al., 1991; Smothers et al., 1997; Grover et al., 1998; Cebere et al., 1999; Lack et al., 2007; Wang et al., 2007, 2010), the results of the present study showed that chronic ethanol exposure induced augmentation of facial stimulation-evoked MF–GC synaptic transmission was prevented by an NMDAR antagonist, which suggests that chronic ethanol exposure enhances the activity of NMDARs. In addition, the chronic ethanol exposure-induced facilitation of N2–N5 responses might be attributed to an increased probability of glutamate release from the presynaptic terminals during the facial stimulation-evoked MF–GC synaptic transmission.

In a previous study, NR2A and NR2C mRNA were detected in cerebellar GCs during the second postnatal week, whereas the NR2B mRNA was transiently expressed in the GCs during the first 2 postnatal weeks in rats (Akazawa et al., 1994). GluN2A has been detected on the somas of the GCs and boutons of the parallel fibers (Glitsch and Marty, 1999; Casado et al., 2000) and contributes to facial stimulation-evoked MF–GC synaptic transmission in mice *in vivo* (Zhang et al., 2020). It has been demonstrated that the GluN2C subunit was preferentially incorporated into triheteromeric GluN1/GluN2A/GluN2C receptors in cerebellar GCs, which might contribute to MF–GC synaptic transmission (Bhattacharya et al., 2018). However, our results showed that blockade of GluN2A induced a strong depression of MF–GC synaptic transmission in chronic ethanol-exposed mice; however, the enhancement of MF–GC synaptic transmission in chronic ethanol-exposed mice was not affected by the blockade of GluN2B. This result indicates that chronic ethanol exposure augments the NMDAR-sensitive components of facial stimulation-evoked MF–GC synaptic transmission *via* GluN2A but not *via* GluN2B. Previous studies also showed that the NR2B mRNA expression was significantly increased after chronic ethanol exposure (Follesa and Ticku, 1995; Hu et al., 1996; Snell et al., 1996; Roberto et al., 2006; Kash et al., 2009), particularly in the prefrontal cortex and in the hippocampus of alcoholics (Zhou et al., 2011; Farris and Mayfield, 2014). NR2B or/and NR2A protein expression was found to be increased in rodent brains after chronic ethanol exposure (Snell et al., 1996; Läck et al., 2005; Kash et al., 2008, 2009; Obara et al., 2009). Ethanol exposure led to an increase in the activity of Fyn kinase in the dorsomedial striatum of rats, resulting in an enhancement of NR2B phosphorylation and long-term facilitation of its activity (Wang et al., 2007, 2010). In addition, chronic ethanol exposure has been found to facilitate mGluR1 function in the cerebellum (Cozzoli et al., 2014). However, our results showed that the blockade of mGluR1 failed to prevent the chronic ethanol exposure-induced enhancement of facial stimulation-evoked MF–GC synaptic transmission in mice *in vivo*.

Collectively, we can conclude that chronic ethanol exposure in adolescence enhances facial stimulation-evoked MF–GC synaptic transmission *via* GluN2A, which might impair the high-fidelity properties of the sensory information transfer in the cerebellar GL in adult mice. Our results provide evidence for the further understanding of cellular and synaptic mechanisms of chronic ethanol exposure and their effects on motor coordination, motor learning, and cognitive functions from adolescence.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by the Animal Care and Use Committee of the Yanbian University.

AUTHOR CONTRIBUTIONS

D-LQ, B-XL, G-HD, and S-BC conceived and designed the experiments. B-XL, G-HD, H-LL, J-SZ, and Y-HB performed the experiments. C-PC and D-LQ analyzed the data. Y-HB contributed to reagents, materials, and analysis tools. D-LQ,

C-PC, and S-BC wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Cerebellar Dopaminergic System

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In the central nervous system (CNS), dopamine (DA) is involved in motor and cognitive functions. Although the cerebellum is not been considered an elective dopaminergic region, studies attributed to it a critical role in dopamine deficit-related neurological and psychiatric disorders [e.g., Parkinson's disease (PD) and schizophrenia (SCZ)]. Data on the cerebellar dopaminergic neuronal system are still lacking. Nevertheless, biochemical studies detected in the mammalians cerebellum high dopamine levels, while chemical neuroanatomy studies revealed the presence of midbrain dopaminergic afferents to the cerebellum as well as wide distribution of the dopaminergic receptor subtypes (DRD_1-DRD_5). The present review summarizes the data on the cerebellar dopaminergic system including its involvement in associative and projective circuits. Furthermore, this study also briefly discusses the role of the cerebellar dopaminergic system in some neurologic and psychiatric disorders and suggests its potential involvement as a target in pharmacologic and non-pharmacologic treatments.

Keywords: cerebellum, dopamine, dopamine receptors, non-traditional large neurons, Parkinson's disease, schizophrenia, autism spectrum disorders

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INTRODUCTION

In the mammalian cerebellum, the neurotransmitter systems traditionally involved in the synaptic and extrasynaptic interactions may include the excitatory glutamatergic system (Clements et al., 1987; Batini et al., 1992; Ottersen, 1993; Zhang and Ottersen, 1993; Batchelor et al., 1994; Grandes et al., 1994; Nusser and Somogyi, 1997; Knöpfel and Grandes, 2002; Hioki et al., 2003; Sanchez-Perez et al., 2005; Benagiano et al., 2011; Mugnaini et al., 2011; Uusisaari and De Schutter, 2011; Mapelli et al., 2015) as well as the inhibitory GABAergic and glycinergic systems (Gabbott et al., 1986; Wuenschell et al., 1986; Batini et al., 1992; Ottersen, 1993; Wisden et al., 1996; Sastry et al., 1997; Benagiano et al., 2000a,b; Flace et al., 2004; Crook et al., 2006; Tabata and Kano, 2006; Uusisaari and De Schutter, 2011; Mapelli et al., 2015), which are both involved in intrinsic and projective cerebellar circuits (Fredette and Mugnaini, 1991; Uusisaari and De Schutter, 2011; Ankri et al., 2015; Mapelli et al., 2015; Gao et al., 2016). Moreover, in several studies, the existence

of a cerebellar cholinergic system (Jaarsma et al., 1997; Prestori et al., 2013; Zhang et al., 2016) and several neuropeptidergic systems have been demonstrated (King et al., 1992; Joo et al., 2004; Schibusawa et al., 2008; Benagiano et al., 2009; Ito, 2009). Currently, data on the presence and distribution of monoaminergic systems in the mammalian cerebellum are still incomplete and not fully analyzed.

Studies reported in the developmental and adult mammalian cerebellum the presence of extrinsic monoaminergic pathways. Studies have been mainly focused on the cerebellar functional role of serotonin (5-HT) and noradrenaline (NA); as a result, until now, the functional role of dopamine (DA) in the cerebellum has been widely disregarded.

In studies using histofluorescence (Hökfelt and Fuxe, 1969) or immunohistochemical methods through specific 5-HT antiserum, in several mammals, including humans, the presence of a cerebellar serotonergic fiber system (Takeuchi et al., 1982; Kerr and Bishop, 1991; Ottersen, 1993; Kitzman and Bishop, 1997; Flace, 2017, 2019a), composed by 5-HT immunoreactive axonal plexuses of fibers and by neuronal cell bodies and processes distributed in the cerebellar cortical layers and in the deep cerebellar nuclei, has been demonstrated (Takeuchi et al., 1982; Bishop and Ho, 1985; Kerr and Bishop, 1991; Crivellato et al., 1992; Flace, 2017, 2019a).

The cerebellar serotonergic fibers originate mostly by the serotonergic cell groups of the reticular formation (B_1-B_3, B_6, B_7, and B_9; Dahlström and Fuxe, 1964; Bishop and Ho, 1985; Törk, 1990, Kerr and Bishop, 1991; Kitzman and Bishop, 1994, 1997). In the cerebellar cortex and the deep cerebellar nuclei, different serotonergic subtype receptors such as 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_3, and 5-HT_{5A} have been demonstrated (Duxon et al., 1997; Pasqualetti et al., 1998; Sari et al., 1999; Geurts et al., 2002; Oostland et al., 2013; Marinova et al., 2015). During the development, a role of 5-HT in dendritic growth and synaptic plasticity mechanisms has been demonstrated (Bishop et al., 1988; Oostland and van Hooft, 2013; Oostland et al., 2013).

In the adult cerebellum, 5-HT play a role in the modulation of the GABAergic and glutamatergic signaling (Strahlendorf et al., 1991; Cumming-Hood et al., 1993; Kitzman and Bishop, 1997; Dieudonné and Dumoulin, 2000; Di Mauro et al., 2003; Saitow et al., 2009; Murano et al., 2011). 5-HT decreases the activity of the Purkinje neurons (Kerr and Bishop, 1992) by means of the serotonergic receptor 5-$HT1_A$ (Mitoma and Konishi, 1996, 1999). 5-HT may set PCs at a preferred firing rate by modulation of transient outward h currents (Strahlendorf et al., 1984; Wang et al., 1992).

5-HT is involved in the long-term cerebellar effects, as the modulation of postsynaptic induction of long term depression (LTD), mainly by means of the serotonergic receptors 5-HT_{2A} and 5-HT_{2B}, which have been expressed on the Purkinje neurons (Maeshima et al., 1998; Cornea-Hébert et al., 1999).

In addition, these serotonergic receptor subtypes activate phospholipase C, resulting in the production of inositol-3 trisphosphate (IP3), which can regulate the threshold of regenerative cycles of Ca^{2+} elevation (Raymond et al., 2001). In chemical neuroanatomy studies, the presence of noradrenergic innervation in the cerebellum of rodents and primates (including humans; Hökfelt and Fuxe, 1969; Siggins et al., 1971; Landis and Bloom, 1975; Yamamoto et al., 1977; Pasquier et al., 1980; Hayashi, 1987; Pompeiano et al., 1989; Powers et al., 1989; Yew et al., 1995; Rosin et al., 1996; Talley et al., 1996; Gould et al., 1997; Melchitzky and Lewis, 2000) by means of fluorescent histochemistry (Falck and Torp, 1962; Hökfelt and Fuxe, 1969), or by specific antisera for dopamine β hydroxylase (DBH), the NA biosynthesizing enzymes has been demonstrated (Fritschy and Grzanna, 1989). Cerebellar noradrenergic fibers mainly originate from the noradrenergic cell groups of the reticular formation (A_4-A_7; Dahlström and Fuxe, 1964; Hökfelt and Fuxe, 1969; Pickel et al., 1973; Pasquier et al., 1980; Dietrichs, 1988; Powers et al., 1989). Such noradrenergic fibers are localized in the three cerebellar cortical layers and in the deep cerebellar nuclei, oriented so as to generate axonal plexuses (Sachs et al., 1973; Pasquier et al., 1980; Dietrichs, 1985; Felten et al., 1986; Powers et al., 1989; Melchitzky and Lewis, 2000).

In the human developmental cerebellum, at 16–18 and 26–28 weeks, a transient expression of noradrenergic neuronal cell bodies and processes occurs in the cerebellar cortex and in the deep cerebellar nuclei has been demonstrated (Yew et al., 1995). In addition, in the cerebellum of mammals, extensive distribution of the β_2 adrenergic subtype receptor (Pompeiano et al., 1989; Voogd et al., 1996) and, to a lesser extent, of β_1, α_1, and α_2 adrenergic subtype receptors have been demonstrated (Pompeiano et al., 1989; McCune et al., 1993; Rosin et al., 1996; Talley et al., 1996; Voogd et al., 1996). In the development, it has been found that the cerebellar noradrenergic system influences mainly the GABAergic synaptogenesis (Sievers et al., 1981; Sievers and Klemm, 1982; O'Leary and Leslie, 2003; Happe et al., 2004; Hirono et al., 2014). In the adult cerebellum, NA plays a pivotal role in the modulation of the glutamatergic and GABAergic synaptic signaling (Moises et al., 1983; Woodward et al., 1991; Hirono and Obata, 2006; Hirono et al., 2014; Lippiello et al., 2015). Noradrenaline exerts on the Purkinje neurons two types of influence. An increase of the intracellular levels of cAMP protein kinase-dependent by means on the beta-adrenergic receptor (Kano et al., 1992; Cheun and Yeh, 1996); the levels of cAMP can, in turn, enhance a form of neuronal plasticity called rebound potentiation (RP; Kano et al., 1992; Cheun and Yeh, 1996; Kawaguchi and Hirano, 2002). Moreover, NA influences in the Purkinje neurons the expression of the immediate-early genes, c-fos and Jun-B (Pompeiano, 1998). The induction of immediate-early genes in the Purkinje neurons appears to play a role in the long-term biochemical changes involved in the maintenance of cerebellar long-term plasticity such as LTD (Pompeiano, 1998).

On the other hand, currently, the presence and the distribution of a dopaminergic system in the cerebellum and its functional role is controversial or neglected (Oertel, 1993; Ottersen, 1993; Kwong et al., 2000). However, several studies demonstrated the involvement of the cerebellum in DA related neurological and psychiatric disorders, such as Parkinson's disease (PD), schizophrenia (SCZ), autism spectrum disorders (ASD), and drug addiction (Glaser et al., 2006; Andreasen and Pierson, 2008; Mittleman et al., 2008; O'Hallaran et al., 2012; Lewis et al., 2013; Wu and Hallett, 2013; Parker et al.,

2014, Carta et al., 2019; Gil-Miravet et al., 2019; Miquel et al., 2020). Therefore, the goal of the present review is to provide a comprehensive overview of the presence, distribution, and functional role of the cerebellar dopaminergic system, also discussing its potential pathophysiological and clinical implications in some neurological and psychiatric DA-related disorders.

MORPHOLOGICAL ASPECTS OF THE DOPAMINERGIC CEREBELLAR SYSTEM

Although the presence of a dopaminergic system in the cerebellum is in part predictable, currently, the cerebellum is not strictly considered a dopaminergic area (Glowinski and Iversen, 1966; Lindvall and Björklund, 1974; Beckstead et al., 1979; Ottersen, 1993; Masilamoni et al., 2010). In biochemical studies, high levels of DA in the human postmortem cerebellum (Adolfsson et al., 1979; Roubein and Embree, 1979; Spokes, 1979; Gottfries, 1980) and in the rat and monkey cerebellum were detected (Versteeg et al., 1976; Mefford et al., 1982; Glaser et al., 2006; Quansah et al., 2018). Furthermore, in the mammalian cerebellum, *in vivo* studies by means of positron emission tomography (PET) revealed a significant presence of selective dopamine transporter ligands (DAT-Ls) (Schoeps et al., 1993; Lundkvist et al., 1995; Hall et al., 1999; Emond et al., 2008; Varrone et al., 2009; Jiang et al., 2019).

Chemical neuroanatomy studies on the detection of dopaminergic neuronal elements in the cerebellum of mammals (including human) makes use of direct antisera against DA and of [^{3}H]-dopaminergic ligands (Panagopoulos et al., 1991; Panagopoulos and Matsokis, 1994) or antisera against the specific dopaminergic marker, the dopamine transporter (DAT), the plasma membrane monoamine transporter involved in DA synaptic reuptake (**Table 1**; Melchitzky and Lewis, 2000; Dunnet et al., 2005; Giompres and Delis, 2005; Delis et al., 2008; Kim et al., 2009; Flace et al., 2019b, 2020), the indirect marker of the dopaminergic neurotransmission, the dopamine and adenosine 3′-5′-monophosphate (cAMP)-regulated protein Mr 32,0000 (DARPP-32), a protein phosphatase-1 inhibitor involved in dopaminergic neuronal synaptic signaling (**Table 1**; Alder and Barbas, 1995; López et al., 2010; Nishi and Shuto, 2017), or, indirectly, by means of antisera against not elective markers for DA, such as tyrosine hydroxylase (TH), the rate-limiting enzyme DA biosynthesis, which catalyzes the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) (**Table 1**; Ikai et al., 1992; Fujii et al., 1994; Melchitzky and Lewis, 2000; White and Thomas, 2012) and vesicular monoamine transporter 2 ($VMAT_2$), the synaptic vesicles transporter of monoamine neurotransmitters such as DA, NA, 5-HT, and histamine (HIS) (**Table 1**; Kim et al., 2009; Lawal and Krantz, 2013).

During the development of the mouse cerebellar cortex, a transient expression of TH in Purkinje neurons in different ages from postnatal day 3 (P3) to 11 months (M11) has been observed (Fujii et al., 1994). The TH expression appears in the Purkinje neurons at P8 in the cerebellar vermis, increases at P13–P15, reduces at P19, and then increases again after 1 month of age, reaching a maximum expression at 11 months (Fujii et al., 1994).

In the adult mouse cerebellum, the TH immunoreactive fibers are in the vermal lobules V and VI, whereas the lowest numbers are located in lobule X, and in each deep cerebellar nuclei, a dense plexus of TH immunoreactive varicose fibers has been mainly detected (**Table 1**; Nelson et al., 1997). Whereas, TH immunoreactive cell bodies of Purkinje neurons have been found in the flocculus, paraflocculus, vermal lobules VI–X, and in the hemispheric lobules IX–X (**Table 1**; Nelson et al., 1997). In pharmacological studies, in the mouse cerebellum DA specific binding sites of [^{3}H]DA and [^{3}H]spiperone has been detected (Panagopoulos and Matsokis, 1994).

Moreover, in the adult mouse cerebellum, specific binding of the DA uptake inhibitor ^{3}[H]GBR12935 in the paraflocculus, lobules IV, VI, IX, X, and lobule simplex Crus I and II has been detected (Delis et al., 2008). In the cerebellar cortex, the specific binding of ^{3}[H]GBR12935 was mainly distributed in the molecular layer and in the granular layer, while DAT immunoreactivity has been mainly detected in the cell bodies of the Purkinje neurons and in some neuron types of the deep cerebellar nuclei (**Table 1**; Delis et al., 2008). Furthermore, in the mouse cerebellum, DARPP-32 immunoreactive Purkinje neuron cell bodies in the laminae of all lobules have been observed (**Table 1**; Alder and Barbas, 1995).

In the rat cerebellum, the DA immunoreactivity presents a uniform distribution pattern in all lobules, and in the layers of the cerebellar cortex the DA immunoreactivity was mainly detected in the molecular layer in climbing fiber-like forms, while a small number of DA immunoreactive fibers within the Purkinje neuron layer and in the granular layer were found (**Table 1**; Panagopoulos et al., 1991).

Furthermore, in the rat cerebellum, the TH immunoreactive fibers in the paraflocculus and crus I and II ansiform lobules have been mainly detected (**Table 1**; Ikai et al., 1992); whereas, a high number of $VMAT_2$ immunoreactive 'puncta' (attributable to axon terminals or short sections of dendrites) has been observed in the lobule IX of the posterior cerebellum (**Table 1**; Kim et al., 2009).

In the rat cerebellar cortex, a low number TH immunoreactive fibers variously oriented in the Purkinje neuron layer and in the granular layer has been detected; instead, in the molecular layer, a high number of climbing-like oriented TH immunoreactive fibers has been observed (**Table 1**; Takada et al., 1993), and $VMAT_2$ small immunoreactive "puncta" were observed between the Purkinje neuron cell bodies and in the molecular layer in close relationship with the dendritic arborizations of the Purkinje neurons (**Table 1**; Kim et al., 2009).

Biochemical analysis revealed significant levels of DA in the deep cerebellar nuclei of rat, with the highest DA levels being localized in the fastigial and dentate nuclei (Glaser et al., 2006), which is in line with a morphological study that revealed the presence of DAT immunoreactive fibers in all deep cerebellar nuclei (Delis et al., 2008). Moreover, a wide distribution of DAT immunoreactive fibers in the three layers of the cerebellar cortex and in the deep cerebellar nuclei has been revealed (Delis et al., 2008).

TABLE 1 | Distribution of the catecholaminergic and dopaminergic markers in the mammalian cerebellum.

Catecholaminergic and dopaminergic marker	Molecular layer	Purkinje neuron layer	Granular layer	Deep cerebellar nuclei	Cerebellar lobules Larsell, 1952
Tyrosine hydroxylase (TH) (catecholaminergic marker)	- Fibers climbing-like oriented - Fibers in the neuropil	- Purkinje neurons cell bodies and processes (lobulesVI-X), - Fibers around Purkinje neuron cell bodies	- Fibers in the neuropil - Mossy fiber rosettes-like	- Fibers in the neuropil of all nuclei	Lobules I, III, V, VI, VIII, IX, X, Crus I, Crus II, paraflocculus
Vesicular Monoamine Transporter 2 ($VMAT_2$) - (catecholaminergic marker)	Axon terminals (puncta) around dendrites of Purkinje neurons	Axon terminals (puncta) around Purkinje neuron cell bodies	–	–	Lobule IX B
Dopamine Transporter (DAT) (dopaminergic marker)	- Fibers in the neuropil - Dendrites of Purkinje neurons	- Purkinje neurons cell bodies and processes - Fibers in the neuropil	- Fibers randomly distributed - Clusters in the sites of glomeruli complex - Granules cell bodies (occasionally) - Cell bodies and processes of Synarmotic neurons and of perivascular neurons	- Fibers and puncta (axon terminals) - Cell bodies and processes of projective and associative neurons in all nuclei	All lobules, (lobules VII, IX in human)
Dopamine and Adenosine 3′-5′-monophosphate (cAMP) Regulated Protein Mr 32,000 (DARPP-32) (indirect dopaminergic marker)	Dendrites of Purkinje neurons	Purkinje neurons cell bodies and processes	–	–	All lobules

In addition, DARPP-32 immunoreactive dendritic arborization of the Purkinje neurons in the molecular layer of all cerebellar lobules has been observed (**Table 1**; Alder and Barbas, 1995).

In the rat cerebellar cortex, the presence of TH immunoreactive cell bodies of Purkinje neurons has been demonstrated in the lobules I and X of the vermis, in the paraflocculus, and in crus I and II ansiform lobules (**Table 1**; Takada et al., 1993) Instead, Kim et al. (2009) evidenced the presence of TH immunoreactive cell bodies of Purkinje neurons predominantly in the lobules VIII–X and a discontinuous presence in the lobules VI and VII, whereas a high number of DAT immunoreactive cell bodies of Purkinje neurons has been detected in the lobule IX of the posterior cerebellum (**Table 1**; Kim et al., 2009).

In the opossum cerebellum, most of TH immunoreactive fibers have been found in the lobules III-VIII of the vermis and, to a lesser extent, in lobules I and X (**Table 1**; Nelson et al., 1997). Moreover, in the opossum cerebellar cortex, the TH immunoreactive fibers were mainly localized in the Purkinje neurons layer; they surround the cell bodies of the Purkinje neurons or run parallel to the plane of the Purkinje neuron layer, whereas, in the molecular layer, only a small amount was detected (**Table 1**; Nelson et al., 1997), and in the granular layer, the TH immunoreactive fibers featured a random distribution (Nelson et al., 1997).

In addition, a moderate number of randomly distributed TH immunoreactive fibers has been detected in the deep cerebellar nuclei (Nelson et al., 1997).

In the cat cerebellum, the highest density of TH immunoreactive fibers were distributed in the vermal lobules V and VI and in the hemispheric lobules VI and crus I and II; meanwhile, the lowest density of fibers has been observed in lobules I–III and VIII–X (**Table 1**; Nelson et al., 1997). In the cat cerebellar cortex, the high density of TH immunoreactive fibers have been observed in the granular layer, where they present a random orientation, and in the Purkinje neurons layer, where they surround the cell bodies of the Purkinje neurons have been observed. Instead, in the molecular layer, only a few densities of TH immunoreactive fibers with a perpendicular orientation that often extend radially to the surface of the pial surface of the cortex have been detected (**Table 1**; Nelson et al., 1997). Finally, a moderate density of TH immunoreactive varicose fibers in the deep cerebellar nuclei have been also found (**Table 1**; Nelson et al., 1997).

In the monkey cerebellum, we found a low density of TH immunoreactive fibers to be distributed in the lobules of the vermis and of both cerebellar hemispheres, whereas the DAT immunoreactive fibers were only observed in the vermis of the following lobules II, III, IV, VIIIA, VIIIB, IX, and X (**Table 1**; Melchitzky and Lewis, 2000).

In the monkey cerebellar cortex, a low density of TH immunoreactive fibers in the granular layer and in the molecular

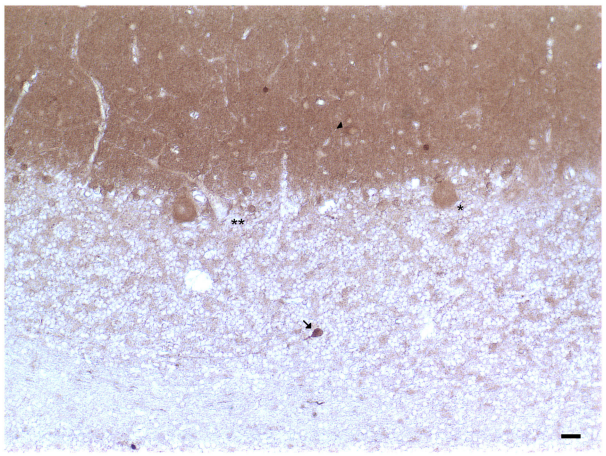

FIGURE 1 | Dopamine transporter (DAT) immunoreactivity in the cerebellar cortex. The DAT immunoreactivity is detectable in neuronal bodies and processes of all the layers of the cerebellar cortex. In the molecular layer, DAT immunoreactivity in basket neurons (*arrowheads*); primary and secondary trunks dendritic and apical dendrites of Purkinje neurons; immunonegative stellate neurons, fine clusters of DAT immunoreactivity in the neuropil of the layer. In the Purkinje neuron layer, DAT immunoreactive Purkinje neuron cell body (*single asterisk*), DAT immunonegative Purkinje neuron (*double asterisk*). In the granular layer, DAT immunoreactivity in space of Held, DAT immunoreactivity in the cell body, and axon-like processes of the synarmotic neuron (*arrow*). (Scale bar: 25 μm).

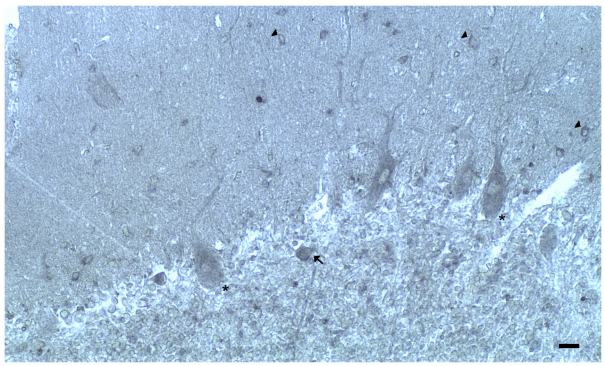

FIGURE 2 | Dopamine receptor type 2 (DRD_2) immunoreactivity is observable in neuronal bodies and processes in the layers of the cerebellar cortex. In the ML:DRD_2 immunoreactive basket and stellate neuron cell bodies (arrows), DRD_2 immunoreactive primary, secondary, and apical dendrites of Purkinje neurons, DRD_2 immunoreactive Purkinje neuron cell bodies (*single asterisk*). In the granular layer, DRD_2 immunoreactivity in space of Held; DRD_2 immunoreactive Golgi neuron cell body (arrow) (Scale bar: 20 μm).

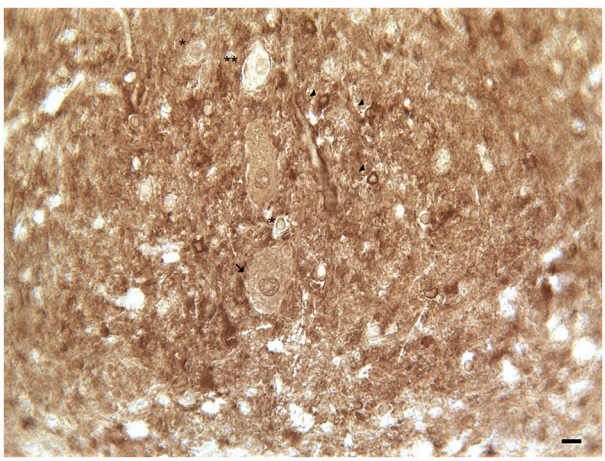

FIGURE 3 | Dopamine transporter (DAT) immunoreactivity in the dentate nucleus. The dopamine transporter (DAT) immunoreactivity is detectable in the dentate nucleus gray substance and in the neighboring white substance. DAT immunoreactive small neuron cell bodies (*arrowheads*); DAT immunonegative small neuron cell body (*single asterisks*) DAT immunoreactive cell body of projective neuron type, central neuron (*arrow*); fine clusters of DAT immunoreactivity in the neuropil of the nucleus and in the neighboring withe substance (Scale bar: 15 μm).

layer, has been detected while a higher density of TH plexuses and axonal terminals just beneath the Purkinje neuron cell bodies has been found. Conversely, DAT immunoreactive fibers to be randomly distributed in the granular layer; however, we also found forming plexuses around the deep pole of the cell bodies of the immunonegative Purkinje neurons has been observed. In contrast, in the molecular layer, no DAT immunoreactive fibers have been detected (**Table 1**; Melchitzky and Lewis, 2000).

Currently, in the monkey cerebellum studies, there is no evidence that proves the existence of dopaminergic neurons. Despite this, a biochemical study demonstrated significant levels of DA in all deep cerebellar nuclei, and the highest levels have been detected in the interpositus and dentate nuclei, (Glaser et al., 2006). Furthermore, in all cerebellar lobules of the monkey cerebellar cortex, a wide presence of DARPP-32 immunoreactive cell bodies and dendritic arborizations of Purkinje neurons has been detected (**Table 1**; Alder and Barbas, 1995).

In the human cerebellum, immunohistochemical experiments revealed the presence of DAT immunoreactive fibers and neuronal cell bodies in lobules VII and IX (crus I and II, ansiform lobules, and tonsilla) and in the dentate nucleus (**Table 1**; **Figures 1**, **2**; Flace, 2017, 2019b, 2020; Flace et al., 2018a, 2019b, 2020). There is a significant presence of DAT immunoreactive dendritic arborization of the Purkinje neurons in the molecular layer of the human cerebellar cortex (**Table 1**; **Figure 1**). Moreover, the DAT immunoreactivity has been detected in form of clusters in the neuropil among the space of Held, the sites of the cerebellar glomeruli (**Table 1**; **Figure 1**; Flace, 2017, 2019b, 2020; Flace et al., 2018a, 2019b, 2020).

In addition, the DAT immunoreactivity in the cell bodies of Purkinje neurons and of synarmotic neurons (Neuron of Landau) has been also detected (**Table 1**; **Figure 1**). This latter, one of the non-traditional large neuron granular layers was involved in corticocerebellar and in corticonuclear projective circuits (Flace et al., 2004, 2018a, 2019b, 2020; Ambrosi et al., 2007; Flace, 2017, 2019a,b, 2020). The DAT immunoreactivity

TABLE 2 | Distribution of the dopaminergic receptor subtypes in the mammalian cerebellum.

Dopamine receptor subtypes	Molecular layer	Purkinje neuron layer	Granular layer	Deep cerebellar nuclei
Dopamine Receptor D1 (DRD_1)	- Stellate and Basket neuronal cell bodies and processes - Dendrites of the Purkinje neurons - Fine clusters of puncta (axon terminals)	- Purkinje neuron cell bodies	–	- Projective and associative neurons cell bodies and processes in the dentate nucleus
Dopamine Receptor D2 (DRD_2)	- Stellate and Basket neuronal cell bodies and processes - Dendrites of the Purkinje neurons - Fine clusters of puncta (axon terminals)	- Purkinje neuron cell bodies	- Clusters in the neuropil in the glomeruli complex sites - In cell bodies and processes: a) Golgi neurons granules b) Lugaro neurons c) candelabrum neurons d) ellipsoidal neurons e) globular neurons f) perivascular neurons	- Fibers and puncta (axon terminals) - Projective and associative neurons cell bodies and processes in the dentate nucleus
Dopamine Receptor D3 (DRD_3)	- Stellate and Basket neuronal cell bodies and processes - Dendrites of the Purkinje neurons - fine clusters of puncta (axon terminals)	- Purkinje neuron cell bodies	–	–
Dopamine Receptor D4 (DRD_4)	–	–	Clusters in the neuropil in the glomeruli complex sites	–
Dopamine Receptor D5 (DRD_5)	- Stellate and Basket neuronal cell bodies and processes - Dendrites of the Purkinje neurons - Fine clusters of puncta (axon terminals)	- Purkinje neuron cell bodies	–	–

in the cell bodies of few granules has been also detected (Flace et al., 2019a,b, 2020). Moreover, DAT immunoreactive nerve fibers variously oriented in the subcortical white substance, has been detected (**Figure 1**; Flace et al., 2019a,b, 2020). In the dentate nucleus, the DAT immunoreactivity in neuronal cell bodies and processes of different neuron types has been detected (**Table 1**; **Figure 3**); the small neuron type is involved in intrinsic circuits, the medium neuron type (**Table 1**; **Figure 3**) mainly involved in intrinsic and also in extrinsic circuits, and four different large neuron types, which include the central neuron, the border neuron, the intermediate asymmetrical neuron, and the intermediate fusiform neuron, involved in projective circuits of the dentate nucleus (data not showed; Chan-Palay, 1977; Maric, 2010; Ristanović et al., 2010; Flace et al., 2017, 2019b, 2020; Flace, 2018). Dopamine transporter immunoreactivity in neuronal cell bodies and processes of the perivascular neuron type has also been observed, a neuron type may be involved in regulatory mechanisms of blood–brain barrier (BBB) permeability and in volume transmission mechanisms (data not showed; Flace et al., 2004; Ambrosi et al., 2007; Flace, 2017, 2018, 2019b, 2020).

Furthermore, through different methods in the cerebellum of mammals, a wide distribution of the dopaminergic receptor subtypes (DRD_1-DRD_5) has been observed (**Table 2**; Camps et al., 1989; Cortés et al., 1989; Levant, 1998; Barili et al., 2000; Kiss et al., 2011; Flace et al., 2019b, 2020). A broad expression of all the dopaminergic receptor subtypes (DRD_1-DRD_5) has been demonstrated in the rodent and human cerebellum (**Table 2**; Martres et al., 1985; Camps et al., 1990; Mengod et al., 1992; Panagopoulos and Matsokis, 1994; Ricci et al., 1995a,b, 1996; Vessotskie et al., 1997; Levant, 1998; Barili et al., 2000; Khan et al., 2000; Hurley et al., 2003; Delis et al., 2004; Kim et al., 2009; Flace, 2017, 2018, 2019b; Flace et al., 2018a, 2019a,b, 2020).

In the three layers of the cerebellar cortex, the dopaminergic receptor subtypes present a different distribution pattern. In the molecular layer, immunoreactivity to DRD_2, DRD_3, and DRD_5 receptors in the cell bodies and processes of stellate neurons, basket neurons, and in the dendritic arborizations of the Purkinje neurons has been detected (**Table 2**; **Figure 2**). Moreover, in the neuropil of the molecular layer, fine clusters of DRD_2 immunoreactivity were detected (**Table 2**; **Figure 2**; Camps et al., 1990; Ricci et al., 1995b, 1996; Khan et al., 1998; Levant, 1998; Barili et al., 2000; Flace et al., 2018a, 2019a,b, 2020).

In the Purkinje neuron layer, DRD_1, DRD_2, DRD_3, and DRD_5 immunoreactive cell bodies of Purkinje neurons have been observed (**Table 2**; **Figure 2**; Camps et al., 1990; Bouthenet et al., 1991; Ricci et al., 1995a,b; Khan et al., 1998; Lazarov et al., 1998; Barili et al., 2000; Kim et al., 2009; Flace et al., 2018a, 2019a,b, 2020). In the granular layer, DRD_2 immunoreactivity in the cell bodies and processes of granules, Golgi neurons (**Table 2**; **Figure 2**), and in different non-traditional large neuron types of the granular layer distributed in three zones has been detected (Flace et al., 2004; Flace, 2017, 2019b, 2020) such as the Lugaro neuron, candelabrum neuron, and perivascular

neuron in the external zone of the layer, the triangular neuron in the intermediate zone, the ellipsoidal neuron, and the globular neuron in the internal zone has been detected (**Table 2**; data not showed; Flace et al., 2004; Ambrosi et al., 2007; Flace, 2017, 2019b, 2020). In addition, DRD_1, DRD_2, and DRD_4 immunoreactive clusters in the neuropil of the granular layer have been found (**Table 2**; **Figure 2**), and DRD_2 and DRD_5 immunoreactivity in cell bodies of granules has been observed (**Table 2**; data not showed; Camps et al., 1990; Brouwer et al., 1992; Ricci et al., 1995a,b; Khan et al., 1998; Lazarov et al., 1998; Barili et al., 2000; Kim et al., 2009; Flace, 2017, 2019b; Flace et al., 2018a, 2019b, 2020). Furthermore, among immunonegative granules, the DRD_2 immunoreactivity in form of clusters in the space of Held, the sites of the cerebellar glomeruli complex has been detected (**Table 2**; **Figure 2**; Flace et al., 2018a, 2019a,b, 2020).

In the mouse and human dentate nucleus, the presence of DRD_1 and DRD_2 immunoreactive cell bodies and processes of different large projective neuron types and small associative neuron types has been demonstrated (**Table 2**; **Figure 4**); the DRD_2 immunoreactivity has also been observed in form of fine clusters in the neuropil of the dentate nucleus (**Table 2**; **Figure 4**; Flace, 2017; Flace et al., 2018a, 2019a,b, 2020; Locke et al., 2018).

In chemical neuroanatomy studies carried out on the cerebellum by means of antisera directed against the TH, the rate-limiting enzyme of DA biosynthesis and the presence of numerous TH immunoreactive fibers in the various lobules and laminae of the cerebellar cortex as well as in the deep cerebellar nuclei have been demonstrated (Austin et al., 1992; Ikai et al., 1992; Takada et al., 1993, Nelson et al., 1997). In addition, regarding the TH immunoreactivity, it should be indicated that it is related to the presence of NA or DA, or both, since by carrying out a selective depletion of NA, most of the immunoreactivity is abolished (Fuxe, 1965; Hökfelt and Fuxe, 1969; Bloom et al., 1971). Moreover, using biochemical techniques, low levels of DA were found in the cerebellum (Carlsson, 1959; Glowinski and Iversen, 1966; Landis and Bloom, 1975). In addition, using antisera against DBH, the enzyme responsible for the biosynthesis of NA, highlights the presence of fibers in the cerebellum, which presented only partial similarity to those observed in studies using directed antisera against DA (Verney et al., 1988; Panagopoulos et al., 1991). Furthermore, more recent studies in the cerebellum of various mammals species and in other regions of the central nervous system (CNS), demonstrated which distribution patterns of TH immuroreactivity were mainly correlated to catecholaminergic and not electively to the dopaminergic neurotransmission but did not exclude it; (Fallon and Moore, 1978; Hökfelt et al., 1984; Asan, 1993; Takada et al., 1993; Nelson et al., 1997). On the contrary, studies that electively used antisera against DAT evaluate specifically the distribution patterns related to dopaminergic neurotransmission (Melchitzky and Lewis, 2000; Delis et al., 2008; Flace et al., 2018a, 2019b, 2020). In addition, the DAT immunohistochemial studies evidenced the presence of a specific subpopulation of dopaminergic neuronal cell bodies and processes in the cerebellum (Melchitzky and Lewis, 2000; Delis et al., 2008; Flace et al., 2018a, 2019b, 2020), which is in agreement with the studies on the distribution pattern of the dopaminergic receptors subtype in the cerebellar neuronal cell bodies and processes (Martres et al., 1985; Camps et al., 1990; Mengod et al., 1992; Ricci et al., 1996; Vessotskie et al., 1997; Levant, 1998; Barili et al., 2000; Khan et al., 2000; Delis et al., 2004; Kim et al., 2009; Flace et al., 2018a, 2019a,b, 2020).

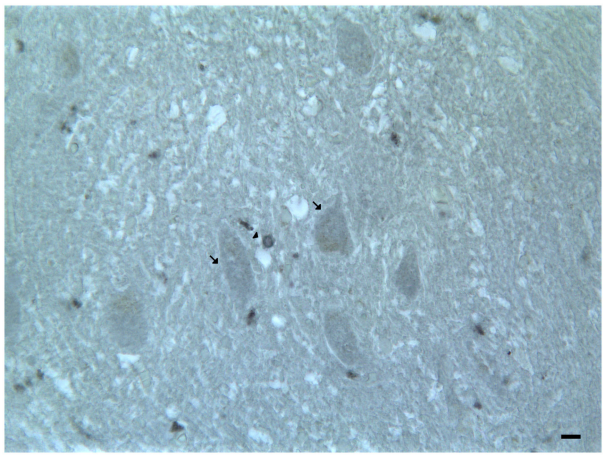

FIGURE 4 | Dopamine receptor type 2 (DRD_2) immunoreactivity in the dentate nucleus. The (DRD_2) immunoreactivity is detectable in the dentate nucleus gray substance and in the neighboring withe substance; DRD_2 immunoreactive small neuron cell bodies (arrowheads); DRD_2 immunoreactive cell body of projective neuron type, central neuron (arrow); diffuse DAT immunoreactivity in the neuropil of the nucleus (Scale bar: 15 μm).

In fact, the relationship of these data suggest the existence in the cerebellum of detailed dopaminergic neurotransmitter mechanisms. For example, in terms of the distribution pattern of the DAT immunoreactivity (Melchitzky and Lewis, 2000; Delis et al., 2008; Flace et al., 2018a, 2019b, 2020) and of the dopaminergic D1-like and D2-like subtype receptors immunoreactivity (Camps et al., 1990; Bouthenet et al., 1991; Ricci et al., 1995a,b; Khan et al., 1998; Lazarov et al., 1998; Barili et al., 2000; Kim et al., 2009; Flace et al., 2018a, 2019a,b, 2020), both were expressed in the Purkinje neurons cell bodies, dendritic arborizations, and axons, and this suggests the existence of a detailed cerebellar modulation by means of dopaminergic neurotransmission mechanisms in intrinsic and extrinsic cerebellar circuits.

PHYSIOLOGICAL ASPECTS ON THE DOPAMINERGIC CEREBELLAR SYSTEM

In animal model studies, it has been indirectly demonstrated an active role of DA in the cerebellum; indeed, the administration of lacosamide and morphine in a hypoglycemic animal model decreased the cerebellar level of dopamine significantly (Guzman et al., 2014). In the cerebellum of albino rats, the long administration of morphine sulfate determines a decrease in the levels of DA and histopathological changes (Bekheet et al., 2010). Hypoxic conditions induced in the cerebellum of neonatal rats a decrease in the DA levels and a reduced expression of

the dopaminergic subtype receptors DRD_1 and DRD_2; these decreases are in part reversed by the supplementation of glucose, oxygen, and adrenaline (Joseph et al., 2010). Moreover, in the cerebellum of rodents, high levels of DA have been involved in neuronal synaptic mechanisms characterized by DA release and uptake (Efthimiopoulos et al., 1991; Dethy et al., 1997). In addition, in mouse cerebellar slices, the presence of a high-affinity Na^+-dependent DA uptake system has been demonstrated, and this has been characterized by a K^+-induced, Ca^{+2}-dependent dopamine release mechanism (Efthimiopoulos et al., 1991). Moreover, in several studies, it has been demonstrated in striatal medium spiny neurons a direct influence of DA in the mechanism of structural plasticity of dendritic spines (Yagishita et al., 2014). In the rat cerebellum, DA may influence in the Purkinje neurons the induction of RP a form of long-lasting synaptic plasticity at inhibitory synapses by means of the cAMP-regulated protein DARPP-32 highly expressed in Purkinje neurons and involved in dopaminergic neuronal synaptic signaling (Alder and Barbas, 1995; Kawaguchi and Hirano, 2002).

Moreover, in rat Purkinje neurons dendrites, a release of DA from vesicular extrasynaptic and postsynaptic sites resulted in dopaminergic receptors paracrine and autocrine activation (volume transmission), which produced a Depolarization-Induced Slow Current (DISC; Kim et al., 2009). Moreover, in pharmacological experiments a close functional relationship in dopaminergic Purkinje neurons between DA signaling and DISC has been demonstrated; in fact, it was blocked by dopaminergic receptor antagonist (e.g., clozapine, haloperidol, and eticlopride), $VMAT_2$ inhibitors (reserpine and tetrabenazine), and dopamine reuptake inhibitors (e.g., rimcazole; Kim et al., 2009). Furthermore, it has been suggested in recent studies which TH immunoreactive Purkinje neurons and DRD_1 immunoreactive large projective neuron types of the dentate nucleus may be involved in the modulation of cerebellar cognitive functions (Locke et al., 2018, 2020). The selective chemogenetic inhibition of the DRD_1 immunoreactive neuron type of the dentate nucleus could be involved in the impairment of cognitive functions such as spatial navigation memory, working memory, and pre-pulse inhibition of the acoustic startle reflex (Locke et al., 2018). In mice, a selective reduction of TH immunoreactive cerebellar Purkinje neurons has been correlated to a specific impairment of cognitive functions, such as behavioral flexibility, response inhibition, social recognition memory (Locke et al., 2020).

From the analysis of these experimental physiological and pharmacological studies, a potential role of the neuronal dopaminergic system at the cerebellar level emerges, especially in the synaptic and extrasynaptic neurotransmission and neuromodulation mechanisms (Efthimiopoulos et al., 1991; Dethy et al., 1997; Kawaguchi and Hirano, 2002; Kim et al., 2009) and, in cognitive functions related to the cerebellar activity (Locke et al., 2018, 2020). Overall, they deserve further evaluation in order to better understand the relevance of the morphofunctional role played by the dopaminergic innervation in the cerebellum and their role in the behavioral functions of the cerebellum.

CEREBELLAR–MIDBRAIN DOPAMINERGIC PATHWAYS

In rodents, lesional and axonal tracing studies has been demonstrated that the cerebellar extrinsic dopaminergic fibers originate from the midbrain dopaminergic cell groups (A_8-A_{10}), which mainly consist of the ventral tegmental area (VTA) (A_{10}) and to lesser extent by the retrorubral nucleus (A_8) and the pars compacta of the substantia nigra (SNpc) (A_9; Dahlström and Fuxe, 1964; Kizer et al., 1976; Chan-Palay, 1977; Oades and Halliday, 1987; Ikai et al., 1992; Melchitzky and Lewis, 2000; Kim et al., 2009).

In addition, in cat and in rat, a direct cerebellar influence on the midbrain dopaminergic nuclei (A_8-A_{10}) has been demonstrated. Fibers from the vermian cerebellar cortex and from the fastigial nucleus reach the ipsilateral VTA, whilst fibers from the interpositus and dentate nuclei reach the contralateral dorsal VTA and the medial and dorsal SNpc; moreover, 20% of the fibers had bilateral interconnections (**Figure 9**; Snider and Maiti, 1976).

In the rat cerebellum, using horseradish peroxidase (HRP) anterograde and retrograde transport methods, the efferents of the dentate and interpositus nuclei to the contralateral midbrain dopaminergic cell groups A_8-A_{10} have been demonstrated (**Figure 9**; Perciavalle et al., 2013).

Electrical stimulation of cat cerebellar dentate nucleus influenced the dopaminergic activity of the ipsilateral SNpc, which in turn increased the release of [^{3}H]-DA in the contralateral caudate nucleus and decreasing such release in the ipsilateral caudate nucleus. Moreover, the electrical stimulation of the fastigial nucleus increased only the release of [^{3}H]-DA in the ipsilateral caudate nucleus (Nieoullon et al., 1978), and the electrical stimulation of the posterior interpositus nucleus increased the release of [^{3}H]-DA in ipsilateral SNpc and in the contralateral caudate nucleus while decreasing the release [^{3}H]-DA in the ipsilateral caudate nucleus (Nieoullon and Dusticier, 1980). In addition, the electrical stimulation of the mouse cerebellar dentate nucleus was elicited mainly in the contralateral nucleus accumbens (NAc), determining an asymmetrical and lateralized DA release (**Figure 9**; Holloway et al., 2019).

Moreover, in the last decades, the developments in neuroscience research of non-invasive and *in vivo* diffusion Magnetic Resonance Imaging and tractography have been increasingly used for the neuroanatomical reconstruction of putative white substance tracts or links of the human brain (Jeurissen et al., 2014; Cacciola et al., 2016a,b, 2017a,b, 2019). Although relatively few studies focused on the connectivity of midbrain nuclei, some of these reported structural connectivities between dopaminergic midbrain regions and the cerebellum (Bareš et al., 2015; Milardi et al., 2016; Cacciola et al., 2017a; Flace et al., 2017, 2018a,b, 2019a, 2020). An early work based on diffusion tensor imaging (DTI) and deterministic tractography aimed at the reconstruction of the median forebrain bundle (MFB), which represents the main white substance pathway connecting VTA and SNpc to the prefrontal cortex (PFC), found also a descending branch reaching to the cerebellum and in particular to the dentate nucleus through the superior cerebellar

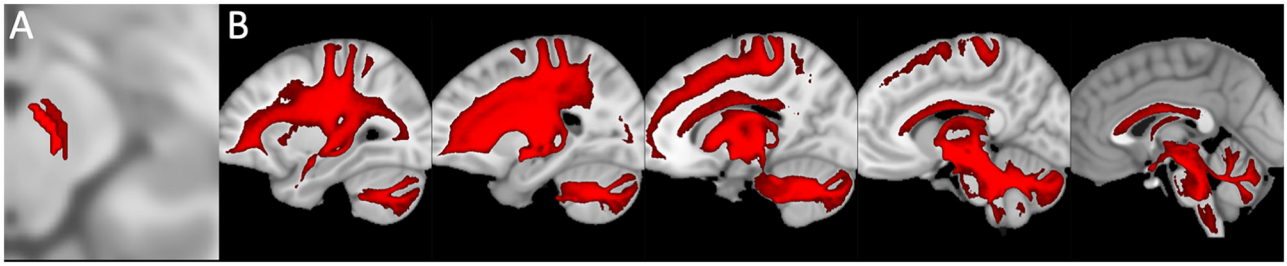

FIGURE 5 | Structural connectivity of SNpc and VTA, including putative midbrain-cerebellar connectivity. Data were obtained from the 100-unrelated-subjects sample of the HCP repository (see Van Essen et al., 2013) Diffusion datasets were processed using a multi-shell, multi-tissue constrained spherical deconvolution (MSMT-CSD) algorithm (see Jeurissen et al., 2014). A number of 10,000 streamlines passing through the left SNpc (dark red) and VTA (light red) regions of interest (see Pauli et al., 2018) **(A)** was generated. Streamlines were mapped to structural scans, transformed to MNI152 standard space, binarized, and summed up to obtain tract maximum probability maps (MPMs). A threshold of 50% was applied to show only tracts overlapping in at least half of the sample **(B)**. Tractography was run on 30 high-quality 3T structural and diffusion data from the Human Connectome Project (HCP). Data were downloaded in a minimally pre-processed form and elaborated using the signal processing technique known as Constrained Spherical Deconvolution (CSD). Regions of interest (ROI) were delineated by means of multi-atlas automated segmentation: Substantia nigra (SN) and Ventro Tegmental Area (VTA) were resliced into subject space from Adcock's probabilistic atlas; dentate nucleus (both dorsal and ventral part) using the deep cerebellar nuclei atlas featured in SPM Anatomy Tract colors are attributed according to the spatial orientation of streamlines: superior-inferior (blue), anterior-posterior (green), and latero-lateral (red).

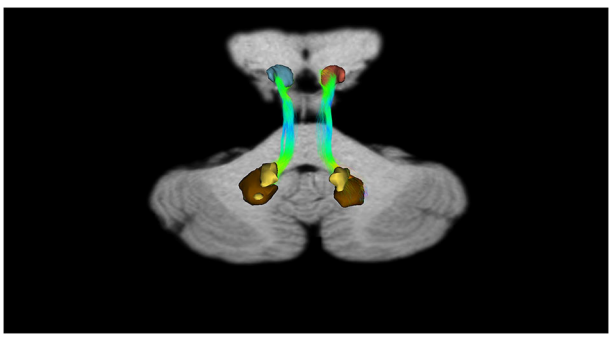

FIGURE 6 | Dentate-nigral interconnections. Coronal view shows the interconnections between the right dentate nucleus and the ipsilateral SN, and the left dentate nucleus and the ipsilateral SN. The fibers exited the cerebellum via the right and left superior cerebellar peduncles.

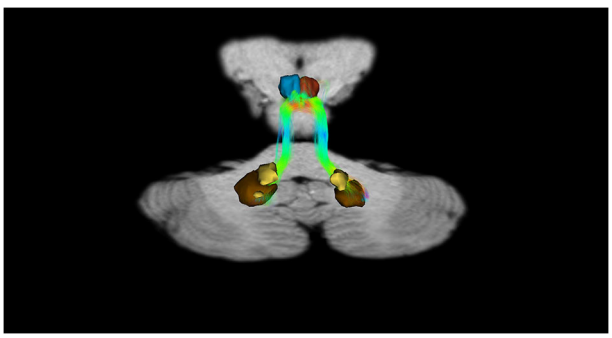

FIGURE 7 | Dentate-VTA interconnections. Coronal view shows the interconnections between the right dentate nucleus and the ipsilateral and contralateral VTA, and the left dentate nucleus and the ipsilateral and contralateral VTA. The fibers exited the cerebellum via the right and left superior cerebellar peduncles.

peduncle (SCP; Coenen et al., 2012). These findings have been replicated in a study by using more advanced signal modeling algorithms and different tracking strategies (Coenen et al., 2018). Nevertheless, results coming from diffusion imaging should be interpreted with care due to the well-known limitations of the tractographic approach, such as the inability to detect axons or synapses and, then, to rule out the precise termination of putative white substance tracts at a cellular level as well as to distinguish between direct or indirect connectivity patterns and passing-by fibers (Jbabdi and Johansen-Berg, 2011). In particular, the inherently low spatial resolution of diffusion-weighted MRI makes it difficult to distinguish between SNpc, SNpr, and VTA, as their precise boundaries are not readily identifiable on conventional MRI scans (Chowdhury et al., 2013; Trutti et al., 2019). In addition, these results may be affected by passing-by fibers from the dento-rubro-thalamic tract (DRTT), which lies in close proximity to midbrain dopaminergic structures, despite a recent study having suggested the potential dissociability of the cerebellar branch of MFB from DRTT (Hosp et al., 2019). In addition, in a human brain structural connectivity tractographic reconstruction of SNpc and VTA, we evidenced the existence of wide interconnections of the cerebellum with the SNpc and also with the VTA (**Figure 5**).

In addition, recently, by means of Constrained Spherical Deconvolution tractography (CSDt), Milardi et al. (2016) carried out a detailed analysis of direct links between the ventral and dorsal dentate nucleus and the ipsilateral SNpc (**Figures 6**, **8**; Milardi et al., 2016). Subsequently, by means of CSDt, the existence of direct interconnections between the ventral and dorsal dentate nucleus and ipsilateral and contralateral VTA, predominantly characterized by an ipsilateral dentate-VTA links, has also been demonstrated (**Figures 7**, **8**; Bareš et al., 2015; Milardi et al., 2016; Cacciola et al., 2017a; Flace et al., 2017, 2018a,b, 2019b, 2020).

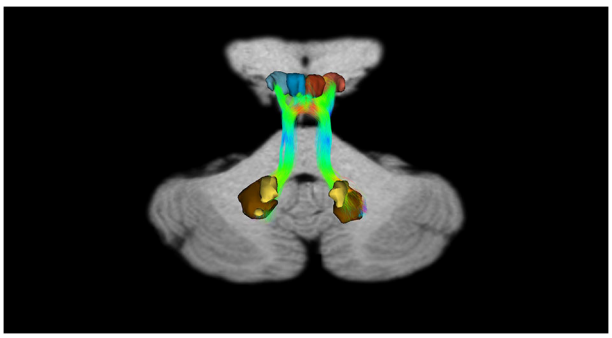

FIGURE 8 | Dentate-SN and dentate-VTA interconnections. Coronal view shows the interconnections between the right dentate nucleus and left dentate nucleus to the ipsilateral SN, between the right dentate nucleus and left dentate nucleus to the ipsilateral and contralateral VTA. The fibers exited the cerebellum via the right and left superior cerebellar peduncles.

The interconnection studies conducted with invasive methods in non-human mammals, and the analyses carried out in humans by means of tractographic neuroimaging methods highlight the presence of relevant interconnections of the cerebellum with the traditional dopaminergic areas of the brain. Moreover, this may likely suggest double direct functional DA interactions between the cerebellar dopaminergic system described in this review and the traditional DA cell groups system of the CNS (**Figure 9**; Björklund and Dunnett, 2007). In addition, these cerebellar-midbrain dopaminergic interconnections could represent part of the cerebellar projective circuits which allow the cerebellum to contribute to motor and cognitive functions (Koziol et al., 2014; Caligiore et al., 2017).

THE ROLE OF THE DOPAMINERGIC CEREBELLAR SYSTEM IN NEUROLOGIC AND PSYCHIATRIC DISORDERS

Though several studies suggested an involvement of the cerebellum in dopaminergic related neurologic and psychiatric disorders as PD (Jellinger, 1999, 2017; Lewis et al., 2013; Wu and Hallett, 2013), SCZ (Andreasen and Pierson, 2008; O'Hallaran et al., 2012; Parker et al., 2014), and ASD (O'Hallaran et al., 2012; Hampson and Blatt, 2015; Phillips et al., 2015), the precise role of the cerebellar dopaminergic system has not been fully characterized yet.

In this review, briefly, we analyzed some considerable experimental and clinical aspects of the cerebellum related to the dopaminergic system and its disorders.

Currently, only in few detailed studies has the direct involvement of a dopaminergic system at the cerebellar level in PD been analyzed. In a 6-hydroxydopamine (6-OHDA) animal model, increases in the DA level and its metabolites in the anterior cerebellum and as well as a decrease in the caudate-putamen have been detected (Kolasiewicz et al., 2012). In the cerebellum of PD patients, a reduced mRNA expression of TH and of some dopaminergic receptor subtypes (DRD_1-DRD_3) has been found (Hurley et al., 2003). In a human PD postmortem brain study it was shown that in the Purkinje neurons, a high expression of the calpain II (calpastatin), a calcium-dependent protease, resulted in overexpression in the dopaminergic neurons of SNpc (Mouatt-Prigent et al., 2000). PTEN-induced putative kinase 1 (PINK1) mutations related to the recessive genetic forms of parkinsonism, in the cerebellum of PD patients in Purkinje neuron and in several neuron types of dentate nuclei have been detected (Blackinton et al., 2007; Dodson and Guon, 2007).

The deposition of cerebellar α-synuclein (α-S) during PD remains unclear (Takahashi and Wakabayashi, 2001; Kingsbury et al., 2004). Indeed, some studies evidenced the presence of decreased or unchanged levels of α-S in the cerebellum (Tan et al., 2005; Westerlund et al., 2008), while others demonstrated a high mRNA expression of the α-S gene (SNCA) in the human cerebellum (Fuchs et al., 2008). Moreover, in the cerebellum of PD patients and of [A30P] transgenic mouse as well as in α-S in the molecular layer, the Bergmann glia (Mori et al., 2003; Piao et al., 2003), in the Purkinje neurons, in the space of Held of the granular layer, in the neuropil and in cell bodies and processes of different neuron types of the dentate nucleus has been found (Kahle et al., 2000; Mori et al., 2003). Furthermore, an α-S neuroprotective activity in cerebellar granules against neurotoxicity of 6-OHDA has been also demonstrated (Monti et al., 2007).

In rat cerebellum, high mRNA expression of clusterin/apolipoprotein J, a glycoprotein involved in the regulation of α-S deposition (Sasaki et al., 2002; Emamzadeh, 2017) in the Purkinje neurons as well as in the neurons of the fastigial and interpositus nuclei, has been detected (Pasinetti et al., 1994).

Currently, no studies are available on the direct involvement of the cerebellar dopaminergic system in SCZ and in autism ASD. However, in several studies, the presence of cerebellar abnormalities in SCZ and ASD patients has been demonstrated. In SCZ, patterns of atrophy in the cerebellar cortex of the vermis have been demonstrated (Weinberger et al., 1980; Reyes and Gordon, 1981; Heath et al., 1982; Snider, 1982; Martin and Albers, 1995). In addition, reduced cerebellar cortical volumes (Laidi et al., 2015), a decreased cerebellar gray substance of Crus I and II ansiform lobules (Kühn et al., 2012), and a reduction in the gyrification index in the cerebellar vermis have also been observed (Schmitt et al., 2011). Moreover, in the cerebellum of SCZ patients, in a microscopical analysis, a loss or a reduced cell size of the Purkinje neurons has been revealed (Stevens, 1982; Tran et al., 1998). Furthermore, a reduced cerebellar expression of the Sp transcription factors and DRD_2, both related to negative symptoms of SCZ, has been found (Pinacho et al., 2013).

In ASD morphological studies, in the cerebellar hemispheres a reduction of the number of the Purkinje neurons related to a reduction of the Nissl staining has been demonstrated (Bauman and Kemper, 1985; Kemper and Bauman, 1993). Furthermore, in the cerebellum of ASD patients, we also found a reduced Purkinje neuron density (Whitney et al., 2008; Skefos et al., 2014) together

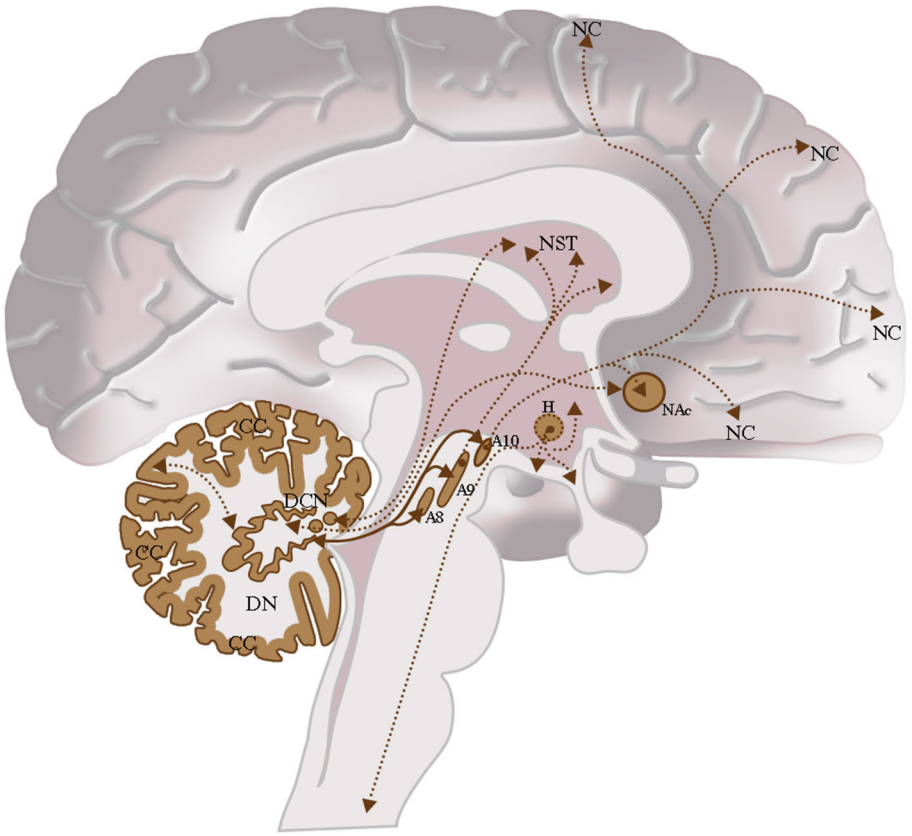

FIGURE 9 | The dopaminergic CNS and their interconnections. Cerebellum: Cerebellar Cortex (CC), Deep Cerebellar Nuclei (DCN); Midbrain: Retrorubral Nucleus (A_8), Substantia Nigra Pars Compacta (A_9), Ventral Tegmental Area (A_{10}); Hypothalamus (H); Nucleus Accumbens (NAc); Neostriatum (NST); Neocortex (NC). *Intrinsic cerebellar dopaminergic interconnections:* Between the dentate nucleus (DN) and the cerebellar cortex (CC); these interconnections are indicated in brown with the double arrow and the bold line. *Extrinsic cerebellar dopaminergic interconnections*: Between the dentate nucleus (DN) and the nuclei of the midbrain A_8, A_9, and A_{10}; interconnections are indicated in brown with a double arrow and bold line. Between the dentate nucleus (DN) and the Neostriatum (NST); among others Deep Cerebellar Nuclei Nuclei (DCN) and the NST or the NAc. These interconnections are indicated in brown with the double arrow and the thin dashed line. *Other Dopaminergic Interconnections of the CNS*: Interconnection between the Ventral Tegmental Area (A_{10}) and the NAc or between the Ventral Tegmental Area (A_{10}) and the Neocortex (NC). These interconnections are indicated in brown with the double arrow and the thin dashed line.

with the decreased cell body size of the Purkinje neuron (Fatemi et al., 2002).

Moreover, studies suggested that SCZ and ASD symptoms, in part, may be derived from abnormalities of cerebro-cerebellar interconnections (Andreasen et al., 1998; Strick et al., 2009; Mosconi et al., 2015).

Furthermore, electrical stimulations of the Purkinje neuron layer and of the dentate nucleus evokes a long-lasting increase of DA efflux in the PFC, and this suggests a possible disconnection between the Purkinje neurons and neuronal population of the dentate nucleus, which in turn can lead to aberrant DA signaling in the PFC and to abnormal behavior related to symptoms of SCZ and ASD (Mittleman et al., 2008; Rogers et al., 2013).

Therefore, the cerebellum and its dopaminergic innervation and their interconnections to the other midbrain dopaminergic areas suggested a direct cerebellar involvement in the PD pathophysiological mechanisms (Lewis et al., 2013; Wu and Hallett, 2013; Yoo et al., 2019). Furthermore, the relevant role of the cerebellum is also strongly indicated in psychiatric disorders such as SCZ and ASD characterized by a significant dysregulation of the dopaminergic system (Andreasen et al., 1998; Strick et al., 2009; Mosconi et al., 2015).

THE ROLE OF THE DOPAMINERGIC CEREBELLAR SYSTEM IN THE TREATMENT OF NEUROLOGIC AND PSYCHIATRIC DOPAMINE-RELATED DISORDERS

Taken together, the data evidenced in the present review, suggested the existence of a cerebellar dopaminergic neuronal system, which can be the target for pharmacological, non-pharmacological, or combined therapeutic treatments (Miterko et al., 2019); here, we will briefly review some of the therapeutic aspects on the cerebellar dopaminergic system in PD, SCZ, and ASD.

In PD, neuroimaging studies have demonstrated L-DOPA administration resulted involved in asymmetrical effects in motor brain regions, highlighting differences in cerebellar activity (Martinu et al., 2014). In PD patients, an increased putamen-cerebellar activity after abstention of L-DOPA administration has been proven, suggesting a role for the cerebellum in compensatory mechanisms (Simioni et al., 2015).

In SCZ antipsychotic treatments, the cerebellum may also represent part of the pharmacologic target. In rat cerebellum, the atypical antipsychotic blonaserin and the anxiolytic buspirone engage extensively in dopamine receptor DRD_3 (Baba et al., 2015; Di Ciano et al., 2017); indeed, in the cerebellum an extensive distribution of the dopamine receptor DRD_3 has been demonstrated (Barili et al., 2000; Kim et al., 2009). Furthermore, in genomic DNA isolated from the cerebellum, the atypical antipsychotic agent olanzapine increased methylation of genes related to the dopaminergic system, such as DRD_5, DOPA decarboxylase (DDC8), and $VMAT_2$ (SCL18A2/VMAT2; Melka et al., 2013).

The cerebellum is extensively interconnected to the other brain regions involved in motor, cognitive, and affective functions (Milardi et al., 2016; Cacciola et al., 2017a, 2019; Caligiore et al., 2017; Bostan and Strick, 2018; Flace et al., 2018b). Although, these cerebellar interconnections have not yet been fully characterized, in studies, it has been demonstrated that the cerebellum may represent the ideal target of non-invasive brain stimulation therapies such as electrical or magnetic stimulations applied in therapies for neurological and psychiatric disorders (van Dun et al., 2017; Miterko et al., 2019; Quartarone et al., 2020). In PD patients, bilateral cerebellar repetitive Transcranial Magnetic Stimulation (rTMS) induced persistent clinical beneficial effects, reducing peak-dose L-DOPA-induced dyskinesia (Koch, 2010).

In healthy subjects, cerebellar vermal theta burst stimulation (TBS) produced downstream changes in neuronal activity in the frontal cortex (Schutter et al., 2003), and pharmacological treatment-resistant SCZ patients can improved cognitive functions (Demirtas-Tatlidede et al., 2010). The rTMS In ASD has been used to study excitatory/inhibitory imbalance (Uzunova et al., 2016) and can represent an innovative therapeutic approach for reducing some of the core and associated ASD symptoms (Oberman et al., 2016).

DISCUSSION AND CONCLUSION

The present review extensively evidenced the available morphological, chemical, and functional data on the existence of a cerebellar dopaminergic system in mammals including humans, which consist of extrinsic fibers which originate mainly from the midbrain cerebellar dopaminergic nuclei (A_8-A_{10}; Ikai et al., 1992; Nelson et al., 1997) and of intrinsic dopaminergic neuronal subpopulations mainly composed of cortico-cerebellar projective neuron types, such as the Purkinje neuron and the synarmotic neuron, and by different cerebello-nuclear neuron types (Nelson et al., 1997; Delis et al., 2008; Flace, 2017; Flace et al., 2018a, 2019b).

In addition, this review evidenced the presence of direct dentate-SNpc and dentate-VTA interconnections (Milardi et al., 2016; Flace et al., 2017, 2018a, 2019b, 2020), which may play a relevant modulatory role in DA release at the PFC (Mittleman et al., 2008; Rogers et al., 2013) and highlight the possible involvement of dopaminergic cerebellar circuits in dopaminergic related disorders such as PD (Wu and Hallett, 2013; Flace et al., 2018a, 2019b, 2020), SCZ (Martin and Albers, 1995; Mittleman et al., 2008; Rogers et al., 2013; Parker et al., 2014), and ASD (Kemper and Bauman, 1993; Mittleman et al., 2008; Rogers et al., 2013).

Finally, we suggest that the cerebellar dopaminergic system and its interconnections may represent an ideal candidate for innovative non-invasive treatments such as electrical or magnetic stimulations in neurological and psychiatric disorders (Demirtas-Tatlidede et al., 2010; Koch, 2010; Oberman et al., 2016; Miterko et al., 2019; Quartarone et al., 2020). These innovative therapeutic objectives constitute relevant elements of study and we hope that they can be achieved in a relatively short time.

AUTHOR CONTRIBUTIONS

PF designed the study, performed the experiments and the analysis of the experimental data, and participated in the writing of the manuscript. PL and DG shared the study project and participated in the writing of the manuscript. GB, ABi, SBe, JB, SBi, and ABr participated in the writing of the manuscript. GG, MG, and GA performed the analysis of the experimental data, participated in the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Social Cognition in Patients With Cerebellar Neurodegenerative Disorders

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Objective: Cerebellar neurodegenerative disorders (CDs) are a heterogeneous group of disorders. It is known that the cerebellum plays a role not only in motor, but also in cognitive and social cognitive functions. The aim of this study was to investigate social cognition in patients with different CDs.

Materials and Methods: Social cognition was examined in 34 patients, 12 with spinocerebellar ataxia type 1 (SCA1), 6 with spinocerebellar ataxia type 2 (SCA2), and 16 with idiopathic late onset cerebellar ataxia (ILOCA). All patients were clinically evaluated using the Scale for the Rating and Assessment of Ataxia. In addition, 34 age, sex, and education-matched healthy control (HC) subjects were similarly analyzed. Social cognition was studied using two tests: the Faux Pas Recognition Test and the Reading the Mind in the Eyes Test (RMET). An appropriate array of neuropsychological tests was used to assess the global cognitive status as well as the frontal functions and mood.

Results: CD patients achieved significantly worse results on both tests of social cognition compared to the HCs. The SCA1 + 2 group achieved the poorest results on the Faux Pas Recognition Test and exhibited poor performance on all cognitive tests, but was only significantly worse compared to the ILOCA group on the Free and Cued Selective Reminding Test (FCSRT) – recognition. The patients in the SCA1 + 2 and ILOCA groups obtained similar scores on RMET. In the SCA1 + 2 group the findings significantly correlated with clinical parameters of disease severity and duration and executive functions (EFs), and with mood and executive functions in the ILOCA group. In the SCA group EFs appeared as the only significant predictor of RMET achievement. The Boston Naming Test (BTN) was a significant predictor of the CD patients' achievement on RMET, while the BTN, the Trail Making Test Part A and FCSRT – Delayed free recall predicted their performance on the Faux Pas Recognition Test.

Conclusion: Patients with CD have social cognitive impairments as demonstrated by the Faux Pas Test and the RMET test results. The SCA1 and 2 patients exhibited a more pronounced impairment compared with the ILOCA patients. The independent cognitive predictors of social cognition impairment were EFs and language.

Keywords: cerebellum, neurodegenerative disorder, spinocerebellar ataxia, idiopathic late-onset cerebellar ataxia, theory of mind, social cognition

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INTRODUCTION

Cerebellar neurodegenerative disorders (CD) encompass a group of diverse disorders affecting the cerebellum and its pathways. Some of these disorders, such as autosomal dominant cerebellar ataxias or spinocerebellar ataxias (SCAs) are characterized by cerebellar signs, as well as additional non-cerebellar signs, including extrapyramidal features, pyramidal signs, peripheral neuropathy, and in some types of SCA, cognitive deficits (Shakkottai and Fogel, 2013; Sullivan et al., 2019). SCA1 and SCA2, the two types of cerebellar ataxias which are caused by trinucleotide expansion, represent the most common types in the Serbian population (Dragasević et al., 2006). Another group of ataxias is idiopathic late-onset cerebellar ataxias (ILOCA) or sporadic adult-onset ataxias, whose etiology still remains unknown. These disorders are non-hereditary and degenerative ataxias characterized by a slowly progressive cerebellar syndrome (Barbosa et al., 2016; Klockgether, 2018).

It is a well-known and widely reported fact that the cerebellum plays a vital role in motor functions (Glickstein, 1992; Manto et al., 2012). It is equally well-known that this role also extends to cognitive and behavioral functioning (Schmahmann, 1991, 1996; Middleton and Strick, 1994; Schmahmann and Sherman, 1997; Riva and Giorgi, 2000; Ravizza et al., 2006; Frings et al., 2007; Baillieux et al., 2008; Stoodley and Schmahmann, 2009; Thompson and Steinmetz, 2009; Stoodley, 2012; Koziol et al., 2014; Hoche et al., 2018). However, scientists still disagree as to the exact role of the cerebellum in cognition (Cooper et al., 2010). Some sources have suggested that different cognitive functions are localized to specific regions of the cerebellum (Cooper et al., 2010). Patients with cerebellar disturbances have significant and relevant deficits in the working memory, visuospatial, language, and executive function (EF) domains (Ahmadian et al., 2019; Silveri, 2020). Patients with different types of hereditary ataxias, especially SCA1 and SCA2, show impairments in EF, verbal memory, and attention (Bürk et al., 2001; Le Pira et al., 2002), while ILOCA patients show impairments in visuospatial function, verbal fluency, and mental flexibility (Rentiya et al., 2018). In addition, patients with degenerative ataxias exhibit changes in emotions (Adamaszek et al., 2017) and social cognition (SC) (Sokolovsky et al., 2010).

The ability to estimate mental states of other people is a fundamental aspect of social cognition (Van Overwalle et al., 2014). Social cognition primarily implies a basic, automatic level of recognizing and attributing emotions to others by immediate perception, which can be assessed by *Reading the Mind in the Eyes Test* (RMET) (Baron-Cohen et al., 2001; Serafin and Surian, 2004; Clausi et al., 2018). In addition to this, the theory of mind (ToM) is considered as a higher level of social interference, defined as the ability to attribute mental states to others and adopting the perspectives of other persons to understand and predict behavior (Premack and Woodruff, 1978; Van Overwalle et al., 2014). According to Baron Cohen, having "theory of mind" means being able to infer a full range of mental states (beliefs, desires, intentions, imagination, emotions), or the ability to reflect on the content of one's own and others' minds (Baron-Cohen et al., 1999). One of the tools commonly used to assess ToM is the *Faux-Pas Recognition Test* (Stone et al., 1998; Liverta Sempio et al., 2005; Clausi et al., 2018).

The cerebellum is incorporated in associative and paralimbic circuits which are involved in social cognition (Van Overwalle et al., 2014; Heleven and Van Overwalle, 2018). Our knowledge of how exactly the neuronal circuitry supports complex human behaviors remains insufficient; however, it is known that it includes fronto-limbic connections, the medial precuneus and medial prefrontal cortex, temporoparietal junction, superior temporal sulcus (Saxe and Kanwisher, 2003; Aichhorn et al., 2009; Van Overwalle and Vandekerckhove, 2013), orbitofrontal regions, dorsal and lateral prefrontal cortex (Abu-Akel and Shamay-Tsoory, 2011), the amygdala (Adolphs, 2004), and the insula (Kipps et al., 2007). Other important participants in social cognition are mirror neurons in the ventral premotor and rostral posterior parietal cortices (Rizzolatti et al., 2006) and middle temporal gyrus (Johnstone et al., 2006).

The cerebellum and its connections have recently been added to the neural network of social cognition. It has previously been shown that not only the patients with complex cerebello-cerebral degeneration, but also those with isolated cerebellar lesions, have specific impairments in social cognition abilities (Abel et al., 2007; Sokolovsky et al., 2010; D'Agata et al., 2011; Hoche et al., 2016). Moreover, imaging studied have shown evidence of cerebellar activation during ToM tasks (Brunet et al., 2000; Calarge et al., 2003; Stoodley, 2012; Van Overwalle et al., 2014; Clausi et al., 2018; Guell et al., 2018).

The aim of this study was to assess social cognition in patients with different hereditary and non-hereditary degenerative ataxias using social cognition tests. Our hypotheses were the following: (1) Patients with hereditary and non-hereditary cerebellar disorders would exhibit impairments on the *Faux Pas Recognition Test* and RMET compared with healthy controls. (2) Patients with SCA1 and SCA2 would exhibit a more pronounced impairment on the *Faux Pas Recognition Test* and RMET compared with ILOCA patients. (3) Patients with SCA1/SCA2 would exhibit different neuropsychological profiles to those with ILOCA. (4) Executive dysfunctions would be correlated with social cognition in both groups. (5) Executive dysfunctions would be a significant predictor of social cognition in both groups of patients.

MATERIALS AND METHODS

Participants

Social cognition was studied in 34 patients [mean age/SD: 48.9/11.8 (years); mean education/SD: 12.7/2.1 (years); M/F: 20/14]: 18 with spinocerebellar ataxias (12 SCA1 and 6 SCA2 patients) and 16 ILOCA patients. All patients presented with diffuse cerebellar atrophy on MRI, while SCA1 and SCA2 patients further exhibited brainstem atrophy and generalized cortical atrophy, and genetic disorders were confirmed by genetic analyses. SCA1 and SCA2 patients carried a heterozygous CAG triplet expansion with 53.5 $\pm$ 5.2 repeats (range 48 to 63) in the coding ATXN1 region and CAG triplet expansion with 37.6 $\pm$ 1.5 repeats (range 36 to 40) in the coding ATXN2

region, respectively. The subjects were diagnosed and tested at the Neurology Clinic of the Clinical Center of Serbia (CCS) in 2017–2020. The patients were taking dietary supplements (vitamin E and selenium, Coenzyme Q10). None of the patients showed any major psychiatric disorders, anxiety or depressive traits, nor were they taking antidepressants or any other psychoactive drugs. In addition to the previously described body of patients with ataxias, 34 age, sex, and education-matched healthy control (HC) subjects were enrolled in the study. An appropriate battery of tests was used to assess global cognitive status, frontal neuropsychological functions, social cognition, and mood. All participants were informed of the purpose, procedures, and scope of all the examination and were included in the screening only after providing their written informed consent for participation.

Clinical Assessment

The patients were clinically evaluated using SARA (*Scale for the Rating and Assessment of Ataxia)*, which assesses a range of different impairments in cerebellar ataxia (Schmitz-Hübsch et al., 2006). This Scale assesses the following aspects: truncal ataxia, speech disturbance and limb ataxia. It has eight categories with an accumulative score ranging from 0 (no ataxia) to 40 (most severe ataxia).

Social Cognition

Faux Pas Recognition Test

A social *faux pas* occurs when a speaker says something without considering that the listener might not want to hear it or might be hurt by what has been said, implying a false or mistaken belief (Baron-Cohen et al., 1999). In normal circumstances, people are usually able to recognize the *faux pas* and understand that the person who said something inappropriate did not know that that the listener would be upset by the *faux pas*. To understand *faux pas* the subject must identify wrong behavior in the context of predicted social interactions. The events that constitute a *faux pas* are unpredicted, and the subject needs to compare events and social expectations constantly while in no-*faux pas* stories the events are expected and require a low level of prediction.

We used a Serbian adaptation of the revised version of the *faux pas* stories (Baron-Cohen et al., 1999; Đorđević, 2013) to evaluate the ability to recognize a social *faux pas*. The detection of a *faux pas* requires both a cognitive understanding of false or mistaken beliefs and an appreciation of the emotional impact of a statement on the listener. Twenty stories were read to the participants, who were provided with copies of the stories to read along as the stories were read and check back over their contents. Ten of the stories involved a social *faux pas* (*Faux Pas* stories), and 10 were control stories in which no *faux pas* occurred (No-*Faux Pas* stories). After listening to each story, the subject was asked whether anyone had said anything they should not have said. When a *faux pas* was identified, specific clarifying questions were asked to verify the participant's understanding of the mental and emotional state of the agent involved in the stories. Samples of *Faux Pas* and No-*Faux Pas* stories with respective questions are reported. Separate reports were made for the: (a) *faux pas*-related questions about the stories containing a *faux pas*, (b) control questions on the faux *pas* stories, (c) *faux-pas*-related questions on the control stories, and (d) control questions on the control stories. Separate reporting helped keep track of the type of errors the participants had made i.e., whether they had more *faux-pas*-related errors (ToM errors) or errors on the factual control questions. If a control question was answered incorrectly, other errors made in connection with that particular story were interpreted with caution. Each correctly answered question related to a *Faux Pas* story was scored as 1, yielding a maximum score of 6 for each correctly identified *Faux Pas* story and altogether 60 for the total of 10 *Faux Pas* stories. For each No-*Faux Pas* story a score of 2 was given if the subject correctly identified the absence of a *faux pas*. Two questions assessing the comprehension of the story material were asked after each story. The results were converted into percentages.

Emotion Recognition Test

To examine the participants' ability to infer the mental states of others, we used a Serbian adaptation of the revised version of the *Reading the Mind in the Eyes Test* (RMET) (Baron-Cohen et al., 2001; Đorđević et al., 2017). The test evaluates the first stage (automatic) mentalizing and consists of 36 photographs of the actors' eye region, each printed on a separate sheet of paper. Four adjectives corresponding to complex internal mental state descriptors were given.

The participants were required to identify the sex of the people in the pictures. They were also asked to decide which of the four words best described what the individuals in the photographs were thinking or feeling. Only one of the four words (the target word) correctly described the mental state of the person in the photograph. Although more than one word might have seemed applicable, the participants were instructed to choose only one, making sure to carefully read all four before making a decision. The answers were not timed. However, the participants were asked to complete the task as quickly as possible. The use of a dictionary was allowed in case of an unfamiliar word. For each correct answer, the participants received 1 point. The maximum number of points was 36. The test results were then divided by the maximum number of points (36) and converted into percentages.

Neuropsychological Screening

Cognitive functions were assessed using selected tests from a neuropsychological battery that included the following:

Global cognitive functioning was measured with the *Addenbrooke's Cognitive Examination* –

Revised (ACE-R) (Mioshi et al., 2006). The test consists of 5 subscales designed to assess attention and orientation, fluency, language, visuospatial skills, and verbal memory. For the assessment of global functioning we used the total score. To test this aspect we also used the standard *Mini-Mental State Examination* (MMSE) (Folstein et al., 1975).

Learning and episodic verbal memory were assessed with the *Free and Cued Selective Reminding Test* (FCSRT) (Buschke, 1984; Grober et al., 1988) using the immediate total free recall (total number of items retrieved over 3 learning trials), delayed free recall (number of words freely recalled after a 30-min delay), and recognition (number of recognized words after delayed free and cued recall).

TABLE 1 | Socio-demographic characteristics of groups, clinical characteristics and mood scales – descriptive statistics.

	SCA1 + 2 (*n* = 18, 10M + 8F)		ILOCA (*n* = 16, 10M + 6F)		HC (*n* = 34, 16M + 18F)	
	Mean/Median (sd)	**Range**	**Mean/Median (sd)**	**Range**	**Mean/Median (sd)**	**Range**
Age (yrs)	43.78/42.5 (12.4)	22–68	54.8/55.5 (7.9)	38–68	49.1/44 (11.8)	22–68
Education (yrs)	12.2/12 (2.3)	8–16	13.1/12 (1.7)	11–16	12.7/12 (2.1)	8–16
Onset of disease (yrs)	32.7/30.5 (10.6)	16–53	47.6/48.5 (8.9)	28–62	–	–
Disease duration (yrs)	10.9/8.5 (9.1)	2–38	7.1/7.5 (4.2)	2–15	–	–
Truncal ataxia	7.4/7 (2.1)	4–12	4.4/4 (1.9)	2–8	–	–
Dysarthria	2.5/3 (0.6)	1–3	1.7/1.5 (1.1)	0–4	–	–
Limb ataxia	5.3/5 (2.2)	3–12	2.9/2.5 (1.6)	0–6	–	–
SARA[1]	15.3/15 (3.8)	10–22	9.0/8.5 (3.7)	3–18	–	–
HDRS[2]	6.7/7.5 (4.1)	0–17	7.1/7 (3.9)	1–15	1.7/0 (2.7)	0–13
HARS[3]	9.6/10.5 (5.9)	0–17	7.3/6 (6.2)	0–17	2.1/1 (3.6)	0–19

[1]Scale for the Rating and Assessment of Ataxia (SARA), [2]Hamilton Depression Rating Scale, [3]Hamilton Anxiety Rating Scale. Source: Author's calculation.

Orientation and attention were tested with the help of several subtests: the *Orientation and attention* subscale from the ACE-R; the *Digit Span*-subtest from the VITI (*Vekslerov Individualni Test Inteligencije*) (Pavlović, 2003), a Serbian adaptation of *Wechsler's Adult Intelligence Scale – Revised*. The subjects were asked to repeat auditorily presented sequences of digits forward (up to 9 digits) and backward (up to 8 digits), and trials were administered until two failures of each span length. The total number of correct answers after the transformation into a scaled score was then used. To assess attention and psychomotor speed, we used the *Trail Making Test Part A* (TMT-A), a timed measure of selective attention to visually presented information (Lezak, 1995). The TMT-A consists of 25 circles distributed over a sheet of paper. The patients were asked to draw lines to connect them in ascending order as fast as possible.

Calculation was assessed using the *Arithmetics*-subtest from VITI (Pavlović, 2003), which consists of a series of verbally presented arithmetic questions of increasing difficulty. Transformed total scores were used.

Confrontation naming was assessed with the *Boston Naming Test* (BNT) using a raw score that represents the total of correctly named objects (spontaneously or after giving a semantic cue) (Kaplan et al., 1983).

Visuospatial processing was tested using the *Hooper Visual Organization Test* (HVOT) (Western Psychological Services, 1983). The total number of correct answers was recorded.

Executive functions were evaluated using several subtests: the *Stroop Color and Word Test (SCWT)* (Lezak, 1995). This test involves an interference task, requiring the naming of color ink, preventing the reading of words for which the color and meaning of the words are incongruent (for example, the word "red" written in green). The analysis includes the time (in seconds) required to complete the task. Verbal working memory was assessed using the *Digit Ordering Test* (DOT) (Cooper et al., 1991): a series of seven digits that has to be memorized and immediately recalled in ascending order. The total number of correct answers and the maximum forward range were used in the analysis. Letter fluency (number of words beginning with the letters S, K, and L produced in 60 s) and category fluency (number of animals produced in 60 s) (Lezak, 1995) were used as measures of verbal divergent thinking. The analysis included the total raw score for all three letters, the score for category fluency, and the corrected values for both of these measures. All tests were conducted by a qualified neuropsychologist in a standardized manner consistent across subjects.

Mood Assessment

Mood was evaluated with the help of two tests:

Depression Assessment

The *Hamilton Depression Rating Scale* (HDRS) (Hamilton, 1960), which consists of 17 questions, was used to assess the patients' levels of depression. The assessment, which was in the form of a structured interview, was conducted by a trained physician. Total scores vary from 0 to 53. For the HDRS, a score of 0–7 is generally accepted as being within the normal range, while a score of 20 or higher indicates at least moderate severity.

Anxiety Assessment

The *Hamilton Anxiety Rating Scale* (HARS) (Hamilton, 1959) was used to determine the presence of anxiety in our patients. The Scale is completed by a trained physician acting as the examiner, based on interviews held with patients. The Scale consists of 14 items which are individually rated from 0 (not present) to 4 (severe). Total scores vary from 0 to 56. Patients with score $\geq$13 were considered anxious.

Data Analysis

The assumption of normality of dependent variables (*Faux Pas Recognition Test*, RMET, neuropsychological tests, the duration of the disease, SARA, mood assessment and EF, and other neuropsychological functions tests) was determined based on the results of the *Kolmogorov-Smirnov* and *Shapiro-Wilk* tests, which indicate the application of non-parametric techniques ($p < 0.05$). The non-parametric *Kruskal Wallis Test*, with *post hoc* pairwise comparisons, was used to compare the three groups (SCA, ILOCA, and HC) in terms of socio-demographic

variables, mood assessment tests, *Faux Pas Recognition Test*, RMET and neuropsychological tests. The *Mann-Whitney U Test* for independent samples was used to detect differences in the scores between the two CD groups, on variables assessed only on these groups, such as duration of the disease, clinical characteristics/SARA. The *Spearman rank-order correlation coefficient* was used to correlate the *Faux Pas Recognition Test* and RMET results with the duration of the disease, clinical characteristics/SARA, psychiatric tests and EF tests in all three groups (SCA1 + 2, ILOCA, HC). *Multiple regression analysis* was used to determine whether EFs qualify as significant predictors on the *Faux Pas Recognition Test* and RMET in SCA and ILOCA groups. Same analysis was used to determine whether all neuropsychological tests could significantly predict scores on the *Faux Pas Recognition Test* and RMET in both CD groups. The statistical analyses were performed using IBM SPSS software 21.

RESULTS

Demographic details of CD patients and HC are displayed in **Table 1**. The *Kruskal Wallis Test* showed a significant difference in the mean age (χ^2 = 6,961; p = 0.031) between the three groups. The test showed no significant difference in the mean level of education (χ^2 = 1,702; p = 0.427) between the three groups. The mood assessment test results seem to be within the normal expected range for each of the three groups, and the *Kruskal Wallis Test* showed a significant difference in the mean HDRS score (χ^2 = 29,414; p = 0.0001) and HARS score (χ^2 = 20,825; p = 0.0001). *Post hoc* pairwise comparisons with Bonferroni correction indicated differences between:

- SCA1 + 2 and ILOCA groups in age (t = −26,781; p = 0.025),
- HC and SCA1 + 2 groups (t = −24,346; p = 0.0001) and HC and ILOCA groups (t = −26,735; p = 0.0001) in HDRS score
- HC and SCA1 + 2 groups (t = −17,173; p = 0.011) and HC and ILOCA groups (t = −24,346; p = 0.0001) in HARS score.

For variables applicable only to the CD groups (SCA1 + 2 and ILOCA), *Mann-Whitney U Tests* indicated significant differences in onset of disease (U = 42.5; z = −3.505; p = 0.0001), truncal ataxia (U = 39.5; z = −3.632; p = 0.0001), dysarthria (U = 78; z = −2.398; p = 0.017), limb ataxia (U = 47; z = −3.372 p = 0.001), and SARA (U = 34.5; z = −3.783; p = 0.0001) between patients in the SCA1 + 2 and ILOCA groups.

Mean values, standard deviations and range are shown in **Table 1**.

Social Cognition Profile in CD Patients vs. HC

We identified significant differences in the performance on the *Faux Pas Recognition Test* and RMET between the CD patients and HCs. Box plots illustrating the differences in the average scores (in%) obtained from CD and HC subjects in each social cognition task (*Faux Pas* stories, No-*Faux Pas* stories and RMET) are shown in **Figure 1**. In the *Faux Pas Recognition Test* the patients with cerebellar hereditary and non-hereditary disorders showed impaired scores compared to HCs [U = 129.5, z = −5.544, p = 0.0001, r = 0.67 (high effect size, 95%CI: 0.523 to 0.788)]. Moreover, the patients with cerebellar hereditary and non-hereditary disorders obtained significantly lower scores than HCs in the RMET [U = 17.0, z = −6.895, p = 0.0001, r = 0.84 (high effect size, 95%CI: 0.756 to 0.899)].

Differences in the Faux Pas Recognition Test and RMET Outcomes Among All Studied Groups

We further investigated the differences in the performance on the Faux Pas Recognition Test and RMET tests between groups. The average score (standard deviation) on the *Faux Pas Recognition Test* was 63.8 (11.6) for SCA1 + 2, 78.8 (13.9) for ILOCA and 91.9 (10.2) for HC. The average score (standard deviation) on RMET was 52.8 (14.4) for SCA1 + 2, 64.4 (10.4) for ILOCA and 85.3 (8.3) for HC. *Kruskal Wallis Test* showed a significant difference in the mean *Faux Pas Recognition Test* score (χ^2 = 36,661; p = 0.0001) and RMET score (χ^2 =49,316; p = 0.0001). *Post hoc* pairwise comparisons with Bonferroni correction indicated differences between:

- The scores for all three groups on the *Faux Pas Recognition Test*; SCA1 + 2 and ILOCA (t = −16,417; p = 0.045), SCA1 + 2 and HC (t = 34,108; p = 0.0001), ILOCA and HC (t = 17,691; p = 0.009). Based on medians, the patients in the SCA1 + 2 group obtained lower scores than the patients in the ILOCA group, while both of these groups obtained lower scores than the HC group participants.
- CD groups in comparison to HC group on RMET scores, SCA1 + 2 and HC (t = 37,250; p = 0.0001), ILOCA and HC (t = 28,219; p = 0.0001). Based on median values, the patients in the SCA1 + 2 and ILOCA group obtained similar scores, which were lower than HC group participants.

Neuropsychological Findings

We investigated intergroup comparisons (SCA1 + 2, ILOCA, and HC) in scores on the neuropsychological tests. Median and significance for intergroup comparisons can be seen in **Table 2**.

The *Kruskal Wallis Test* showed a significant difference in the mean MMSE score (χ^2 = 11,299; p = 0.004), ACE-R – total (χ^2 = 27,801; p = 0.0001), FCSRT – total free recall (χ^2 = 21,097; p = 0.0001), FCSRT – delayed free recall (χ^2 = 12,177; p = 0.002), FCSRT – recognition (χ^2 = 18,528; p = 0.0001), ACE-R – verbal memory (χ^2 = 19,121; p = 0.0001), TMT-A (χ^2 = 30,569; p = 0.0001), Digit Span (χ^2 = 23,136; p = 0.0001), Arithmetic-VITI (χ^2 = 41,979; p = 0.0001), ACE-R – phonemic fluency (χ^2 = 19,495; p = 0.0001), HVOT (χ^2 = 23,541; p = 0.0001), SCWT (χ^2 = 15,779; p = 0.0001), ACE-R-Language (χ^2 = 11,356; p = 0.003), ACE-R-visuospatial skills (χ^2 = 8,273; p = 0.016), DOT Total (χ^2 = 20,185; p = 0.0001).

Post hoc pairwise comparisons with Bonferroni correction indicated differences between both CD groups in comparison to the HC group on:

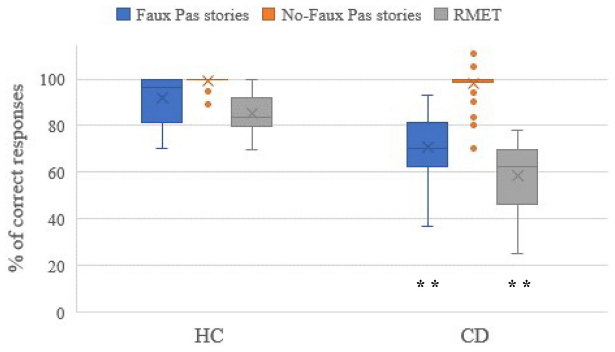

FIGURE 1 | The scores of the social cognition battery. Data are presented as the percentage of the total number of correct responses for the Faux Pas stories (max = 60) and the No-Faux Pas stories (max = 20), and for the RMET (max = 36). The mean scores of the accuracy percentage, where 0% is totally wrong and 100% is totally correct, are reported for the CD and HC groups, and significant differences of $p < 0.01$ are indicated by **.

- MMSE score, ACE-R – total, FCSRT – total free recall, ACE-R – verbal memory, TMT-A, Digit Span, Arithmetic-VITI, ACE-R – phonemic fluency, HVOT, SCWT, DOT Total. Based on median values, the patients in SCA1 + 2 and ILOCA group obtained similar scores, and worse than HC group participants.

On some scales, *post hoc* pairwise comparisons with Bonferroni correction indicated differences only between SCA1 + 2 and HC group:

- FCSRT – delayed free recall, ACE-R-Language, ACE-R-visuospatial skills. Based on medians, the patients in SCA1 + 2 group obtained worse scores than HC group participants, while patients in the ILOCA group obtained scores between the other two.

And lastly, on FCSRT – recognition scale, *post hoc* pairwise comparisons with Bonferroni correction indicated differences between the SCA1 + 2 and HC groups (t = 17,905; p = 0.0001), and between the SCA1 + 2 and ILOCA groups (t = −13,424; p = 0.019). Median values indicate that the patients in SCA1 + 2 group obtained lower scores than the other two groups, patients in the ILOCA group and HC participants.

Associations of the Social Cognitive Profile With Sociodemographic, Clinical, and Genetic Features of CD Patients With Their Neuropsychological Findings and Mood State

The duration of the disease (r = −0.555, 95%CI: −0.119 to −0.811, p = 0.017), truncal ataxia (r = −0.557, 95%CI: −0.122 to −0.812, p = 0.016) and SARA score (r = −0.561, 95%CI: −0.128 to −0.814, p = 0.015) showed a significant inverse (negative) correlation with the *Faux Pas Recognition Test* in the SCA1 and SCA2 groups of patients, while the *SCWT* (r = −0.482, 95%CI: −0.002 to −0.781, p = 0.050) correlated inversely with RMET. In the ILOCA group of patients, RMET correlated with HDRS (r = 0.498, 95%CI: 0.004 to 0.796, p = 0.050) and HARS (r = 0.541, 95%CI: 0.062 to 0.817, p = 0.030) and *ACE-Phonemic Fluency* (r = 0.545, 95%CI: 0.068 to 0.819, p = 0.029). There was no significant correlation in the SCA1 and SCA2 groups of patients between the number of repeats in the expanded allele and the achievement on *Faux Pas Recognition Test* and RMET.

Predictors of Social Cognition Impairment in CD Patients

The final goal of this study was to determine whether EFs are significant predictors of performance in social cognition tests in SCA1 + 2 and ILOCA patients. The predictor variables (SCWT, DOT Total, ACE-R-Phonemic Fluency) did not show significant prediction of the *Faux Pas Recognition Test* scores in the SCA1 + 2 group (F = 1.802; df = 3.13; $p > 0.05$), nor in the ILOCA group (F = 1.269; df = 3.11; $p > 0.05$). In addition, in the ILOCA group, EFs (SCWT, DOT Total, ACE-R-Phonemic Fluency) did not show significant prediction of RMET (F = 1.95; df = 3.11; $p > 0.05$). On the other hand, in the SCA1 + 2 group, EFs appeared as significant predictors of the *Emotion Recognition Test* (F = 4.05; df = 3.13; p = 0.031), explaining 48.3% of the variance. The only significant predictor was *SCWT* (β = −0.631, 95% CI from −1.04 to −0.22, t = −3.006, $p < 0.05$). If the *SCWT* score were to increase by one standard deviation, the achievement scores on the RMET would likely decrease by 0.63 units of standard deviation in the patients of the SCA1 + 2 group. Since only one EF test could predict social cognition impairment, we wanted to determine which other domains of neuropsychological tests might be significant predictors of failure in social cognition in both groups of CD patients.

First, we entered all neuropsychological tests in the regression model, but some of them showed suppression effects that needed to be removed from the model. The final list of neuropsychological predictors (MMSE score, FCSRT – Delayed free recall, TMT-A, BNT – Total, SCWT and DOT Total) showed significant prediction of *Faux Pas Recognition Test* (F = 7.458; df = 6.23; p = 0.0001) in CD patients, explaining 66% of the variance. Standardized beta coefficients show that BNT – Total (β = 0.47, 95%CI from 0.16 to 0.77, t = 2.97, p = 0.007) has the greatest effect, followed by TMT-A (β = −0.37, 95%CI from −0.09 to −0.65, t = −2.64, p = 0.014) and FCSRT – Delayed free recall (β = 0.26, 95%CI from 0.01 to 0.51, t = 2.07, p = 0.049), while MMSE score, SCWT and DOT Total did not appear as significant predictors.

Before predicting the *Emotion Recognition Test* (RMET) findings, after removing suppressors, the final list of predictors contained FCSRT-Total free recall, FCSRT – Delayed free recall, ACE-R Verbal Memory, TMT-A, BNT, and ACE-R-Language. Regression model was significant (F = 11.088; df = 6.24; p = 0.0001) in CD patients, explaining 73.5% of the variance. Standardized beta coefficients show that only BNT – Total (β = 0.612, 95%CI from 0.34 to 0.88, t = 4.406, p = 0.0001) represents a significant predictor of achievement on RMET in CD patients.

DISCUSSION

Our study shows that patients with CD (SCA1, SCA2, and ILOCA) exhibit impaired performance on both the *Faux Pas Recognition Test* and the RMET compared with HC. The patients have difficulty understanding the mental states of others in everyday interactions and from their facial expressions.

Our study examined two groups of patients: a group of SCA1 and SCA2 patients with severe cerebellar and extra-cerebellar signs and a group of ILOCA patients with primarily isolated cerebellar degeneration. The poor performance of both groups possibly suggests that a cerebellar pathology alone produces social cognition impairment, as previously shown by Hoche (Hoche et al., 2016). SCA patients achieved the worst results on the social cognition tests used in our study, which may suggest that social cognition also involves extra-cerebellar structures (Van Overwalle et al., 2015).

Cerebellar disorders are a group of subentities with origins in various pathophysiological mechanisms; they are also characterized by different levels of social cognitive impairment. Some studies suggest that patients with a left lateral cerebellar tumor (Sokolov et al., 2010) and patients with ponto-cerebellar ischemia (Roldan Gerschcovich et al., 2011) can also exhibit social cognition impairment. Schizophrenia and autism spectrum disorders are further characterized by dysfunctions of cerebellar-cortical networks and an impairment of the "mentalizing" process (Andreasen and Pierson, 2008; Penn et al., 2008; Green et al., 2015).

The duration of the disease was similar in all the patients who took part in our study. The SCA group consisted of younger patients with a more severe clinical presentation and disability (SARA), exhibiting a more serious truncal and limbic ataxia and dysarthria before the commencement of the study. The deleterious effect of the disease in SCA patients, corroborated by the neuropsychological tests, was also evident in other domains of cognition. Unlike our ILOCA patients, the SCA group consistently achieved poorer results compared with the HCs in all examined domains. Routine clinical practice may not have detected these deficits if only MMSE tests had been used, as the SCA patients' group scores were within the prescribed normal values. However, a detailed neuropsychological evaluation and screening tests such as ACE-R can detect a more serious cognitive deficit. The severity of ataxia in all SCA patients positively correlated with the patients' cognitive deficit (Ma et al., 2014), although some sources suggest that cognitive functions are affected

TABLE 2 | Neuropsychological screening – descriptive statistics and group comparison.

	SCA1+2 (*n* = 18)		ILOCA (*n* = 16)		HC (*n* = 34)		SCA1+2 - HC	ILOCA - HC
	Mean/Median (sd)	Range	Mean/Median (sd)	Range	Mean/Median (sd)	Range	t	t
Global cognitive functioning								
MMSE[1]	27.2/27.5 (2.8)	19–30	27.8/27.5 (1.7)	25–30	29.1/30 (1.2)	27–30	16.428*	15.22*
ACE-R-total[2]	82.6/85.5 (12.0)	56–99	89.9/89 (4.9)	80–98	95.9/97(4.2)	86–100	29.601**	19.41**
Learning and episodic verbal memory[3]								
FCSRT-total free recall	20.6/20.5 (6.8)	5–33	22.1/22.5 (4.9)	15–32	29.2/34 (6.9)	8–40	23.662**	19.756**
FCSRT-delayed free recall	8.4/8.5 (2.7)	5–13	10.4/10 (2.5)	5–15	11.3/12 (2.6)	4–15	19.941**	
FCSRT-recognition	14.4/14.5 (1.7)	12–16	15.5/16 (1.5)	10–16	15.9/16 (0.2)	15–16	17.905**	
ACE-R-verbal memory	21.7/23 (4.9)	6–26	23.3/23 (2.2)	19–26	25.3/26 (1.4)	21–26	22.26**	17.774**
Orientation and attention								
ACE-R-orientation and attention	16.6/17 (1.8)	12–18	17.3/17.5 (0.9)	16–18	17.6/18 (0.7)	16–18		
TMT-A	83.6/74 (36.6)	30–157	49.3/42.5 (17.0)	22–82	33.4/30 (14.7)	18–78	31.183**	17.169*
Digit-span	7.7/8 (2.1)	4–11	8.3/8 (2.9)	4–13	11.3/11.5 (2.1)	7–15	24.977**	20.088**
Calculation								
Arithmetic-VITI[4]	9.1/9 (3.2)	3–14	11.3/11 (1.6)	9–14	13.8/14 (0.5)	12–14	32.647**	24.014**
Language								
ACE-R-language	23.2/25 (3.2)	15–26	24.8/25 (0.8)	24–26	25.4/26 (1.2)	22–26	17.188**	
BNT-Total	50.3/52 (6.4)	40–58	53.3/54 (3.1)	45–57	54.4/55 (3.9)	40–59		
Visuospatial processing								
HVOT[5]	17.2/17 (6.3)	8–25	21.3/21.5 (3.1)	16–25	24.6/25 (2.9)	17–29	26.103**	18.39**
ACE-R-visuospatial skills	13.2/14 (3.1)	8–16	15.3/16 (1.0)	13–16	15.3/16 (1.4)	11–16	14.634**	
Executive functions								
SCWT[6]	91.6/90 (37.6)	45–154	97.3/98 (41.2)	36–180	57.9/53.5 (21.5)	10–98	18.088**	19.488**
DOT Total[7]	5.3/5 (1.9)	2–9	6.0/6 (1.3)	4–9	7.9/8 (2.1)	4–12	23.5**	18.188**
ACE-R-phonemic fluency	3.8/4 (1.6)	1–7	4.4/4 (1.5)	2–7	5.7/6 (0.9)	4–7	23.034**	17.086*

*[1]Mini Mental State Examination, [2]Addenbrooke's Cognitive Examination – Revised, [3]Free and Cued Selective Reminding Test, [4]Serbian adaptation of the Wechsler Adult Intelligence Scale – Revised, [5]Hooper Visual Organization Test, [6]Stroop Color and Word Test, [7]Digit Ordering Test. Source: Author's calculation (** indicate $p < 0.01$, while * indicates $p < 0.05$).*

first and have a slower progression than motor dysfunctions (Fancellu et al., 2013).

Compared to healthy subjects, our SCA patients exhibited consistently poorer results on tests measuring attention and verbal memory than ILOCA patients, which other authors have also previously recorded (Bürk et al., 2001; Le Pira et al., 2002; Fancellu et al., 2013). The ILOCA patients exhibited worse results than the HC in most cognitive domains, but verbal memory, speech and visuospatial deficits were less frequent. Finally, the executive functioning of both the ILOCA and the SCA patients was equally impaired, which previous studies have also found (Bürk et al., 1999, 2001; Rentiya et al., 2018), while the differences in visuospatial tasks proved less consistent (Wallesch and Horn, 1990; Schmahmann and Sherman, 1998; Rentiya et al., 2018). The extent of cognitive impairment, especially that of attention and executive functioning, verbal and semantic memory, language and speech competence, may explain the patients' poor performance on social cognition tests (Haxby et al., 2000; Siegal and Varley, 2002).

The duration of the disease, functional disability and truncal ataxia significantly correlated with the SCA patients' performance on the *Faux Pas Recognition Test*. SCWT and *Phonemic Fluency Test,* and significantly correlated with the RMET in the SCA and ILOCA group, respectively, but no correlation was determined with verbally presented social situations in the *Faux Pas* stories.

Although prior studies have shown that social cognition impairments are often associated with executive dysfunction (Aboulafia-Brakha et al., 2011), the literature offers conflicting data (Fine et al., 2001; Clausi et al., 2021). Analysis of connectivity suggests that the cerebellar modules active during social cognition are more likely to be involved in socio-cognitive and not executive networks (Van Overwalle et al., 2015).

Depression and depressive symptoms were the most common non-cognitive symptoms in several studies of patients with cerebellar disorders (Leroi et al., 2002; Liszewski et al., 2004). Although the mean scores in both our groups of patients were within the range for the healthy population, significant difference was observed between the CD patients and the HC. Further, several patients in the SCA1 and 2 groups had a score above 14. The ILOCA group's anxiety and depression scores correlated with the patients' performance on the RMET. A larger sample of CD patients is necessary to determine the impact of depression on social cognition. It is possible that the patient's impaired perception hampers the understanding of other people's mental states.

The predictive value of EFs in the assessment of social cognition was ambiguous. The EF tests we used did not significantly predict the *Faux Pas* test performance in our SCA patients. SCWT showed significant predictive value for the RMET performance in the SCA group, but not in the ILOCA patients. The most significant predictor in all groups and for both tests was the BNT language and speech test. Language and speech, skills inherent to humans, are primarily an instrument for interpersonal communication (Schmahmann, 2019) and involve the comprehension of words, sentences and stories arising from and serving social interaction. It is thus natural that speech proved to be the best predictor of social cognition among our CD patients (Mariën and Beaton, 2014; Mariën et al., 2014). The social cognition impairment in our CD patients involved diminished semantic lexicon. Errors of this segment inevitably cause difficulties in conducting original cognitive functions and normal social functioning.

Our patients with primary cerebellar disease exhibited impairments in the *Faux Pas Recognition Test* and the RMET, which are traditionally considered indicators of social cognition. As mentioned above, the deficit was primarily caused by semantic processing impairment, but the extent of damage in other cognitive domains determined the severity of social deficit. The literature describes the role of the cerebellum in the cognitive deficit of SCA1 and 2 pathologies, which is commonly attributed to extra-cerebellar degeneration and damaged ties primarily between the basal ganglia and the thalamocortical circles (Gilman et al., 1996; Kawai et al., 2009). Other studies agree with our results, which associate social cognition with specific regions of the brain: mesial and orbitofrontal cortex (Amodio and Frith, 2006; Frith and Frith, 2006; Völlm et al., 2006) and mesial temporal cortex (Gallagher and Frith, 2003; Völlm et al., 2006). Furthermore, (Charlton et al., 2009) it has been shown that poor performance on social cognition tests can be associated with changes in the white matter. We support the assertion that mentalizing processes depend on a complex network which connect different regions and involves ties in the brain's white matter.

It is unclear whether the obtained data give insight into the patients' overall social abilities or only into routine components necessary for opinion forming. The metric characteristics of the tests, ecological as well as criterion validity, are of special importance in assessing social cognition. Cognition in real social settings is a dynamic, changeable, and context-dependent process. We concur with (Byom and Mutlu, 2013) that the assessment of social cognition in experimental settings may lead to the under- or overestimation of this complex function, resulting in inconsistent results.

In summary, the findings from this study is that social cognition impairment is present in both the SCA 1 + 2 and the ILOCA patients and that the predictors of this impairment are Efs and language. The conclusions of this study are limited due to the small sample of patients and the fact that they were in the advanced stage of the disease, with great physical and cognitive deterioration. The SCA group was in itself heterogeneous and included two somewhat different entities, where the SCA2 group consisted of patients with severe cognitive impairments, even dementia (Bürk et al., 1999). Because of this, the implication that some brain regions contribute to social cognition must be considered with caution. Future studies must avoid the current study's limitations.

The body of evidence suggesting the existence of cognitive and mentalizing deficits in CD is growing. We hope our study will encourage theories which embrace the possibility of a completely

different profile of the deficit within this heterogeneous disorder. Socialization is the core of all human relationships, which is why the implications of impaired social cognition need to be taken seriously when considering treatment options.

Future research should branch into two directions: researching the cognitive changes in CD and determining the profile of some entities of this heterogeneous disorder. Special attention should be dedicated to operationalizing the mentalizing process, determining the main neuropsychological processes and neural correlates involved, and defining adequate assessment instruments.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Board of Neurology Clinic, Medical Faculty University of Belgrade. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OT and ND-M contributed to the conception and design of the study. OT wrote the first draft of the manuscript. DS performed the statistical analysis. MK, AK, ES, BĐ, AM, MĐ, and NG contributed to the organization and data collection. All authors contributed to manuscript revision, read, and approved the submitted version.

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Mental Visualization in the Cerebellum: Rapid Non-motor Learning at Sub-Lobular and Causal Network Levels

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It is generally understood that the main role of the cerebellum is in movement planning and coordination, but neuroimaging has led to striking findings of its involvement in many aspects of cognitive processing. Mental visualization is such a cognitive process, extensively involved in learning and memory, artistic and inventive creativity, etc. Here, our aim was to conduct a multidimensional study of cerebellar involvement in the non-motor cognitive tasks. First, we used fMRI to investigate whether the cognitive task of visualization from an immediate memory of complex spatial structures (line drawings) engages the cerebellum, and identified a cerebellar network of both strongly activated and suppressed regions. Second, the task-specificity of these regions was examined by comparative analysis with the task of perceptual exploration and memorization of the drawings to be later visualized from memory. BOLD response patterns over the iterations of each task differed significantly; unexpectedly, the suppression grew markedly stronger in visualization. Third, to gain insights in the organization of these regions into cerebellar networks, we determined the directed inter-regional causal influences using Granger Causal Connectivity analysis. Additionally, the causal interactions of the cerebellar networks with a large-scale cortical network, the Default Mode Network (DMN), were studied. Fourth, we investigated rapid cognitive learning in the cerebellum at the level of short-term BOLD response evolution within each region of interest, and at the higher level of network reorganization. Our paradigm of interleaved sequences of iteration between two tasks combined with some innovative analyses were instrumental in addressing these questions. In particular, rapid forms of non-motor learning that strongly drive cerebellar plasticity through mental visualization were uncovered and characterized at both sub-lobular and network levels. Collectively, these findings provide novel and expansive insights into high-order cognitive functions in the cerebellum, and its macroscale functional neuroanatomy. They represent a basis for a framework of rapid cerebellar reorganization driven by non-motor learning, with implications for the enhancement of cognitive abilities such as learning and memory.

Keywords: mental visualization, cerebellum, plasticity, learning, memory, fMRI, Granger Causal Connectivity

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INTRODUCTION

Traditionally, the cerebellum has been thought to be involved in motor control and coordination (e.g., Evarts and Thach, 1969; Gilbert and Thach, 1977; Brooks and Thach, 2011). Over the last years, increasing functional Magnetic Resonance Imaging (fMRI) evidence has been accumulating that the cerebellum is contributing to a wide range of cognitive functions (Ito, 1984; Llinas, 1985; Kelly and Strick, 2003; Buckner et al., 2011; Diedrichsen and Zotow, 2015; D'Angelo and Casali, 2013; Brissenden et al., 2018; King et al., 2019; Schmahmann et al., 2019). Working memory, language, executive function and affective tasks have been shown to elicit largely non-overlapping patterns of activation within cerebellar cortex (Allen et al., 1997; Kelly and Strick, 2003; Chen and Desmond, 2005). Additionally, functional connectivity studies in humans (Stoodley and Schmahmann, 2009; Buckner et al., 2011) have shown that cerebellar regions communicate with non-motor networks of the cerebral cortex, manifesting a coarse functional organization unsuspected until fairly recently. These findings of a significant role of the cerebellum in functions traditionally reserved for the cerebral cortex are consistent with recent estimates of its large area, now understood to be close to 80% of the area of the cerebral cortex (Sereno et al., 2020).

Cerebellar Macroscale Functional Anatomy

Motor vs. non-motor cerebellar lobules. Macroscale cerebellar neuroscience is already well-developed in a large body of work (e.g., Habas et al., 2009; Stoodley and Schmahmann, 2009, Stoodley et al., 2010, 2012; O'Reilly et al., 2010; Buckner et al., 2011; Keren-Happuch et al., 2014; Van Overwalle et al., 2014; Brissenden et al., 2016; Guell et al., 2018a,b; Marek et al., 2018; King et al., 2019; Schmahmann et al., 2019; Guell and Schmahmann, 2020). As a result, "the cerebellum is now appreciated as a structure relevant for virtually all aspects of behavior in health and disease" (Van Overwalle et al., 2014).

A didactic summary on the *cerebellar macroscale functional anatomy and organizational principles* derived from numerous functional imaging studies that have mapped motor and non-motor task processes, as well resting-state networks in the human cerebellum, was recently published by Guell and Schmahmann (2020). These principles include the existence of multiple areas of both motor and non-motor representations, with a specific ordering of the functional domains (motor and non-motor), which "together define the position of, and relationship between, each functional territory in cerebellar macroscale functional anatomy." Their data-driven analysis of functional gradient (see **Figure 1**) revealed that *motor* processing is represented twice in each cerebellar cortical hemisphere, though limited to lobules I–VI, and lobule VIII (with a focus on VIIIa), while *non-motor* processes are represented three times - in lobules VI-Crus I, in lobules Crus II–VIIB, and in lobules IX–X (see also Snider and Eldred, 1952; Buckner et al., 2011; Guell et al., 2018a,b).

Cerebellar Functional Boundaries and Organization

The finer-scale *functional boundaries* in the human cerebellum have also been actively investigated (e.g., Diedrichsen and Zotow, 2015; King et al., 2019). In particular, King et al. (2019) used a *multi-domain task battery* to assess a *broad range of cognitive processes*. A battery of 26 diverse tasks comprising 47 unique conditions, was run over four sessions in 1,000 subjects using intrinsic functional connectivity MRI (fcMRI), allowing them to derive a comprehensive functional parcelation of the cerebellar cortex, which was further evaluated by predicting functional boundaries in a novel set of tasks. The organization of a variety of *both motor and non-motor* subdivisions have been also estimated by other methods, such as intrinsic functional connectivity (e.g., Yeo et al., 2011; Buckner et al., 2011).

Rationale and Overview of the Study Design

Here, we perform a multidimensional fMRI feasibility study of the involvement of the cerebellum in the cognitive task of visualization from an immediately acquired memory of complex spatial structures (line drawings). The study is designed to probe the involvement of the human cerebellum in the task of mental visualization, and examine the task-specificity of the cerebellum regions involved by a comparative analyses with the task of perceptual exploration and memorization of the drawings that had to be later visualized from memory (see overview in **Figure 2**). Granger Causal Connectivity analysis (GCCA) is used to determine the directed causal influences among the cerebellar network nodes; furthermore, the causal interaction of the cerebellar networks with a key large-scale cerebral cortical network, such as the Default Mode Network (DMN) are determined as well.

Moreover, this study is also designed to evaluate a number of questions of the role of the cerebellum in *learning*. Does *rapid learning-driven reorganization* occur in the cerebellum during visualization-from-memory iterated on a short-time scale? As the learning proceeds, what types of reorganization take place at sub-lobular and at network level in the cerebellum? What large-scale cerebral networks do they couple/uncouple to/from as a function of this rapid learning? And furthermore, how do these processes differ during the visualization phases relative to the perceptual viewing/memorization phases of the same images?

While cognitive functions, such as visual working memory, are well established within the cerebellum, to the best of our knowledge, the special class of (spatial) memory visualization and furthermore, its involvement in learning, have not been previously studied. The current results include the finding of a *well-structured cerebellar network* for visualization, cerebellum-based *rapid learning effects in this high-order cognitive task* at both the local sub-lobular and the network levels, and strong *causal cerebellar-cerebral* interactions. These results provide novel insights into the significant role of the cerebellum in cognition, in particular in the cognitive processes of learning and memory, and its macroscale functional organization.

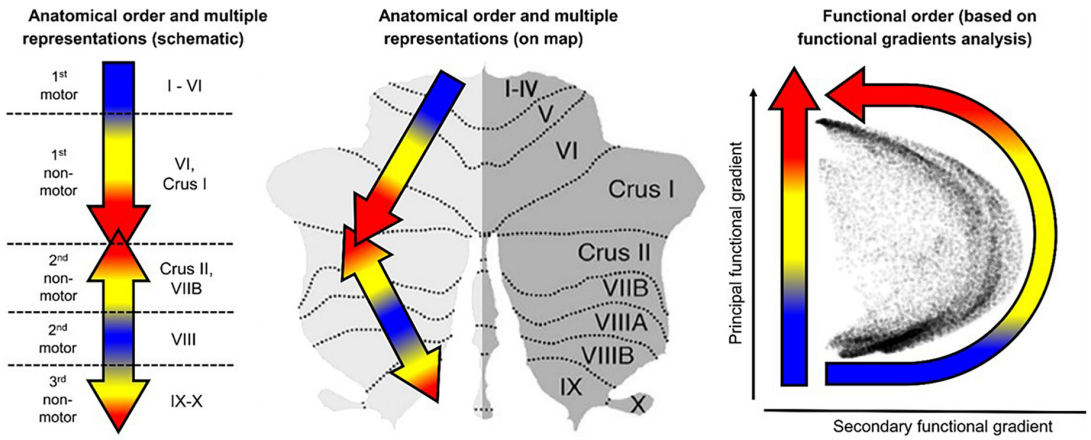

FIGURE 1 | Didactic summary of cerebellar functional anatomy based on human fMRI evidence. Data-driven analyses of cerebellar fMRI indicate three major fundamental poles of cerebellar functional neuroanatomy. (**Left,Center**) Motor processing (blue) is represented twice in each cerebellar cortical hemisphere (lobules I–VI; lobule VIII). Non-motor processes (red and yellow) are represented three times in each cerebellar cortical hemisphere (lobules VI-Crus I; lobules Crus II–VIIB; lobules IX–X). A specific anatomical order is conserved throughout the cerebellar cortex, and propagates from first motor toward first non-motor representation (i.e., from lobules I–VI to Crus I), from second motor toward second non-motor representation (i.e., from lobule VIII to Crus II), and from second motor toward third non-motor representation (i.e., from lobule VIII to lobule IX/X). (**Right**) The principal axis of macroscale functional organization in the cerebellar cortex progresses from motor, to attentional/executive, to default-mode processing. This progression is captured in the anatomical order of cerebellar functional territories as shown in the center and right panels, and also revealed by a data-driven analysis of functional gradients in the cerebellar cortex based on resting-state functional connectivity between cerebellar cortical areas (After Guell and Schmahmann, 2020; reproduced with permission).

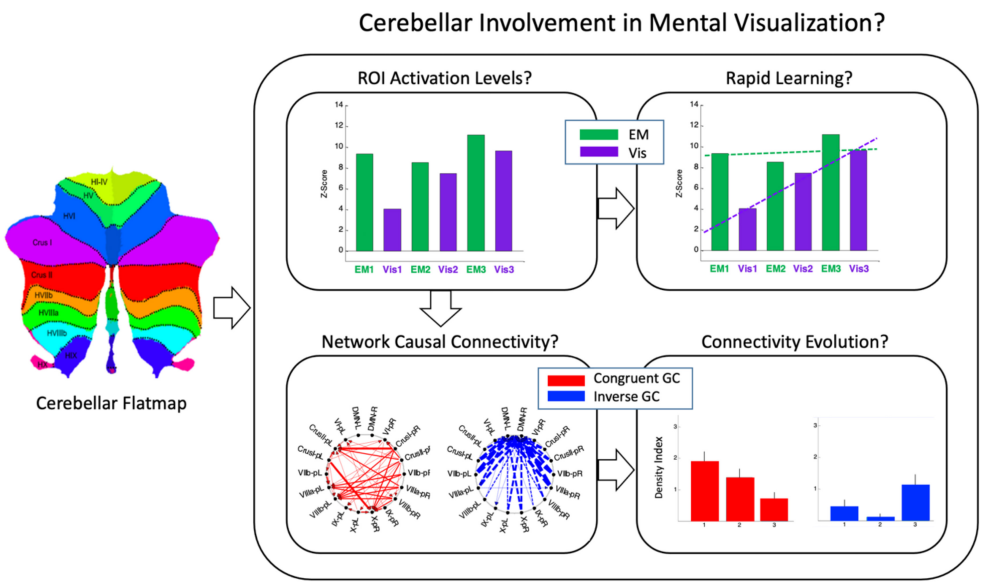

FIGURE 2 | A schematic preview that shows at glance the overall structure of the methodological design. Average cerebellar activation was mapped to an unfolded cerebellar flatmap (icon at left) where the pattern of cerebellar involvement in non-motor cognitive tasks was used to determine the activation levels in each local region of interest (ROI), and its rapid change over three repeats of each task (*top row*); Granger Causal connectivity was assessed within the respective networks of these ROIs, and the connectivity evolution over the three repeats plotted in terms of a Connectivity Density Index (*bottom row*). Two interleaved tasks: ***EM*** = *Explore and Memorize*; ***Vis*** = *Visualization from memory* (see **Figure 3** in Experimental Design).

MATERIALS AND METHODS

Participants

The participants were volunteers with normal or corrected-to-normal visual acuity (5 male, 2 female; ages 34-70). The experimental protocol was approved by the Smith-Kettlewell Institutional Review Board; prior to participating, all volunteers provided their informed consent. Participants were compensated for their time. All procedures were conducted in conformity to the Declaration of Helsinki.

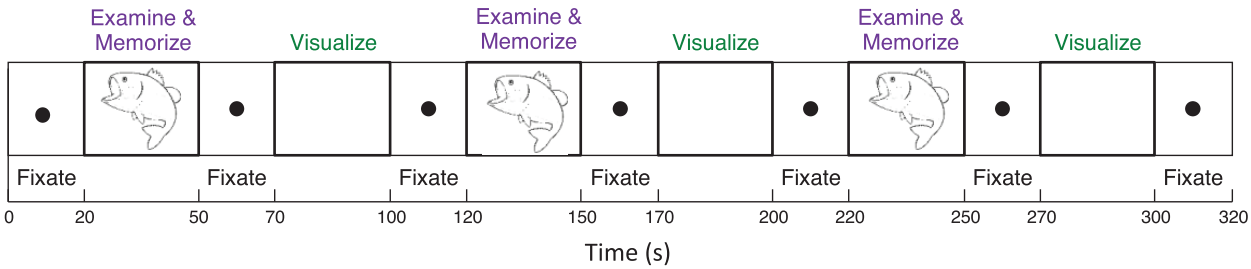

FIGURE 3 | Functional Magnetic Resonance Imaging experimental design included a sequence of two tasks (i) perceptual exploration and memorization of complex graphic material (30 s) and (ii) visualization-from-memory of these images (30 s), interleaved with fixation periods (20 s); this sequence was repeated three times for each image.

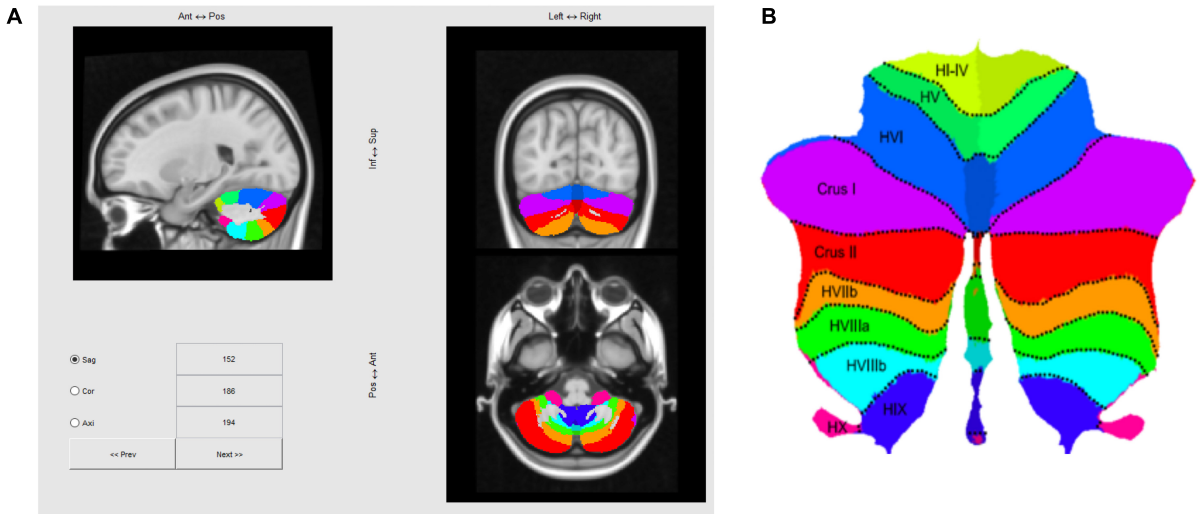

FIGURE 4 | (A) Three-slice volume view of the maximum probability atlas transformed by SUIT to the MNI152 T1 MRI scan used as the structural reference for registering multi-subject fMRI data in this study. **(B)** Probabilistic atlas of the cerebellar lobules projected to a flatmap of the cerebellum from the SUIT Matlab toolbox (Diedrichsen and Zotow, 2015; http://www.diedrichsenlab.org/imaging/suit_flatmap.htm).

Experimental Design

To analyze mechanisms of visualization from immediate memory and rapid learning, sighted adults performed a sequence of alternating (i) *Explore and Memorize* (***EM***): perceptual exploration and memorization of complex graphic material (30 s) and (ii) *Visualization-from-Memory* (***Vis***): visualization of these images from memory of the prior exposure in ***EM*** (30 s), interleaved with fixation periods (20 s); this sequence was repeated three times for each image in a 3T Siemens Prisma scanner (see **Figure 3**). The images were scientific and artistic line drawings.

MRI Data Collection, Analysis, and Visualization

SUIT: Cerebellum-Specific Anatomical Processing

The cerebellum was segmented using the SUIT Matlab toolbox developed by the Diedrichsen Lab ([1]Diedrichsen, 2006; Diedrichsen et al., 2009, 2011; Diedrichsen and Zotow, 2015; King et al., 2019), based on a T1 anatomical scan after reconstruction by Freesurfer[2], which yielded a 1 mm isotropic resolution. This is the structural volume to which our fMRI data are registered, so once this volume is processed with SUIT, fMRI activation maps could be transformed to a standard flattened representation of the cerebellum, as depicted in **Figure 4**. Note that in the text positions of regions of interest (ROIs) will be referenced in the rostral/caudal and medial/lateral framework of the flatmap, e.g., those in lobules such as V, or VI will be referred as "rostral" relative to lobules such as VIII, IX, or X, which will be labeled as "caudal."

Data Acquisition and Pre-processing

Functional Magnetic Resonance Imaging Acquisition

MR data were collected on a 3T Siemens Prisma Fit magnet equipped with a 64-channel head + neck coil. BOLD responses were obtained using an EPI acquisition (TR = 2 s, TE = 30 ms,

[1]http://www.diedrichsenlab.org/imaging/suit.htm

[2]https://surfer.nmr.mgh.harvard.edu

flip angle = 45, voxel size = 2.5 × 2.5 × 2.5) consisting of 54 axial slices extending across the whole brain. Pre-processing was conducted using FSL (Analysis Group, FMRIB, Oxford, United Kingdom) and included slice-time correction and two-phase motion correction, consisting of both within-scan and between-scan 6-parameter rigid-body corrections. No spatial smoothing of the 3D fMRI data was imposed. Activation maps were averaged across the depth of cerebellar gray matter in 20% increments from white to pial surface models to generate the data shown on the 2D representations of the flattened cerebellum.

To facilitate segmentation and registration, a whole-brain high-resolution T1-weighted anatomical scan was also obtained for each participant (voxel size = 0.8 × 0.8 × 0.8 mm). White matter segmentation in this T1 scan was conducted using FreeSurfer and gray matter was generated with the mrGray function in the mrVista software package[3].

Functional Magnetic Resonance Imaging Time-Course Analyses

The data were averaged from the individual participant brains into the Montreal Neurological Institute average of 305 individuals[4]. The data were analyzed with the Stanford VISTA Lab software. The effective neural activation amplitudes (e.g., Friston et al., 1994) for each task across the repeats of multi-task sequences in the 1.5 h scan were estimated by the following procedure. A General Linear Model (GLM) consisting of boxcar neural task activations and an auditory stimulus regressor was convolved with an estimated hemodynamic response function (HRF) and fitted to the blood-oxygen-level-dependent (BOLD) responses along with a 4th order polynomial to remove baseline trends. BOLD amplitudes were defined as "task-positive" or "task-negative" according to the sign of the GLM beta fit.

Regions of Interest Activation Analysis

Regions of interest (ROIs) were generated for each of the visualization task-positive and task-negative BOLD activation regions in the cerebellum; the Talairach locations specified in **Table 1**. The cerebral Default Mode Network (DMN) ROI was taken from Yeo et al. (2011) 7-network cortical parcelation, and converted from a Freesurfer average subject to the MNI base anatomy used in this project. The effective neural activation amplitudes for each condition in each defined ROI was estimated by the same GLM procedure applied to the average signal across all voxels within the ROI.

Rapid Learning Slope Analysis

The rapid learning effect as expressed by changes in the strength of the BOLD signal across repeats for each task were analyzed by calculating the slope of a linear regression of the z-score of the GLM amplitude for each of the 3 repeats of a task. ROIs that were classified as "task-negative" had the sign of their responses inverted prior to slope calculations. Slopes were normalized to the mean absolute value of z-score of the 3 repeats, so that they represent fractional changes relative to the mean.

[3]https://web.stanford.edu/group/vista/cgi-bin/wiki/index.php/MrVista

[4]http://nist.mni.mcgill.ca/?{p}=957

TABLE 1 | Talairach Locations of the Cerebellar ROIs.

ROI name	*X* Tal	*Y* Tal	*Z* Tal
VI-pL	−22	−67	−25
VI-pR	23	−58	−24
CrusI-pL	−38	−62	−31
CrusI-pR	35	−56	−29
CrusII-pL	−40	−63	−48
CrusII-pR	17	−70	−40
VIIb-pL	−31	−60	−49
VIIb-pR	27	−61	−48
VIIIa-pL	−22	−54	−49
VIIIa-pR	28	−9	−49
VIIIb-pL	−17	−47	−45
VIIIb-pR	19	−42	−45
IX-pL	−14	−46	−44
IX-pR	12	−47	−44
X-pL	−23	−34	−38
X-pR	21	−31	−38
CrusI-nL	−36	−68	−32
CrusI-nR	33	−69	−32
VI-vermis-n	0	−63	−24
CrusII-nL	−24	−74	−37
CrusII-nR	24	−74	−36
IX-nL	−7	−49	−41
IX-nR	5	−47	−44

ROI, region of interest; Tal, Talairach coordinates; VI, VIIb, VIIIa/b, IX, X, CrusI, Crus II, cerebellar lobules; n, negative ROI; p, positive ROI; L, left hemisphere; R, right hemisphere.

Granger Causality Analysis Procedures

These analyses followed the procedures described in Cacciamani and Likova (2017). Starting from seed ROIs, Granger causality maps were generated in two directions, from the seed to every voxel in the brain (x to y), and from every voxel to the seed region (y to x), for each of three tasks (PE, MD, S) during the fMRI scan cycle. First, 50-s temporal segments of BOLD data were extracted starting at the onset of each 30-s task through the end of the 20-s rest interval following the task (in order to account for any task-related functional connectivity effects that may persist into this interval). The 2-s repetition time (TR) gave were 25 BOLD volumes in these segments, from which the average time course of all voxels that were members of the seed ROI was computed. Multiple linear regressions were performed to fit the 2nd-25th volumes of each voxel in the brain as a function of the 1st-24th volumes of themselves and as a function of the seed ROI, plus a constant term (x to y), and analogously for the y tox direction. Regression coefficients between the ROI and these individual voxels were converted to z-scores by dividing by the estimated standard error of the coefficient. Those with z-scores sufficiently different from zero implied a causal linkage (Granger, 1969), with the sign of the z-score indicating whether the causality was congruent with or inverse to the source signal (see section "Results" for details).

For pairwise ROI waveform Granger causality analyses, the "full" model containing the prior time points both ROIs was compared to a "reduced" model containing only the prior time

point of the ROI being modeled. The variance ratio of reduced and full models was tested against a null hypothesis of 1, with *p*-Values coming from the F distribution. The *p*-Values were converted into z-scores based on the standard normal distribution in some analyses for ease of interpretation.

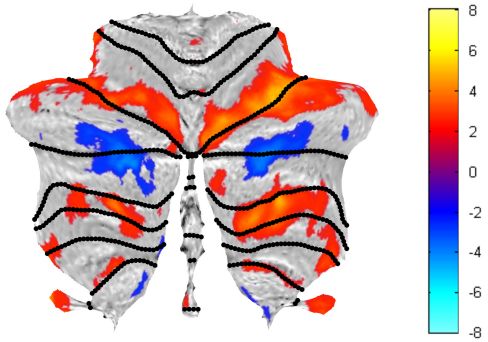

FIGURE 5 | Cerebellar flatmap representation of the average activation across the three Visualization repeats, thresholded at z-score of ±0.5. Positive BOLD activation coded in warm colors and negative BOLD activation in cool colors. The regions of activated voxels within each lobule were used to define the ROIs for further analysis.

Rapid Connectivity Reorganization

The time course of the connectivity reorganization was accessed by the *density* of causal connections in a network of ROIs where the pairwise *p*-Value of Granger Causality as described above was below a specified threshold. *Connection density* among a particular network of ROIs was defined as the number of connections divided by the total number of ROIs in the network.

RESULTS

Cerebellar Network for Visualization From Memory

A well-structured visualization network of activated and suppressed BOLD regions was identified in the cerebellum (**Figure 5**). This visualization network involves both *task-positive* (see **Figure 6**) and *task-negative* (see **Figure 7**) regions. Their BOLD response characteristics were analyzed as described in the following sections.

Average GLM Cerebellar Activation Patterns

The average BOLD activation signal for each ROI was analyzed by the standard general linear model (GLM) approach, with a separate regressor for each of the six 30 s task periods

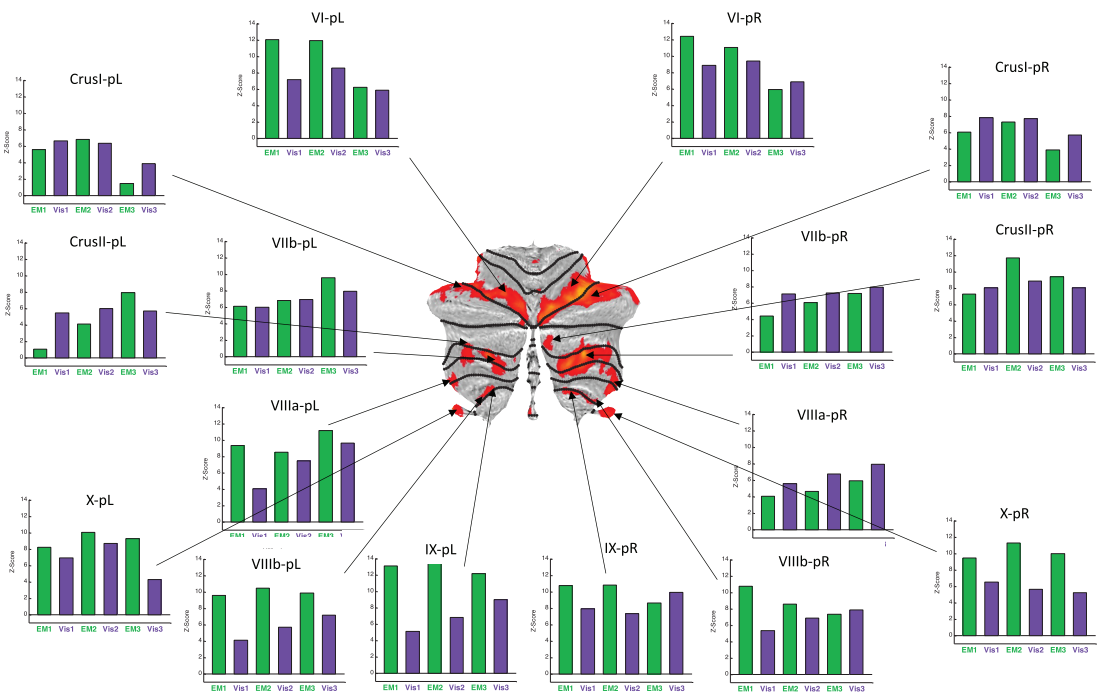

FIGURE 6 | Activation patterns for the positive cerebellar ROIs identified in the present protocol. *Visualization* (***Vis***) and *Explore and Memorize* (***EM***) task periods are coded by the **green** and **purple** bars, respectively. Note that the activation strengths in both tasks was generally similar for left and right hemisphere in the most rostral and caudal ROIs (in the flatmap framework). Note that the responses are plotted as z-scores. For this sample, z-scores of >2.45 are significant at $p < 0.05$ (two-tailed) and z-scores >5.95 are significant at $p < 0.001$ (two-tailed), etc. All specified ROIs reach the higher criterion for significance in at least one repeat in each of the tasks.

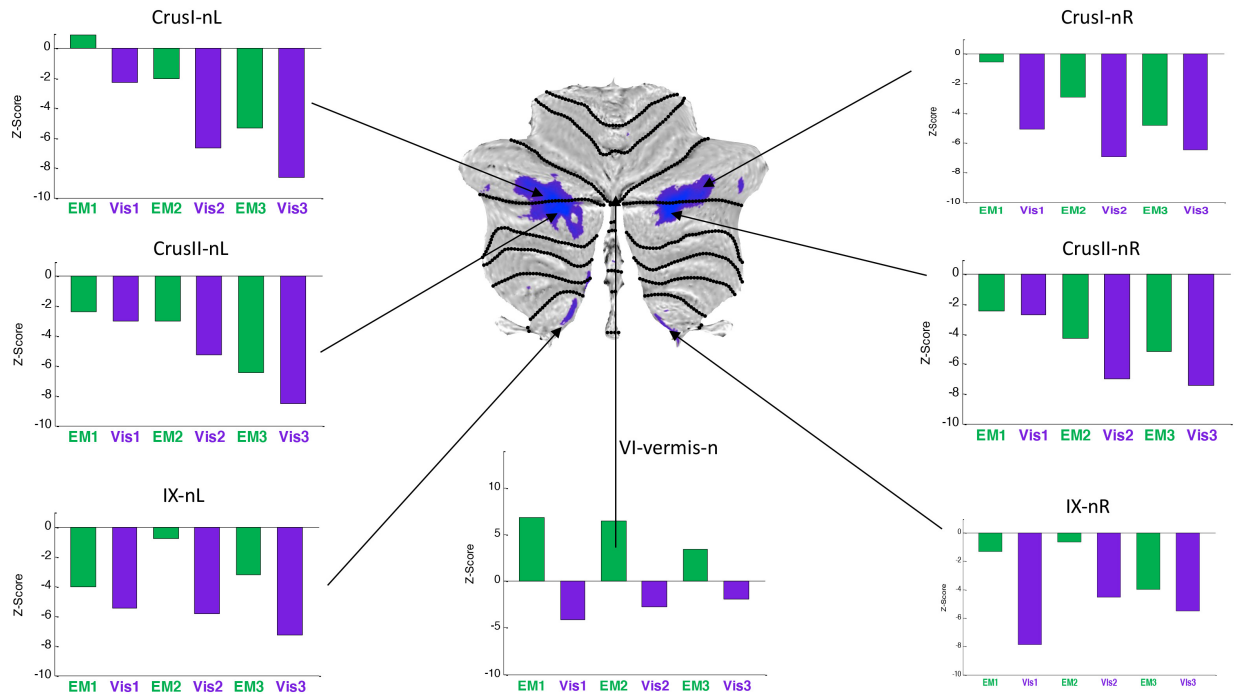

FIGURE 7 | Activation patterns for the *task-negative* cerebellar lobular ROIs, expressed as z-scores in the same format, and to the same statistical criteria, as for **Figure 6**. Note that, the responses were negative for both *Visualization* (***Vis***) and *Explore and Memorize* (***EM***) tasks, and tended to become increasingly negative over the three repeats in Crus 1 and Crus II bilaterally. To the significance criteria specified in **Figure 6**, responses for *Vis* in all specified negative ROIs reach the higher criterion for significance in at least one repeat, except for the VI-vermis-n ROI, where ***EM*** reached this criterion. Lobule IX showed a hemispherically asymmetric pattern in both tasks, as opposed to the symmetric pattern in Crus I/II, and to the predominant case for the task-positive ***Vis*** ROIs of **Figure 4**. The VI-vermis-n ROI produced weak negative ***Vis*** responses, but in contrast the rest of these ROIs, its ***EM*** responses inverted to positive activation; in general, both ***Vis*** and ***EM*** responses became significantly more negative over the repeats.

(see Materials and Methods). The z-scores of the average BOLD response from the GLM, averaged across the participants, are shown as the bar graphs placed around the respective cerebellar flatmap (see **Figures 6**, **7**). The green bars code is for the Exploration and Memorization (***EM***) epochs, and purple bars - for the Visualization (***Vis***) epochs. A z-score range of ± 1 corresponds to the standard error of the z-score means.

BOLD activation patterns for the task-positive cerebellar ROIs identified in the present protocol are shown in **Figure 6**, averaged over the battery of images used in the study. Note that in most cases the engaged ROIs exhibited bilaterally symmetric response patterns. These responses exhibited significant changes as function of task repetitions, showing the tendency to significantly increase over the repeats in some ROIs, or to decrease in others. Importantly, in many cases these tendencies were different for the ***Vis*** and the ***EM*** task sequences within a particular ROI, showing that this learning manifests task-specificity, as is further analyzed below. These tendencies represent a *rapid evolution* of the cerebellar response strengths with task repetitions, reflecting plastic reorganization in cerebellar involvement over this short time scale as a form of rapid learning.

Average response patterns for the cerebellar ROIs suppressed in ***Vis*** are shown in **Figure 7**. The responses of all of these ROIs - except that of lobule VI-vermis-n - were also negative in the ***EM*** task. Note that the strength of the response in most ROIs systematically changes over the three task repetitions. In particular, the suppressed Crus I and Crus II ROIs responses tend to become increasingly negative over the repeats in both the ***Vis*** and ***EM*** tasks. ***Vis*** generated significantly stronger responses than ***EM*** in all task-negative ROIs (with the VI-vermis being the only exception).

Analysis of Rapid Learning Effects

To investigate the temporal evolution of the rapid learning effects seen in **Figures 6**, **7**, we analyzed the change in activation across the perceptual exploration and memorization, ***EM*** and across the visualization, ***Vis*** repeats in each region through a formal *slope analysis* (see Methods) separately for each task, and plotted in **Figures 8**, **9** below the slopes of the change of response strengths as a function of task repeats for the sets of ROIs from **Figures 6**, **7**, respectively. Slopes are coded in terms of ***absolute*** BOLD response strength, of either negative or positive sign, so that an increasing slope for a *task-negative ROI* implies that the BOLD response strength is becoming increasingly negative.

For the ***Vis*** task sequence, the ***task-positive*** **ROIs** in the left lobules VIIIa, VIIIb, and IX had significant slopes (**Figure 8**), implying that they had increasing response strength as the learning proceeded. Note that for the Vis task sequence (**Figure 8A**), three ROIs in the left lobules VIIIa, VIIIb, and IX had significant positive slopes – increasing response strength as

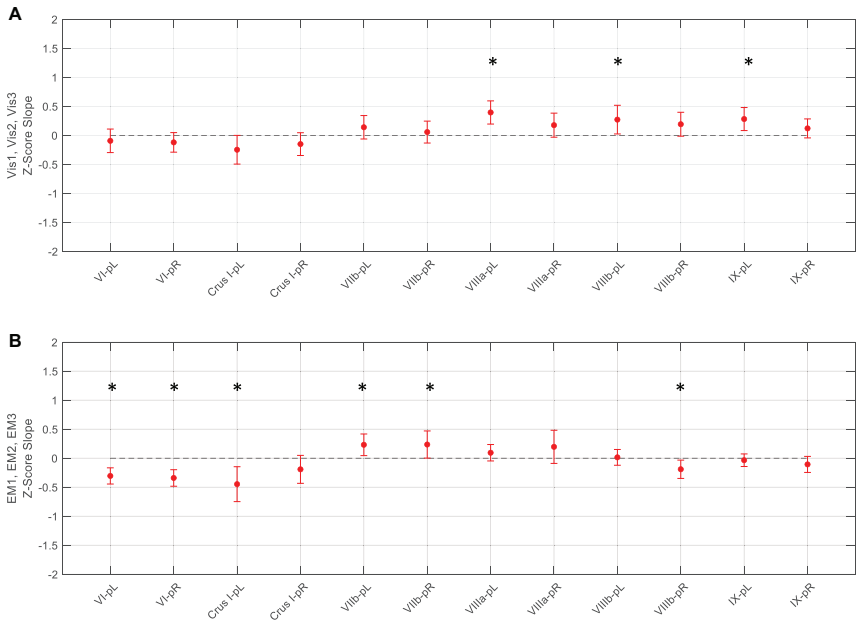

FIGURE 8 | Slopes of the evolution of average response strengths (red dots) for the task-positive ROIs from **Figure 5** as a function of task repeats for the ***Vis* task** (**upper panel A**) and ***EM* task** (**lower panel B**). Note that for the ***Vis*** task sequence **(A)**, three ROIs in the left lobules VIIIa, VIIIb, and IX had significant positive slopes - increasing response strength as the learning progressed. In contrast, the ***EM*** task sequence **(B)**, showed both significant decreases and increases in different ROIs during learning. Error bars are 95% confidence intervals for the difference of the slopes from a zero-slope; asterisks indicate significant slopes at $p < 0.05$.

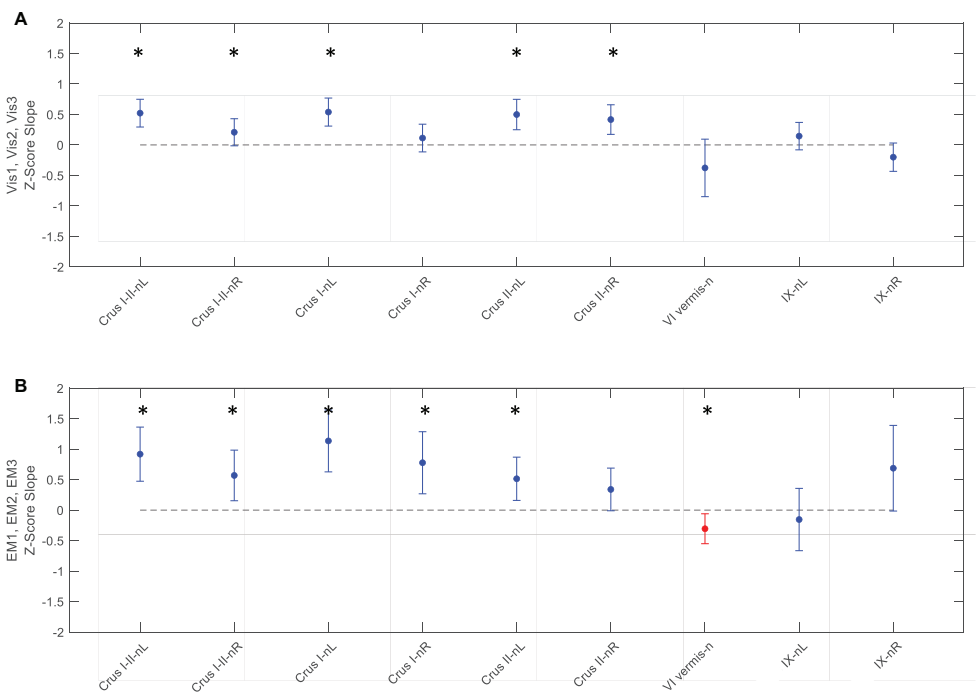

FIGURE 9 | Slopes of the evolution of response strengths (blue dots) for the task-negative ROIs from **Figure 6**, with the same format and significance criteria as for **Figure 8**. One ROI had positive activation (red dot) for the ***EM*** task **(B)**. Note that most of the task-negative Crus ROIs had significant slopes for the ***Vis* task** sequence **(A)**, with increasing negative response strength as the learning proceeded, thus deepening the suppression in these regions. A similar picture, with even greater suppression, is seen for the ***EM* task** sequence **(B)**. Asterisks indicate significant slopes at $p < 0.05$.

the learning progressed. In contrast, in the EM task sequence (**Figure 8B**), the first three (rostral) ROIs – in lobules VI left/right, and Crus I, left - showed significant decreases, i.e., negative slopes, as did the most caudal ROI (VIIIb, right), indicating reduced involvement with learning. Two ROIs, on the other hand – VIIb L/R – showed significant increases during the EM repeats, implying increased cognitive involvement during learning.

In contrast to the task-positive ROIs, the slope analysis in the *task-negative* ROIs revealed stronger bilateral learning effects for both ***Vis*** and ***EM*** tasks. Slopes of the evolution of response strengths for these ROIs are shown in **Figure 9**. There were significant slopes for the large task-negative (Crus I and Crus II) ROIs for the ***Vis*** task, implying increase of the suppression strength in these regions as the learning proceeded. A similar reorganization pattern was seen for the ***EM*** task sequence. Note that short-term learning effects more complex than a first-order assessment (i.e., than linear slopes) are beyond the scope of this analysis.

Granger Causal Connectivity Analysis

It is important to have clear terminology for the respective polarities of the BOLD activity in the source brain region, the polarity of the causal influence, and the polarity of the effect in the recipient brain region. Thus, for the BOLD activity, we will use the terms "positive BOLD" (or "activation") for an increase from the resting level, and "negative BOLD" (or "suppression") for a decrease from the resting level. Visualization task-positive and visualization task-negative networks are analyzed in Section "Granger Causal Connectivity Analysis for the Task-Positive Network" and "Granger Causal Connectivity Analysis of the Task-Negative Network," respectively (Note that "suppression" is used here in the sense of a relative reduction, not absolute elimination).

For causal influences, we will use the term "*congruent* causal influences" for those that provide a positive correlation with the source activity, and "*inverse* causal influences" for those that provide a negative correlation with the source activity. The rationale for this terminology is that the source signal could be either positive or negative BOLD, so that a congruent influence will itself be positive or negative, respectively, according to the sign of the source signal, while an inverse influence will be the converse (negative for a positive source, and vice versa). Moreover, the effects of these influences could correspondingly be facilitatory or inhibitory according to the sign of the BOLD signal in the recipient brain region.

Granger Causal Connectivity Analysis for the Task-Positive Network

Visualization From Short-Term Memory

Average Granger Causal connectivity was analyzed separately for each repeat during the *Visualization* task sequence, and was followed by an innovative analysis to assess if there was a rapid learning reorganization in the connectivity over the task repeats. The directed Granger connectivity for the task-positive cerebellar ROIs of **Figure 6** with each other, and with the left and right hemisphere ROIs for the Default Mode Network (DMN) (which has been shown to have strong connections with Crus I/II of the cerebellum; e.g., Buckner, 2013), are shown in circular plots in **Figure 10**.

For the first Visualization repeat (***Vis 1***), the congruent causal influences were primarily directed from many cerebellar ROIs to Crus II and lobule VIIIa/b ROIs on the left, and to the lobule X ROI on the right side, with no connections either to or from the cortical DMN (**Figure 10A**, upper row). The inverse causal connectivity for these ROIs had a dramatically inverted pattern, with virtually all cerebellar ROIs sending inverse influences to the cortical DMN ROIs bilaterally, and none inversely influencing each other (**Figure 10A**, bottom row); both the density and the strength of these decreased dramatically over the repetitions.

In the second Visualization period (***Vis 2***) the directed connectivity was similar to that for ***Vis 1***, but with notable modulations (**Figure 10B**). The intra-cerebellar *congruent* connectivity increased significantly relative to ***Vis 1***, with the main congruent influences being from the lobule VIIIa and VIIb ROIs to the rest of the cerebellar ROIs (**Figure 10B**, upper row). The cortical DMN ROIs again remained unconnected in either direction. The *inverse* connectivity generally replicated the pattern to that for ***Vis 1*** repeat, but with notably reduced strength throughout (**Figure 10B**, lower row).

In the last Visualization repeat (***Vis 3***) the *congruent* directed connectivity retained the general bilateral pattern of ***Vis 2*** (**Figure 10C**), but with progressive differentiation between the caudal cerebellar ROIs, whose intra-cerebellar influences shifted to involve bilateral lobules VIIb-L/R, VIIIa-R influencing the more caudal ROIs (VIIIb and IX), and lobule VI-L/R strongly influencing lobule IX; while the rostral ROIs VI and Crus I-left, received fewer and weaker influences from the caudal ones. The cortical DMN ROIs again remained unconnected in either direction (**Figure 10C**, upper). The *inverse* connectivity, on the other hand, further weakened from its pattern in ***Vis 2*** (**Figure 10C**, lower).

Exploration and Memorization

In the task-positive network, the lack of any involvement of the cortical DMN ROIs represents the main general similarity of the directed ***congruent*** causal influences for ***EM*** to that for ***Vis*** (**Figure 11**). For ***EM 1***, the congruent causal influences are directed mainly to lobule VIIIa/b on the left side, bilateral Crus 1 and right lobule X (**Figure 11A**, upper), with the most rostral and caudal lobules - VI and bilateral IX - being the main sources of these causal influences. For the *inverse causal influences* from/to the ***Vis 1*** ROIs, the pattern is a weaker version of the inverted pattern for ***Vis 1***, with most causal influences directed from the cerebellar ROIs toward the left DMN ROI (**Figure 11A**, lower).

In ***EM1***, Crus I bilaterally, lobule VIIIb left, and X right were the main hubs of converging *congruent* influences, the DMN not either impacting or being impacted by *congruent* cerebellar influences, however, DMN was the target of all *inverse* causal influences.

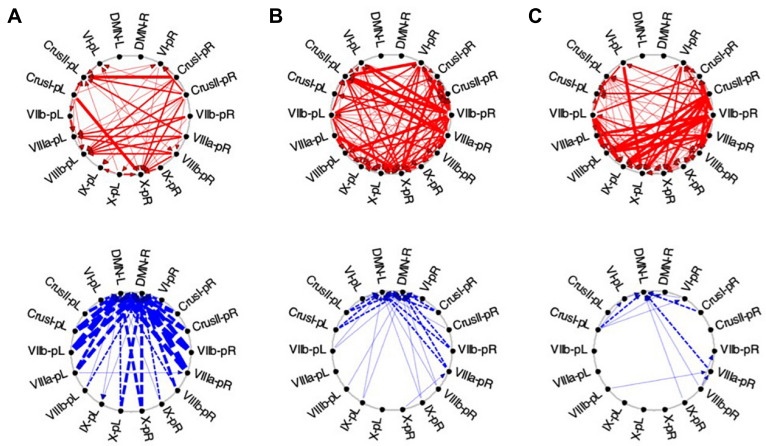

FIGURE 10 | Average Granger causal connectivity in *Visualization* (*Vis*) for the *task-positive cerebellar ROIs* with each other and with the *cortical DMN*. Connections are shown as arrowed lines if the directed connectivity is significant at $p < 0.05$, with line thickness coding connectivity strength, and red/blue color coding whether the influence is congruent or inverse relative to the BOLD signal (in separate upper and lower plots). **(A–C)**: Granger causal connectivity for *Vis 1*, *2*, *3* (the first through third visualization repeats). There is no congruent connectivity to the DMN in this task-positive ROIs, while the dominant inverse connectivity flows from almost all of these ROIs to the DMN initially, decreasing dramatically with task repeats.

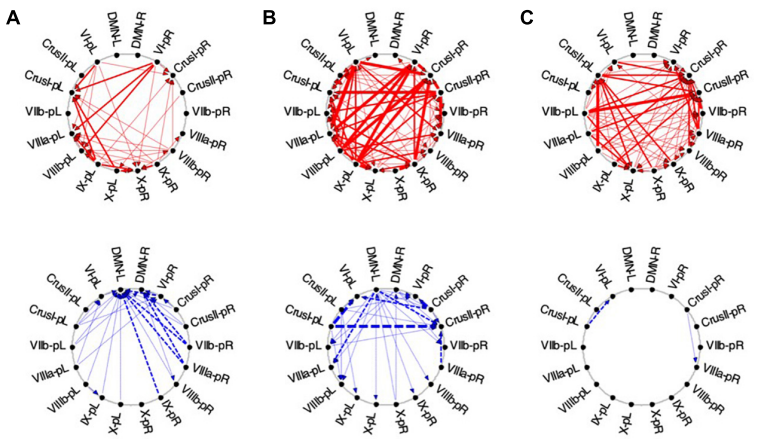

FIGURE 11 | Average Granger Causal connectivity for the perceptual *exploration and Memorization* **(*EM*)** task in the *task-positive* network; shown with the same format and significance criteria as for **Figure 10**. The connectivity patterns had some general similarities to that for the *Vis* task in **Figure 10**, but also major differences, in that the dominant inverse connectivity flowed from the DMN to these ROIs in the second repeat.

As was the case for Vis 2, the congruent causal connectivity for EM 2 strengthened relative to EM 1, but now primarily between mid-caudal to rostral ROIs (VIIIa/b, VI and Crus I), with the cortical DMN ROIs remaining almost entirely disconnected (**Figure 11**, upper row). The inverse causal influences, however (with respect both to EM 1 and to Vis 2), predominantly headed from the DMN ROIs back to the Crus I and lobule VIIIa/b ROIs (**Figure 11**, lower row).

By the third EM period, the pattern reorganized again, with the intra-cerebellar congruent influences now focusing on the right hemisphere ROIs, though still failing to connect with the cortical DMN ROIs at all (**Figure 11B**, upper). The inverse influences almost entirely dropped away (**Figure 11B**, lower).

Granger Causal Connectivity Analysis of the Task-Negative Network

Visualization

The average Granger causal connectivity for the *task-negative* network during visualization are shown in **Figures 12**, **13**, but it should be reiterated that the *congruent* causal connectivity (red arrows) now represents a negative influence on the recipient ROI, since it is deriving from a negative (or suppressive) BOLD signal. The *inverse* causal connectivity (blue arrows), on the other hand, represents an inversion of the negative influence of the source ROI, and hence a positive signal at the recipient ROI.

Initially, the *congruent* drive for the task-negative network mainly flowed from DMN to the Crus I, Crus II-nR and

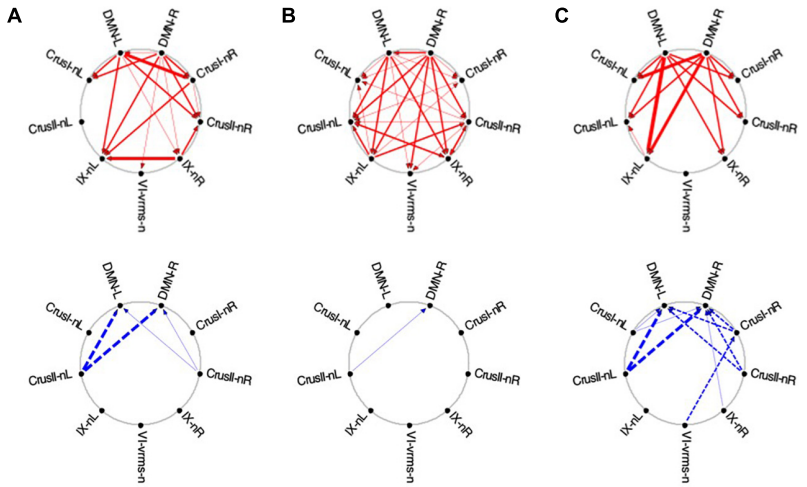

FIGURE 12 | Average Granger causal connectivity for *Visualization* in the *task-negative network* (shown in the same format and significance criteria as for **Figure 10**). Upper row: Congruent *causal influences* within the network of cerebellar ROIs and the cortical DMN. Lower row: Inverse *causal influences*. The Granger Causal Connectivity demonstrates rapid network reorganization over the *visualization* task repeats. The DMN in strongly involved bilaterally, sending congruent GC influences to these task-negative ROIs during all three repeats, and receiving weak inverse influences from the Crus ROIs.

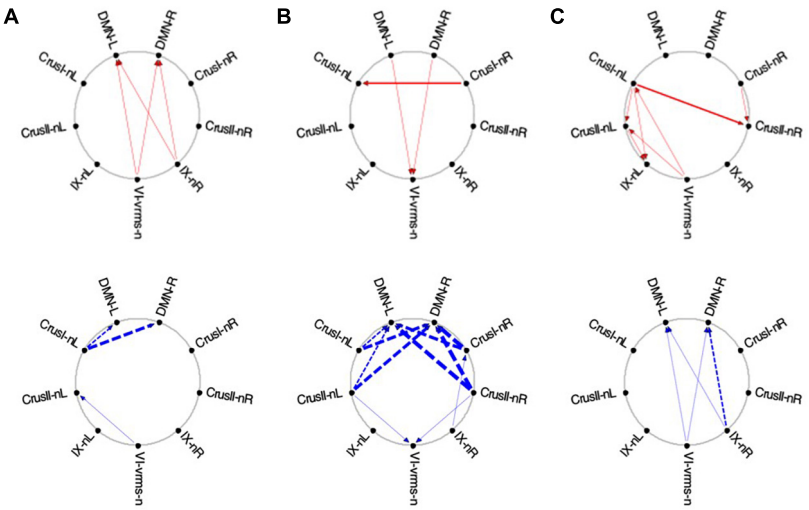

FIGURE 13 | Average Granger causal connectivity maps in the *EM* condition for the task-negative network (shown in the same format and significance criteria as **Figure 10**). The congruent influences were dramatically weaker than for the visualization task, while inverse influences were reorganized. Influences flow inconsistently from and to the DM at different times, but strongly to the DMN from the Crus ROIs for inverse influences during the second repeat.

lobule IX ROIs (**Figure 12A**, upper row), with a reciprocal influence back from Crus I-nR to DMN-R. *Inverse* influences fed back from Crus II to the DMN ROIs (**Figure 12A**, lower). In ***Vis 2***, the *congruent* drive from the cortical DMN ROIs strengthened (**Figure 12B**, upper row). *Inverse* influences were almost absent for these task-negative ROIs (**Figure 12B**, lower). Remarkably, however, by ***Vis 3***, the pattern of reciprocal connectivity focused entirely strong *congruent* influences flowing bilaterally from the cortical DMN ROIs to all the cerebellar ROIs in the network (**Figure 12C**, upper row), while reciprocal *inverse* influences from Crus I/II flowed back to DMN (**Figure 12C**, lower row).

Exploration and Memorization

Finally, for the ***EM*** task, its task-negative network showed reduced connectivity as a whole. Across all task repeats, the *congruent* influence in ***EM 1*** was dramatically weaker (**Figures 13A-C**, upper) than was seen in the ***Vis*** conditions in **Figure 10**. The *inverse* influences were somewhat stronger, heading back to the DMN ROIs (**Figures 13A-C**, lower). Notably, in ***EM 2***, the *congruent* DMN influences have largely evaporated (**Figure 13B**, upper), whereas strong *inverse* influences now head from both Crus I and Crus II bilaterally to the DMN ROIs (**Figure 13B**, lower). This pattern closely resembles that in ***Vis 3***

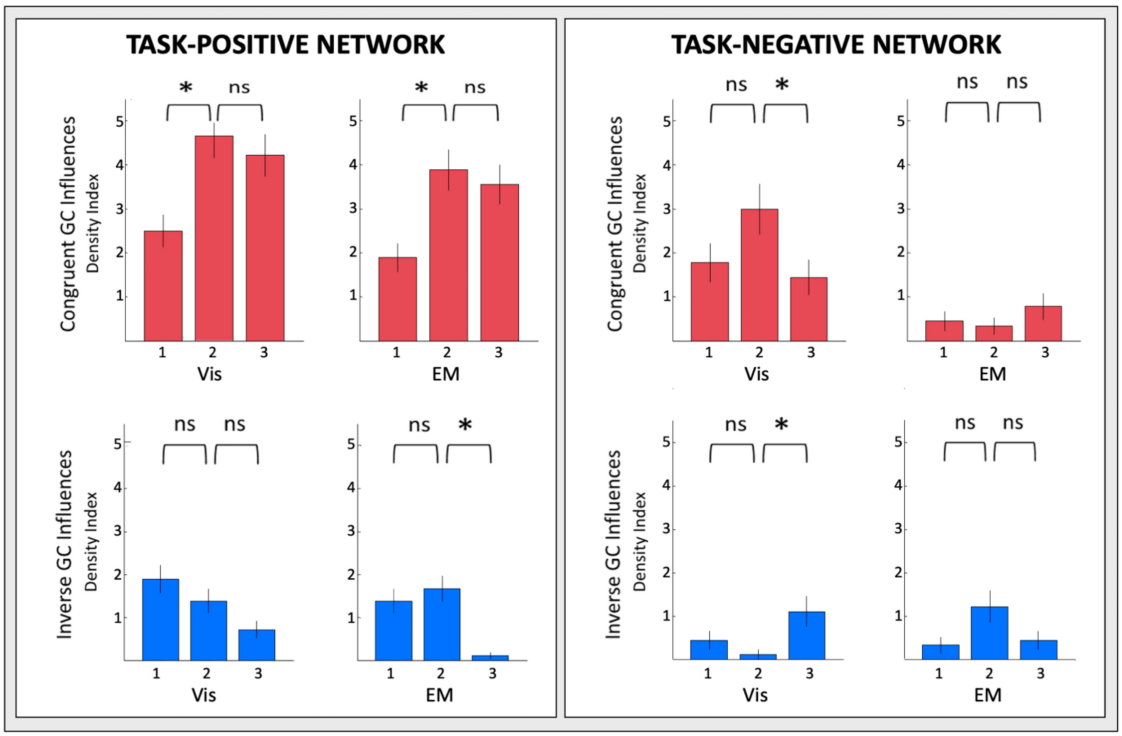

FIGURE 14 | Overview of the density of connections under each circular plot of **Figures 9–12**. Error bars are 1 SEM of the counts. Sequential pairwise differences significant at $p < 0.05$ are indicated by asterisks.

above (**Figure 11C**, lower row). By ***EM 3***, the *congruent* influences have disappeared, with some Crus I, Crus II and IX interconnectivity appearing (**Figure 13C**, upper), and reciprocal *inverse* influences run from Crus II back to the DMN (**Figure 13C**, lower).

Evolution of the GC Connectivity

The changes of the GC connectivity pattern over task repeats were quantified in terms of ***connectivity density***, or the number of significant connections relative to the number of ROIs in the task-positive or task-negative networks in each condition. A summary overview of the numbers of significant GC influences in each condition is provided in **Figure 14**. For the *task-positive* network, the *congruent* GC influences (**Figure 14**, upper left plots) increased significantly from ***Vis 1*** to ***Vis 2***, then does not change significantly. The same pattern of ceiling in the third repeat is seen for the ***EM*** conditions. The *inverse* influences (**Figure 14**, lower left plots) showed a contrary pattern, decreasing almost linearly with repeat number, and significantly so from both ***Vis 1*** to ***Vis 2*** and ***EM 1*** to ***EM 2***.

For the *task-negative* network, on the other hand (**Figure 14**, righthand plots), the GC influences in general are significantly weaker than those for the ***Vis 1*** ROIs. The *congruent* influences in the visualization task (**Figure 14**, upper right plots) show an inverted-V pattern: they first increased from ***Vis 1*** to ***Vis 2*** and then decreased from ***Vis 2*** to ***Vis 3***, while there was no significant change in the very few ***EM*** congruent influences. On the other hand, the *inverse* influences in the ***Vis*** repeats (**Figure 14**, lower right plots), though only marginally significant, seemed to start low but to increase at the third ***Vis*** repeat, while the ***EM*** influences appeared to follow a weak form of an inverted-V function, peaking at the second repeat ***EM 2*** and then falling back again at ***EM 3***.

DISCUSSION

Our aim was multidimensional. First, we investigated whether the entirely cognitive, no-motor-response task of visualization from an immediately acquired memory of complex spatial structures (line drawings), engages the cerebellum. This investigation led to the establishment of a respective, wide-spread cerebellar network. Second, we examined the level of task-specificity of the cerebellum regions involved by running comparative analyses with the perceptual exploration and memorization of the drawings that had to be later visualized from memory. Third, new insights about the cerebellar network organization were gained by Granger Causal Connectivity analysis, which determined the directed causal influences among the network nodes; furthermore, the causal interaction of the cerebellar networks with a key large-scale cortical network, such as the DMN was studied as well. Fourth, rapid learning effects on both the BOLD response reorganization in each region of interest, as well as at the higher – network – level, were investigated. Taken together, this array of analyses provides novel and expansive insights into

the entirely cognitive functions, such as mental visualization from non-motor memory in the cerebellum, and its macroscale functional neuroanatomy. To our best knowledge, this is the first study of cerebellum reorganization on the very short time scale of immediate non-motor learning through visualization.

Visualization-From-Memory in the Cerebellum

Overview

Cerebellar Macroscale Organization

First, the results will be interpreted in the basic *framework of macroscale organizational principles of the cerebellum,* developed by Guell and Schmahmann (2020), which summarizes a wide range of data on cerebellar activation patterns into a scheme of *motor* and *non-motor* cerebellar function (**Figure 1**). This scheme shows that cerebellar lobules 1-VI and VIII are involved in motor processing of various kinds, while lobule VI/Crus I, Crus II, VIIB and IX-X are involved in diverse aspects of cognitive (non-motor) processing.

Cerebellar Functional Boundaries

Second, the results are further discussed in the context of *cerebellar functional boundaries and organization*, based on the landmark multidimensional investigations of cognitive and motor functions in the cerebellum (Diedrichsen and Zotow, 2015; King et al., 2019). To characterize the functional diversity of the cerebellum, and determine if it is organized into *distinct functional subregions*, they ran a Multi-Domain Task Battery (MDTB) battery of 47 unique conditions, thus providing an extensive atlas of cerebellar function to which the present results can be related.

Cerebellar Flatmap

The relative locations of the involved lobular and sub-lobular ROIs are referenced in the context of the cerebellar flatmap used for functional atlases.

As a whole, the analysis showed that memory visualization powerfully engages a network of positive and negative sub-lobular regions in the human cerebellum, and drives rapid learning at both local and network levels.

Visualization-Positive Network

First, in terms of the cerebellar *macroscale organization*, the *task-positive* visualization network (**Figure 6**) encompassed regions across all three *non-motor* territories (lobules VI-Crus I; lobules Crus II–VIIB; and lobules IX–X), plus - to some degree – the "*second motor* representation" (lobules VIII) of Guell and Schmahmann (2020) (**Figure 1**; but see, e.g., Brissenden et al., 2018, and King et al., 2019, below for the involvement of these lobules in non-motor functions as well). Notably, the largest positive visualization clusters were in the *non-motor* regions along most of lobule VI/Crus I border bilaterally, and in lobule VIIb. The clusters in lobule VIIIb gravitated to the borders with its neighbors – lobules IX and VIIIa. Well-structured clusters, in particular, followed the transitional region along lobules VIIIb/IX border bilaterally. Remarkably, the whole of lobule X was activated bilaterally – a rare occurrence in other fMRI studies of this tonsillar, which is usually only partially activated (e.g., Diedrichsen and Zotow, 2015; King et al., 2019).

Second, from the perspective of *functional boundaries* or the *cognitive descriptors* for the *functional regions* in the MDTB parcelation (King et al., 2019[5]), the complex pattern of the *positively only* activated network (**Figure 6**) in the present *visualization-from-immediate-memory* task, had some commonalities with the "*active maintenance*" *and* "*working memory*" patterns of the MDTB. In particular, the lobule VI/Crus I border and lobule VIIb ROIs activated in *visualization* are also involved in *active maintenance*: *working memory* paradigms have been previously found to activate a constellation of lobule VI, Crus I, and lobule VIIIa (Stoodley et al., 2012); a functional dissociation between both visual working memory and visuospatial attentional processing has been found within VIIb/VIIIa (Brissenden et al., 2018); and the nearby lobule VIIIb/IX border bilaterally is the main region activated in "*spatial imagery*" (King et al., 2019). The upper part of lobule X is implicated in tasks such as "*visual working memory*" and "*saccades*;" but again, note that uniquely, this lobule was fully activated in the current study.

This comparative analysis of the regions in the visualization-positive network is in line with a view of *cerebellar computational modules*, flexibly reconfigured as components in the architecture of different tasks.

Visualization-Negative Network

The *visualization-negative* network (**Figure 7**) exhibited a bilaterally symmetric pattern located entirely within *non-motor* (see **Figure 1**) cerebellar territories. The largest clusters run across the central section of the Crus I/Crus II border, accompanied by suppression of the most medial part of lobule IX.

First, it is interesting to find that, in the context of Guell and Schmahmann (2020) *macroscale functional anatomy* of the cerebellum (**Figure 1**), our task-negative visualization network (**Figure 7**), closely resembles a constellation of Crus I, II and lobule IX ROIs representing the cerebellar component of the *Default Mode Network (DMN)*. Consistent with this finding, the Granger Causal Connectivity analysis of cerebrum/cerebellar interactions revealed that, the DMN is the one that causally drives the suppression in the whole *Visualization-negative network* (**Figure 12**, top row).

Second, the results were further examined in the context of the *functional boundaries* delineated by the comprehensive Multi-Domain Task Battery flatmaps (King et al., 2019; see text footnote 5). A core component of our visualization-from-memory task is working memory (WM). Key modules of the Baddeley model of WM are the *visuospatial sketchpad* (pictorial information) and the *phonological loop* (verbal, phonological information), which are proposed to store information separately in memory. Further, the *episodic buffer* integrates these two types of information for more effective transfer from and to long-term memory (Baddeley, 1992, 2003; Lohr and Gall, 2008).

In terms of this model, our visualization of *visuo-spatial, pictorial* stimuli, accompanied by neither spoken nor written

[5]http://www.diedrichsenlab.org/imaging/mdtb.htm

verbal information, and requiring no response (neither motor nor non-motor) to be planned or executed, should engage the *visuospatial sketchpad*, not the phonological loop. Moreover, note that the task of recall in our experiment is also spatial/pictorial – the participants have to "*see*" the explored images on their *mental "sketchpad,"* not to name or recognize them in any other form.

In spite of our heavily visuo-spatial/pictorial paradigm, is it still possible that some covert verbal form of processing, such as (covert) naming, may explain the results? According to the Dual-Coding Theory proposed by Allan Paivio in 1971, both visual and verbal information can be used to enhance the storage and recall of information (e.g., Paivio, 1971, 1986) (There are, however, limitations of the dual-coding theory and alternative theories, such as the propositional and the common coding theories.) Marvel and Desmond (2010) proposed that "the cerebellum enhances working memory by supporting inner speech mechanisms," and that it is tied to verbal working memory. This concept is elaborated in the Marvel et al. (2019) review, which emphasizes that this motor system support includes cerebral regions that are involved in motor planning and preparation, together with their cerebellar counterparts. Such motor planning and preparation activities further include decision making, attentional and choice activities, which are generally considered to be cognitive processes, although specific to the motor response domain.

Our study was not designed to test hypothetical contribution of any inner/covert verbal mechanisms, so we can only speculate on this issue. First, as summarized above, the experiment does not involve any (overt) motor or verbal stimulus component, preparation or execution task, and maximally isolates any potential covert form of these. In principle, it is possible to have covert naming but if that was happening, it would occupy only a negligibly small segment of the 30 sec long visualization phases, and would not explain the strong prolonged activation in non-verbal working memory sub-lobular regions, such as along the VI-Cruz I border or lobule VIIb.

Second, previous studies have found strong lateralization of cerebellar activation during speech activity. Our visualization response pattern, on the other hand, is almost entirely bilaterally symmetric, implying that it is not mediated by any form of verbal response.

Third, more detailed analysis in the terms of the cognitive descriptors for the ten functional subdivisions in the MDTB parcelation, where each is described by the three features that best characterize it (King et al., 2019; see text footnote 5), shows that the negative signal that we found in Crus I/II, in particular, represents *suppression* of the functional subdivisions for narrative event sequence network, such as based on a story telling vs. math subtraction, and language processing (left hemisphere), and suppression of word comprehension, verbal fluency, narrative, word comprehension and language processing (right hemisphere). Importantly, this finding implies that the task of visualization of memorized spatial/pictorial information may need, and even benefit from, the active *suppression* of competing systems of a linguistic nature.

In summary, though there could be some covert motor component, such as inner speech, underlying activation in cognitive tasks, this is not found for the present task. As reviewed above, there is a systematic distinction between the cerebellar lobules engaged in cognitive tasks vs. those involved in motor tasks (e.g., Guell and Schmahmann, 2020). Furthermore, large test battery studies, such as the 47-conditions in King et al. (2019), demonstrate a broad variety of distinct activation patterns for a diverse array of cognitive tasks, implying that the mechanisms engaging the cerebellum cannot be put under the one common denominator of motor activity, be it overt or covert. Our analysis above, in particular, the finding of *active suppression* of the language related areas in the cognitive task of visualization of pictorial information, provides further support for this position.

The Pattern of Cerebellar Activation/Suppression

A possible expectation could be that the visualization activation/suppression pattern as a whole would resemble that of tasks such as *spatial imagery*, *object working memory*, or even mental manipulations such as *mental rotation*. This was not the case, however (see the functional atlas of King et al., 2019). The visualization pattern differed significantly from that for each of these tasks. There was some partial overlap, such as with a few regions of the (2-back) working memory task, however, the differences were dramatic.

Interestingly, the visualization activation/suppression pattern closely approximated the spatial map network in that atlas. What is in common between the *Visualization* and the *spatial map* tasks is that both deal with spatial structures. The complex line-drawing stimuli recalled *during Visualization*, can be put in the larger context of the representation of spatial maps. However, our *Visualization* task more closely corresponds to that of "*subsequent recall*," which is not what they measured. Beyond the similarity of the *Visualization* and "spatial map" activation patterns, there are differences. One main difference was found in VI-vermis, which is strongly activated in the "*spatial map*" task, as opposed to being *suppressed* in *Visualization*. The two tasks also differently engage lobule X - there was only a partial activation in "spatial map" vs. full activation in *Visualization*.

Thus, the present analysis shows that the task of *visualization-from-immediate-memory* engages a different and far more elaborate network of functional cerebellar regions than the previously studied tasks of similar categories.

Rapid Learning-Driven Cerebellar Reorganization in a Cognitive Task

Cerebellar Region Level: BOLD Response Changes in Each ROI

The slope analysis we developed for identifying a (first-order) systematic increase/decrease in response strength over the three repeats of the learning sequence revealed significant rapid learning changes in both ***Vis*** and ***EM***.

For the ***Vis*** task sequence, three *task-positive* ROIs in left lobules VIIIa/b and IX had a significant slope (**Figure 8**), implying that it had increasing response strength as the learning proceeded. Interestingly, a rapid learning effect, expressed as significantly negative slopes, was broadly present in the ***EM*** task sequence (three rostral and the most caudal right positive ROIs)

indicating reduced engagement with learning. This reduction may be interpreted as either task optimization or reduction of attention as the image became progressively more familiar through the processes of learning and memorization.

In contrast to the task-positive visualization ROIs, the slope analysis in the *task-negative* ROIs revealed stronger bilateral learning effects for both ***Vis*** and ***EM*** (**Figure 9**). In particular, positive slopes in the DMN-connected regions Crus I and II implied increase of the suppression strength in these regions as the learning proceeded. The reorganization pattern in the ***EM*** task sequence had similar characteristics.

Cerebellar Network Level: Rapid Reorganization of Causal Connectivity

The widespread activation in all sectors of the cerebellum in these visualization and perceptual/memorization tasks supports the extensive reports of cerebellar involvement in a variety of forms of cognitive processing (see above).

To investigate how these multiple cerebellar regions interact with each other, we used Granger Causal (GC) Connectivity analysis, which allowed us to establish not only the presence of an interaction but to determine its causal nature and direction. Furthermore, our examination was not limited to the "congruent" (or positively correlated) causal influences, as is most often done, but included the " inverse" (or negatively correlated) ones as well (see **Figures 10–13**).

In term of GC influences between the cerebral Default Mode Network and the cerebellar networks for the ***Vis*** and ***EM*** tasks, a remarkable result was that the DMN did not exercise any GC influence on any task-positive cerebellar ROI, but only on the task-negative ROIs Crus I, Crus II and lobule IX bilaterally. DMN received, however, inverse GC influences from both positive and negative cerebellar ROIs (**Figures 10–13**).

Furthermore, it was fascinating to uncover *rapid learning reorganization* even at the *network level* of causal influence. ROI-specific connections, their strength and even their directions were changing markedly over the learning repeats. To quantitatively capture some global effects, we developed a "*Density Index*," which reflects the "extent of communication," or proportion of GC influences, within each network. Significant rapid connectivity reorganization, as expressed by the Density Index, was found in the *task-positive network*, with similar Density Index profiles in ***Vis*** and ***EM*** for both their congruent and inverse GC connections: (i) the density of *congruent* causal interactions ramped up highly significantly from the first to the second repeat, with this increase staying sustained in the third repeat; (ii) the density of the *inverse* ones declined with repeats. On the other hand, the *task-negative network* showed a variety of density changes, with the stronger effect on its congruent ***Vis*** GC influences in an inverted-U form, picking up in the second repeat (see **Figure 14**).

Time-Scale of Reorganization

The present paradigm was targeted to explore possible reorganization in a cognitive task, and furthermore, to explore it on the *short time-scale* of a typical fMRI scan, instead of a time-scale of days or months. Thus, this study allowed us to "zoom in" to observe temporal evolution happening over just a few minutes, driven by the process of *cognitive* task repetition.

With respect to longer-term evolution, we have previously investigated the effect of 5 days of 2 h/day of specialized training - the Cognitive-Kinesthetic memory-drawing training in the blind (Likova, 2015). The fMRI assessments were run at *three time points*: (1) before starting the training, (2) immediately on completing the week's training, and (3) again after a two-month consolidation period without further training. The results revealed a remarkable temporal sequence of training-based brain reorganization in both the hippocampal complex and the temporal-lobe object-processing hierarchy just after the training, with the reorganization continuing to evolve over the prolonged consolidation period. These changes were not just statistically significant, but were often of the same order of magnitude as the activations themselves.

For example, a hippocampal pattern of profound learning-based transformations was strongly reflected in the primary visual cortex V1, with the retrieval function showing massive growth during blind memory-drawing as result of the Cognitive-Kinesthetic training and consolidation, while the initially strong hippocampal response during tactile exploration and memory encoding disappeared. Furthermore, after training, a cascade of discrete ventral regions in the form of an alternating local patch structure underwent radical transformations to reach complete functional specialization for either encoding or retrieval, implying a complex reorganization of the object processing sub-networks through the learning period. These results showed, for the first time, such a *learning-based* reorganization in the form of a *posterior-anterior cascade of* functionally *dissociated patches.* This novel finding of a multifold learning-based reorganization of the "temporal stream" is consistent with the model of the ventral stream as incorporating a number of recursive subnetworks (Kravitz et al., 2013), rather than being just a simple feedforward pathway.

In support of profound reorganization on the same timescale, a recent study (Stevenson et al., 2021) has shown that a similar duration (4-days) of training in the *motor* domain of acrobatic tasks increased both Purkinje-cell synaptogenesis and astrocytic volume in the rat cerebellum relative to a control group. Such cerebellar changes happening over only a *few days* were considered *"rapid"* in comparison to the *months* of typical motor training effects. In this context, the changes on the scale of minutes that we found in the current study as a result of a series of repetitions during fMRI scanning may have to be designated as *ultra-rapid*.

CONCLUSION

Overall, the results revealed a well-structured cerebellar network for *visualization from memory* for the first time. This network involved both activated and suppressed regions. Surprisingly, the generally overlapping *perception/memorization* network did not evoke the consistently stronger activation that might have been expected. All suppressive responses, in particular, were markedly stronger in visualization.

Remarkable rapid reorganization was observed in the response patterns over the task iterations in most cerebellar activation sites. In terms of the temporal evolution of the rapid learning process, some cerebellar sites showed significantly increasing activation as the learning through the task sequence progressed, while others showed significantly increasing suppression, revealing a progressive differentiation of the cerebellar responses. These effects were *task-specific*.

At a network level, both congruent and inverse causal connectivity influences were identified between non-motor cerebellar regions. Furthermore, our paradigm of interleaved sequences of task repeats revealed an (ultra) rapid reorganization in the cerebellar connectivity relationships as well as in their individual response strengths discussed above.

These multidimensional fMRI and connectivity findings provide a solid basis for a novel framework for the investigation of rapid cerebellar and cerebellar-cerebral reorganization during non-motor cognitive tasks. To our knowledge, this study is the first to reveal this form of (ultra) rapid non-motor/cognitive learning and neuroplasticity in the cerebellum, as well as being the first to investigate this process both at a sub-lobular regional level and at the level of causal network connectivity. Collectively, the findings offer important insights into fundamental questions of cerebellar function, and also have implications for the development of methods for enhancing the cognitive abilities of learning and memory. Further studies are needed to systematically address the evolution of learning-driven brain plasticity across time scales, tasks domains and learning approaches.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Smith-Kettlewell Institutional Review Board, Smith-Kettlewell Eye Research Institute. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL conceived and designed the study, led the project, analyses and interpretation, and wrote the manuscript. KM contributed to the data collection, run the analyses and subject management, and contributed to the interpretations. SN performed the MRI scanning and pre-processing. All authors discussed the experiment and the results, and contributed to the manuscript.

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Cortico-Cerebellar Hyper-Connections and Reduced Purkinje Cells Behind Abnormal Eyeblink Conditioning in a Computational Model of Autism Spectrum Disorder

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Empirical evidence suggests that children with autism spectrum disorder (ASD) show abnormal behavior during delay eyeblink conditioning. They show a higher conditioned response learning rate and earlier peak latency of the conditioned response signal. The neuronal mechanisms underlying this autistic behavioral phenotype are still unclear. Here, we use a physiologically constrained spiking neuron model of the cerebellar-cortical system to investigate which features are critical to explaining atypical learning in ASD. Significantly, the computer simulations run with the model suggest that the higher conditioned responses learning rate mainly depends on the reduced number of Purkinje cells. In contrast, the earlier peak latency mainly depends on the hyper-connections of the cerebellum with sensory and motor cortex. Notably, the model has been validated by reproducing the behavioral data collected from studies with real children. Overall, this article is a starting point to understanding the link between the behavioral and neurobiological basis in ASD learning. At the end of the paper, we discuss how this knowledge could be critical for devising new treatments.

Keywords: autism, associative learning, hyper-connectivity, system-level neuroscience, spiking neuron models, cerebellar-cortical circuit, sensory-motor cortex, prefrontal cortex

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1. INTRODUCTION

Autism spectrum disorder (ASD) is a neurobiological disorder characterized by difficulties in social communication and restricted behavioral patterns, often including stereotyped or repetitive motor movements, inflexible adherence to routines, and ritualized action practices (Lai et al., 2014; Romanczyk et al., 2016). Further, there may be hyper- or hypo-reactivity to sensory input (Dakin and Frith, 2005; Robertson and Baron-Cohen, 2017) and unusual learning trajectories (Shah and Frith, 1993; White et al., 2009; Baron-Cohen and Lombardo, 2017). In this regard, several works have demonstrated that ASD children show abnormal response on delay eyeblink conditioning (DEBC) (Sears et al., 1994; Oristaglio et al., 2013; Welsh and Oristaglio, 2016). DEBC is a learning paradigm consisting of an association between a conditioned stimulus (CS), typically a tone, and

an overlap unconditioned stimulus (US) eliciting eyelid closure, such as an air puff to the cornea. After repeated CS-US pair presentations, conditioned eyelid closure (conditioned response, CR) occurs as a response to CS. Full eyelid closure for the CR typically occurs close to the US onset time (Thompson and Steinmetz, 2009). During DEBC involving ASD children, the CR learning rate is higher in the ASD group than the typical development group (Sears et al., 1994). Additionally, the peak latency, defined as the time between CS onset and the CR signal maximum, occurs significantly earlier for the ASD group (Oristaglio et al., 2013; Welsh and Oristaglio, 2016). The neural mechanisms underlying this atypical learning behavior are not fully clear. This article uses an improved version of the physiologically constrained spiking neuron model of the cerebellar-cortical circuits recently proposed by Caligiore and Mirino (2020) to address this issue. The cerebellum is a fundamental processing unit for various cognitive and motor tasks (Ivry and Baldo, 1992). Several studies have demonstrated the importance of the cerebellum for the acquisition and extinction of CRs in DEBC sessions (see section 2.2.1). The learning capabilities of the cerebellum are related to plasticity mechanisms that change the synaptic weights of connections between different groups of cells (Mar, 1969; Albus, 1971; Ito, 1997). Notably, this work wants to underline the crucial role of cerebellar function from a more complex, systems-level perspective that fully acknowledges its close interplay with different brain areas (Caligiore et al., 2017; Lindeman et al., 2021). In particular, the model aims to demonstrate how two anatomic-physiological features of the autistic brain are critical to explaining the abnormal ASD learning path during DEBC. Firstly, the model reproduces the fewer number of Purkinje cells, often characterizing the autistic brain (White et al., 2009; Skefos et al., 2014; Hampson and Blatt, 2015). Secondly, it reproduces the effects of the cortico-cerebellar hyper-connectivity (Khan et al., 2015; Oldehinkel et al., 2019) also typically present in the autistic brain. The computer simulations run with the model show that the first neural feature is critical to explain the behavioral result on a higher CR learning rate showed by real ASD children (Sears et al., 1994). The second feature is instead critical to explain the results on the earlier peak latency (Oristaglio et al., 2013; Welsh and Oristaglio, 2016). These results represent a first step for understanding the relationship between the behavioral and neurobiological basis of learning in ASD. Notably, this knowledge could be critical for devising new treatments, as discussed at the end of the paper.

2. MODEL

2.1. Simulation Tools

The model was developed using the *PyNEST* (Eppler et al., 2009) Python programming language interface of the Neuron Simulation Tool *NEST* (Gewaltig and Diesmann, 2007). In particular, each neuron of the model was modeled through the *iaf_psc_exp NEST* function, reproducing the features of a leaky integrate and fire unit with exponential shaped postsynaptic currents (Tsodyks et al., 2000). The neuron dynamics are numerically integrated based on a computation time step of $t = 10$m. All arriving and transmitted spikes are limited to happen in the resulting time grid steps. Overall, the simulation takes 2,500ms.

TABLE 1 | Values of connection weights (w), external current (I_e) and connections delay parameter (d).

Connection weights	External currents	Delay parameters (Control/ASD)
$w_{CS\to GR} = 500$	$I_{e_{GR}} = 370$	$d_{CS\to GR} = 100/50$
$w_{CS\to DN} = 500$	$I_{e_{PC}} = 380$	$d_{CS\to DN} = 100/50$
$w_{US\to IO} = 100$	$I_{e_{IO}} = 370$	$d_{US\to IO} = 100/50$
$w_{IO\to PC} = -500$	$I_{e_{DN}} = 370$	$d_{DN\to M1} = 100/50$
$w_{IO\to DN} = 60$	$I_{e_{M1}} = [300, 365]$	
$w_{PC\to DN} = -7$	$I_{e_{mPFC}} = [300, 365]$	
$w_{DNr\to M1} = 100$		
$w_{DNp\to mPFC} = 50$		
$w_{Noise\to DN} = [0.1, 0.5]$		
$w_{GRr\to PCr} = 5$		
$w_{GRp\to PCp} = 20$		
$w_{mPFC\to M1} = 0.1$		

The $w_{Noise\to DN}$, $I_{e_{M1}}$ and $I_{e_{mPFC}}$ values were randomly chosen in the given range according to a uniform distribution. Thus, each simulated subject has different values for these parameters. The $w_{GR\to PC}$ and $w_{mPFC\to M1}$ values are those initial since GR-PC and mPFC-M1 connections are plastic.

Most of the model parameters assume the default values of the *NEST* neuron model *iaf_psc_exp*, reflecting the values of the related physiological parameters derived from studies with animals or humans. **Table 1** summarizes the parameters related to the connections between neurons and those critical to simulate the difference between ASD and control groups. The code of the model is accessible from this link https://github.com/ctnlab/cerebellum_autism_DEBC_model.

2.2. Model Architecture and Functioning

Nine neural populations of spiking neurons linked through excitatory and inhibitory connections formed the model system-level architecture (**Figure 1**). Of these, two represent the primary motor cortex (M1) and the medial prefrontal cortex (mPFC). The remaining seven neural populations reproduce the functioning of different parts of the cerebellum. The architecture mainly focuses on the cerebellar anatomical and physiological features while, for simplicity, it does not reproduce the thalamocortical dynamics. Two critical anatomic-physiological components characterize the model architecture: (i) a system-level organisation through parallel cerebellar-cortical circuits (see section 2.2.1); (ii) granule cells subpopulations with different time-sensitivity (see section 2.2.2). Below, we discuss in detail these two features.

2.2.1. Parallel Cerebellar-Cortical Circuits

The cerebellar model builds on well-established spiking neuron architectures (Antonietti et al., 2018; Geminiani et al., 2018). In particular, 1536 Granule cells (GR), 48 Inferior olive cells (IO), 48 Purkinje cells (PC), and 24 Deep cerebellar nuclei (DN) made it. The input signals go to GR and DN (CS) and IO (US) through connection weights, respectively, simulating the signal

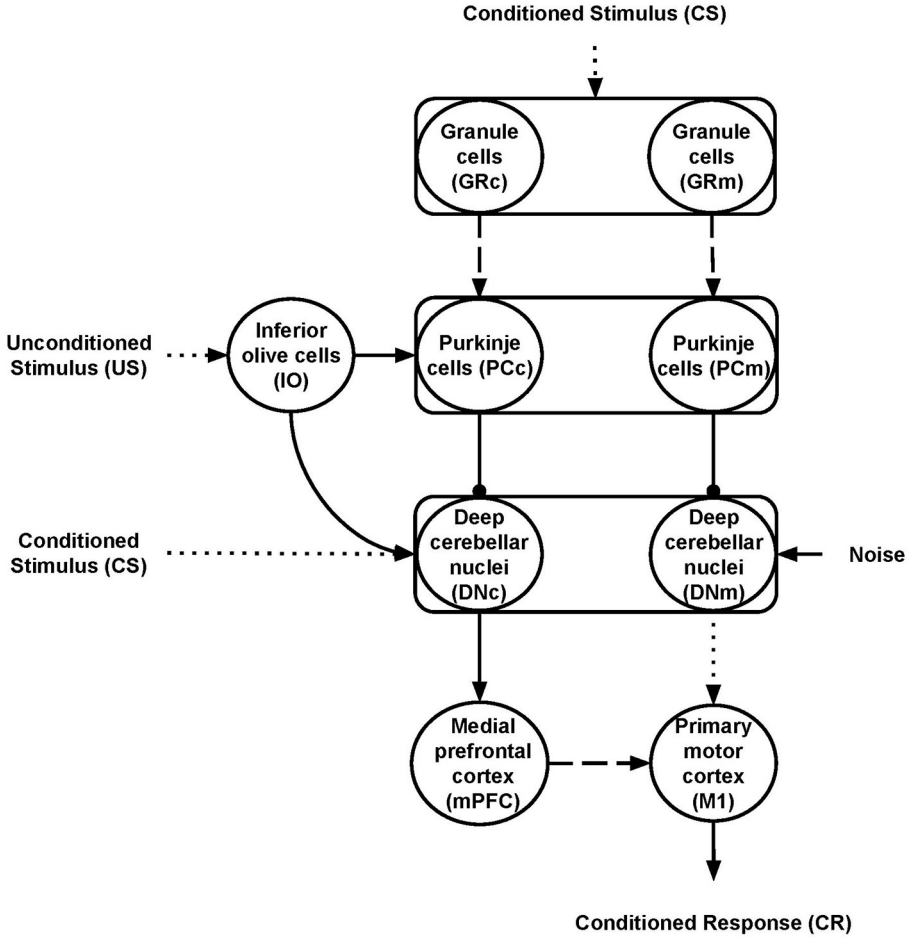

FIGURE 1 | Model architecture. The rectangles indicate the cerebellar regions; the circles represent the cerebellar, inferior olive, and cortical neural populations. The connections linking different areas can be plastic (dashed lines) or fixed (solid lines) or fixed and hyper-connected in ASD model (dotted lines); excitatory (arrows) or inhibitory (lines ending with a dot). The subscripts "m" and "c" indicate the motor and cognitive pathways, respectively.

preprocessing action of mossy and climbing fibers. In this way, the spreading of the activation through the cerebellar regions is only possible if there is some input (CS or US). Otherwise, all the cerebellar regions are silent and, in turn, mPFC and M1 are quiet too. The number of units within each region makes the simulations computationally feasible while resembling the biological ratios (DAngelo et al., 2016). Two parallel cerebellar-cortical circuits anatomically compose the model (**Figure 1**), each containing half of the total number of neurons: the motor pathway (GRm-PCm-DNm-M1); the cognitive pathway, including mPFC (GRc-PCc-DNc-mPFC-M1).

These two pathways process the signal with a different time-sensitivity (see section 2.2.2 below). Moreover, the cognitive pathway influences the system motor behavior through the connections linking mPFC to M1. This organization agrees with data suggesting that the cerebellum is connected with various parts of the frontoparietal cerebral network through a set of parallel circuits, channels (Middleton and Strick, 2000; Dum and Strick, 2003), managing different cortical contents including, for example, actions or memory patterns (Strick et al., 2009; Caligiore et al., 2013, 2017). In particular, Bernard et al. (2014) firstly report a motor network involving the dorsal dentate, anterior regions of the cerebellum, and the precentral gyrus in the motor cortex and a cognitive network involving the ventral dentate, Crus I, and prefrontal cortex. The motor pathway is essentially involved in DEBC, whereas the cognitive route could have a modulatory role (McCormick and Thompson, 1984; Hardiman and Yeo, 1992; Ernst et al., 2016). Moreover, several data support the influence of the prefrontal region over primary motor areas (Miyachi et al., 2005; Narayanan and Laubach, 2006; Nardone et al., 2019). Some works indicate that M1 is weakly involved in learning during DEBC (Ivkovich and Thompson, 1997), mainly supporting the motor role of the red nucleus (RD) (Pacheco-Caldern et al., 2012). Other studies show precisely the opposite, providing ample evidence for the fundamental role of M1 in modulating CR (Aou et al., 1992; Birt et al., 2003; Ammann et al., 2016) and the auxiliary function of RD (Chapman et al., 1988; Anderson and Keifer, 1997). The RN is

quite rudimentary in humans, likely due to the development of the corticospinal tract and the pyramidal system (Ulfig and Chan, 2001; Hicks et al., 2012).The model proposed here intends not to establish which of the two hypotheses is correct but rather to reproduce the core dynamics present in the ASD cerebellum. Notably, the model simulated a central mechanism that explains CR acquisition in DEBC operating within cerebellar circuits before reaching the brain regions that implement movement. Therefore, for simplicity, the model presents only the M1 neural population as the cortical target region of the motor cortico-cerebellar pathway.

2.2.2. Granule Cells Subpopulations With Different Time-Sensitivity

The model reproduces one of the most remarkable cerebellum properties: its control in motor operations timing (Mauk and Buonomano, 2004). For this purpose, the model simulates the observed cerebellar granular neurons time-sensitivity according to which different cells are active to varying moments during conditioned stimuli (Medina et al., 2000). The interplay between mossy fibers, granule, and Golgi cells supports this process. According to the time-window matching hypothesis (D'Angelo and De Zeeuw, 2009), the mossy fibers inputs to the granular layer are transformed into well-timed spike bursts by intrinsic granule cell processing. The feedforward Golgi cells inhibition sets a limit to the duration of such a spike. These activities are spread over particular fields in the granular layer to generate ongoing time-windows to control interacting motor domains properly. The different time-sensitivity of granule cells has vast implications for associative learning processes operating within the olivo-cerebellar-cortical system. Indeed, the synaptic plasticity might favor the activation of specific granule cell groups concerning particular time windows. The model uses two temporal kernel functions (**Figure 2**) to capture the effects of granule cells time sensitivity on long-term depression (LTD) processes operating within the parallel fibers.

These functions correlate the past activity of a single granule cell with each spike from the inferior olive (US) in different ways to construct predictive dynamic responses during associative learning. The IO neurons afferent to the PC emit a spike with $t = -0.02\ s$ because the US stimulus has a duration of 20 *ms* and finishes with the CS stimulus at $t = 0$, to comply with the DEBC paradigm. The "motor" kernel (**Figure 2** dashed line) mainly influences the activity of the GRm-PCm-DNm-M1 path and supports high CS-US correlation when the stimulus duration is small (function peak at 150 *ms*). This kernel function starts to produce an effect on the input signal 100 *ms* before IO-spike arrival, in agreement with the physiological delay suggested by the biology (Kettner et al., 1997; Ros et al., 2006). By contrast, the "cognitive" kernel (**Figure 2** solid line) mainly modulates the activity of the GRc-PCc-DNc-mPFC-M1 path and allows high CS-US correlation when the stimulus duration is more extended (function peak at 250 *ms*). These features make the model able to process stimuli of different duration and address both trace and delay paradigms (Caligiore and Mirino, 2020). The following

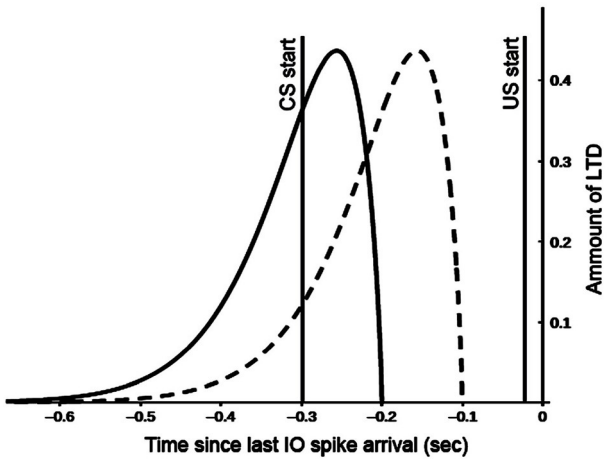

FIGURE 2 | Kernel functions used for GR and PC synaptic long term depression (LTD). Both functions are convolved with the spike train of the afferent parallel fibers (all spikes emitted for $t < 0\ sec$). This provides a measure of past parallel fibers activity setting the synapse eligibility to depression when the inferior olive (IO) neuron afferent to the PC emits a spike ($t = -0.02\ sec$). Motor and cognitive kernels are respectively indicated with dashed and solid lines.

equation generates the kernel functions:

$$K(t) = a \cdot exp\left(-\frac{\left|(t+c)\cdot a\right|^{b}}{f}\right) \cdot -sin\left(\frac{t+c}{e}\right)^{d} \qquad (1)$$

where $a = 15, b = 1.8, d = 0.75, f = 1.3$ are parameters used to both normalize the kernel function and to regulate the strength of the associative learning processes, e is the Napier number, and c is a parameter used to control the function translation along the x-axis ($c = 0.1$ and $c = 0.2$, respectively for the motor and cognitive kernels). The Equation (1) corresponds to a second-order differential system solution and its rationale to model GR time sensitivity can be found in Ros et al. (2006), Carrillo et al. (2008), and Luque et al. (2011). The effects of the different granule cells time-sensitivity propagate over M1 and mPFC, supporting these cortical areas functioning at different time-scale, with M1 processing information faster than mPFC (Kiebel et al., 2008).

2.2.3. Connections

The motor and cognitive pathways have the same cerebellar anatomical organisation. For each pathway, GR units receive CS and are connected to PC neurons through the parallel fibers. The IO neurons process US and project to PC through the climbing fibers (Thompson and Steinmetz, 2009). Both CS and US are spike trains generated with the *NEST* function *spike_generator*, setting a spike frequency of 100 spikes per second (*sp/s*). PC neurons combine the information coming from both GR and IO. The DN neurons represent the cerebellar output. This area receives CS, excitatory signals from IO and inhibitory connections from PC (Dum and Strick, 2003; DAngelo et al., 2016). The DN neurons belonging to the motor and cognitive pathways project, respectively, to M1 and mPFC (Kelly and

Strick, 2003). Finally, mPFC projects to M1 modulating its activity (Miyachi et al., 2005). The average firing rate of M1 neurons represents the CR. Aside from the IO-PC connections, which are "one-to-one," the connections linking the model areas are "all-to-all."

All neurons are stimulated by an external current *Ie* simulating the effects of the external signals supplied by other areas not reproduced in the model (Tsodyks et al., 2000). For each model area, we set the values of *Ie* to pre-activate cells avoiding at the same time too spurious activity covering the effects of the main signals CS and US. Also, we used a noise signal (*Noise*) to stimulate DN neurons, simulating the spurious effects on neural activation due to the intrinsic neural noise (Schweighofer et al., 2004). Spike train, generated through a Poisson process having a given frequency rate, represents the *Noise*. This assumption agrees with empirical evidence and models showing that Poisson processes approximated cortical spikes temporal distribution (Poznanski, 2011). The *NEST* function *poisson_generator* simulated the Poisson process with the following parameters: mean firing rate (rate = 2500 sp/s); time origin of the simulation (origin = 1 *ms*); beginning of device application to origin (start = 1 *ms*); termination of device application to origin (stop = $2,500$ *ms*). Within the model nine synaptic connections are static (CS-GR, CS-DN, US-IO, IO-PC, IO-DN, PC- DN, DN-M1, and DN-mPFC) (**Figure 1**, solid or dot lines) while the other two (GR-PC, mPFC-M1) are plastic (**Figure 1**, dashed lines). **Table 1** summarizes the *Ie* values and the connections parameters used in the model. The **Table 1** also shows the connections *delay* parameters we used to reproduce the effects of different connectivity between ASD and the control group (see section 2.2.5 for more details).

2.2.4. Plasticity Mechanisms

The plasticity rules described below drive the weights change of the plastic connections during the training sessions, increasing the weights by long term potentiation (LTP), or decreasing them by long term depression (LTD). The LTD implemented at the GR-PC synapses is an associative weight decrease triggered by spikes from IO (Ito, 2001). The LTD algorithm uses the temporal kernels shown in the **Figure 2**, which correlate each spike from IO (US) with the past activity of GR (CS) (Caligiore et al., 2019a; Caligiore and Mirino, 2020). The spike train supplied to the GR-PC afferent connection (all CS spikes emitted for $t < 0$ s in the **Figure 2**) is separately convolved with both motor and cognitive kernels. In this way, it is possible to have a measure of past parallel fibers activity that is used to set the synapse eligibility to depression when the IO neurons afferent to the PC emit a spike (from $t = -0.02$ s to $t = 0.0$ s in the **Figure 2**). This rule maximizes learning (LTD) at synaptic sites in which the input parallel fibers delayed activity positively correlates with the IO signal. Hence, the kernel functions showed in the **Figure 2** help the cerebellum to acquire the capacity to produce a predictive output. This feature is critical in associative sensory-motor paradigms, such as delay or trace eyeblink conditioning. In this case, indeed, the cerebellum learns to predict the precise timing between two stimuli, CS and US, and produces a CR precisely timed to anticipate the US onset (DAngelo et al., 2016). Non-associative weight increase implements the LTP at the GR-PC synapses (Lev-Ram et al., 2003). The long term plasticities for the GR-PC connections are responsible for CR acquisition (LTD) and extinction (LTP) (Antonietti et al., 2016). Below the equation regulating the GR-PC LTD and LTP plasticity processes:

$$\Delta w_{GR_i \rightarrow PC_j}(t) = \begin{cases} -\int_{-\infty}^{t_{IO}} K(t-x)\delta_{GR_i}(t-x)dx \\ \textit{if } PC_j \textit{ is active and } t = t_{IO} \\ \\ \alpha \textit{ if } PC_j \textit{ is active and } t \neq t_{IO} \\ \\ 0 \textit{ otherwise} \end{cases} \quad (2)$$

where t_{IO} is the time of the last IO spike arrival; K is the integral kernel function that for learning within the motor pathway has its peak at 150 *ms* before t_{IO}, whereas for learning within the cognitive pathway has its peak at 250 *ms* before t_{IO}; $\delta_{GR}(t)$ is the Dirac function representing the CS spike train on GR_i cell; α is the LTP learning rate set to 0.05.

Regarding the learning processes modulating the value of the PFC-M1 connection weights, if activation of mPFC is detected 0.04 s before the activity of M1, then increases the value of the connection weights between the mPFC-M1 synapses (LTP) (Sjöström et al., 2001; Nevian and Sakmann, 2006). In this way, we assume that the spike in mPFC contributes to generating the spike on M1. Otherwise, there is LTD. Below the equation regulating these learning mechanisms:

$$\Delta w_{mPFC_i \rightarrow M1_j} = \begin{cases} \beta \textit{ if } M1_j \textit{ is active} \\ \textit{and } t_{mPFC_i} \in [t_{M1_j} - 0.04, t_{M1_j}] \\ \\ \gamma \textit{ if } M1_j \textit{ is active} \\ \textit{and } t_{mPFC_i} \notin [t_{M1_j} - 0.04, t_{M1_j}] \\ \\ 0 \textit{ otherwise} \end{cases} \quad (3)$$

For each simulated subject, β and γ are randomly chosen according to a uniform distribution, respectively, in the $[0.2, 0.5]$ and in the $[-0.015, -0.035]$ ranges; t_{mPFCi} and t_{M1j} are the time of the spike occurring, respectively, within the *mPFCi* and *M1j* cells.

Before associative learning, the weights of the GR-PC connections have positive values. In this case, a CS produces a great activity within PC layers, which generates a strong inhibition of DN units. During associative learning, the LTD process gradually reduces inhibition from PC to DN (Ishikawa et al., 2014). The consequent DN activity, in turn, contributes to obtain a greater activation of M1 (motor pathway) producing CR, and of mPFC (cognitive pathway). The GR-PC LTD (Equation 2) is responsible for CR acquisition, whereas the mPFC-M1 LTP (Equation 3) makes the influence of mPFC on M1 activity stronger after each training session (see section 3.3 for more details).

2.2.5. Modeling Differences Between ASD Group and Control Group

The ASD group consists of computational models that diverge from the models used to simulate the control group in two features: (i) reduced number of Purkinje cells (Whitney et al., 2009; Skefos et al., 2014; Hampson and Blatt, 2015) and (ii) hyper-connectivity of the cerebellum with sensory and motor cortex (Khan et al., 2015; Oldehinkel et al., 2019). To computationally reproduce (i), we reduced the PC number of both pathways from a population of 48 units to one of 30 units. This reduction rate agrees with literature indicating that autistic brains show 24–50% fewer of Purkinje cells (Fatemi et al., 2002). To simulate (ii), we modulated the signal transmission speed by tuning a *delay* parameter connecting different neural populations. We assumed that the hyper-connected connections have a lower delay in signal transmission. Thus, to reproduce the ASD hyper-connection of the cerebellum with sensory and motor cortex, we reduced the *delay* parameter from 100 to 50 *ms* (see **Table 1**). The connections involved in the hyper-connectivity of the cerebellum with sensory and motor cortex are CS-GRm, CS-GRc, CS-DNm, CS-DNc, US-IO, and DNm-M1.

2.3. Training Protocols

We used DEBC protocols with 10 training sessions. Each training session consists of three trials. Each trial starts just after the previous one ends. Similarly, each training session begins just after the last one ends. Standard training trials consist of 300 *ms* CS with 20 *ms* US final overlapping. The delay protocol allows controlling if the model reproduces behavioral data about the CR learning rate, which is higher in the ASD group than in the typical development group, and the CR peak latency of the ASD group that occurs significantly earlier than those of the control group.

Two groups of 15 simulated children each were trained using the protocol described above. One represents the "control group" formed by healthy children models; the other represents the "autistic group" formed instead by models with a reduced number of Purkinje cells and hyper-connectivity of the cerebellum with sensory and motor cortex (see section 2.2.5).

The model simulates different children using various *NEST* random number generator seeds to produce different noise signal values and different model parameters whose values were randomly drawn from a uniform distribution (see **Table 1**). The model generates data comparable to those drawn from experiments with real children devised by Sears et al. (1994), Oristaglio et al. (2013), and Welsh and Oristaglio (2016). These data are relevant because they provide the first report of abnormal conditioned response on DEBC in ASD.

3. RESULTS

This section shows the data obtained through the simulations run with the model and aiming at: (i) reproducing the main results on a higher CR learning rate and faster timing-response (Peak Latency - PL) obtained with real ASD children involved in DEBC experiments (Sears et al., 1994; Oristaglio et al., 2013; Welsh and Oristaglio, 2016); (ii) understanding the system-level neural mechanisms underlying such results.

3.1. Higher CR learning rate on DEBC in ASD

We first tested the ability of the groups to acquire CRs during the DEBC task. For each training session, the *CR Rate* (%) was computed according to the following equation:

$$CR\ Rate\ (\%) = \frac{< FR_{M1} > \times 100}{FR_{M1_{max}}} \tag{4}$$

where $< FR_{M1} >$ and $FR_{M1_{max}}$ are, respectively, the average and the maximum M1 firing rates. These values are calculated in a separated "test phase" at the beginning of each training session, where there is only the CS signal in the system. In the test phase, CR is computed in the $[0, 450]$ *ms* time interval for the control group and in the $[0, 400]$ *ms* time interval for the ASD group. This choice of using two different time intervals was made to accurately capture the firing rate related to the CR and not to other stimuli produced by the noise.

Figure 3 shows the behavior acquired by the two groups during DEBC tasks. In particular, it compares the average CR rate of each subject of the control and ASD groups. Like the results obtained through experiments involving real subjects (Sears et al., 1994), even with the model, the percentage of CRs is higher in the ASD group than in the control group.

The model suggests that the neural mechanism mainly contributing to obtain this behavioral result is the reduced number of PC in ASD. In this respect, **Figure 4** suggests that a reduced number of PC leads to reduced DN inhibition, which shows an early higher activation for ASD (fewer learning sessions are sufficient to obtain the DN disinhibition). Consequently, earlier disinhibition of DN causes an earlier activation of M1 and, in essence, an increase in the percentage of CR in fewer sessions in ASD (see Equation 4).The difference of DN activation between the two groups vanishes and even changes direction after PC learning, favoring the control group to recover the CR expression gap. Notably, another critical mechanism in CR expression is the increase in weight between mPFC and M1, which plays a role in the variation in CR expression after PC learning (see section 3.3).

3.2. Anticipatory Peak Latency on DEBC in ASD

The simulations run with the model show that the CR peak latency values are lower for the simulated ASD group (**Figure 5**). We obtained the peak latency (*PL*) by averaging the time when the maximum value of the M1 firing rate occurs ($t_{FR_{M1}}$) over the time steps (n) included in a specific time window, which is $[0, 550]$ *ms* for the control group and $[0, 450]$ *ms* for the ASD group. We use two different time intervals to accurately reflect the timing of the M1 firing rate related to the CR and not to other stimuli generated by the noise. Below the equation used to calculate the peak latency:

$$PL = \frac{\sum_{i=0}^{n} t_{FR_{M1}}}{n} \tag{5}$$

The result showed on **Figure 5** agrees with data collected with real ASD and control subjects (Sears et al., 1994; Oristaglio et al.,

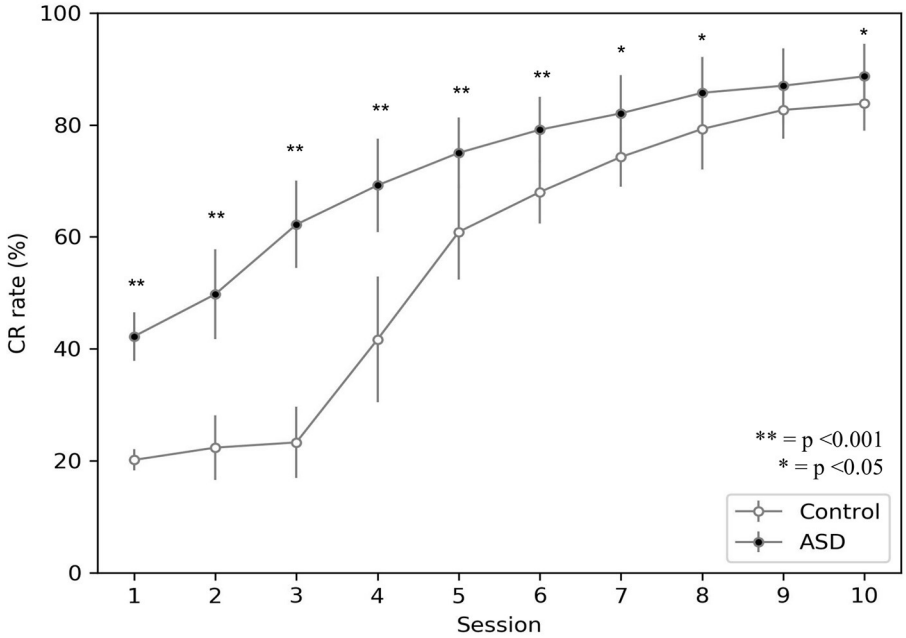

FIGURE 3 | Acquisition of conditioned response during DEBC by simulation. Data obtained with groups of 15 simulated subjects over 10 training sessions. We compared the CR of subjects of the two groups, as the average of each session. The distribution does not respect the assumptions for the use of parametric tests. Applying the Mann-Whitney *U*-test to all sessions, the difference is significant for all sessions except for session 9. Respectively $p < 0.001$ for sessions from 1 to 6; $p = 0.005$ for session 7; $p = 0.030$ for session 8; $p = 0.067$ for session 9; $p = 0.021$ for session 10. Note that since we have two sets of non-parametric sample data, we use the Mann-Whitney *U*-test to test the null hypothesis without correction for multiple comparisons.

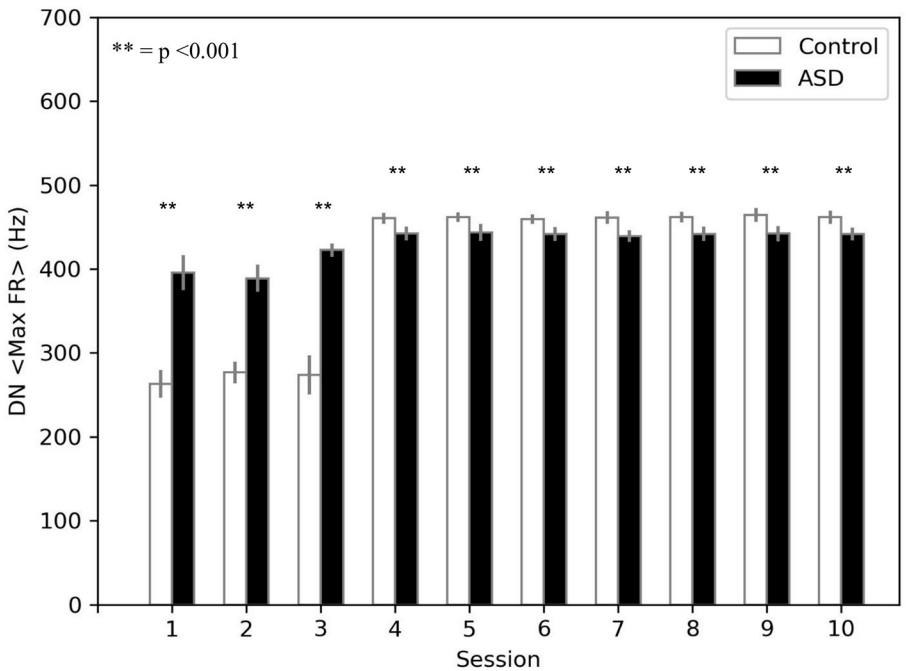

FIGURE 4 | Average max firing rate of dentate nuclei (both DNm and DNc) (*DN* < *MaxFR* >) during DEBC. Data obtained with groups of 15 simulated subjects over 10 training sessions. We compared *DN* < *MaxFR* > of subjects of the two groups, as the average of each session. The distribution does not respect the assumptions for the use of parametric tests. Applying the Mann-Whitney U test to all sessions, the difference is significant for all sessions $p < 0.001$.

2013; Welsh and Oristaglio, 2016) and indicates that CR signal reaches the peak faster for the simulated ASD group with the same training trial.

The model suggests that the neural mechanism contributing to this behavioral result is the hyper-connectivity between the cerebellum and sensory-motor network in ASD. In this respect, **Figure 6** shows that this hyper-connectivity leads to fast DN disinhibition. Consequently, earlier disinhibition of DN causes an earlier activation of M1 and, in essence, lower CR peak latency values in the simulated ASD group.

3.3. Brain Mechanisms Underlying ASD Behavior and mPFC Involvement in DEBC

Figure 7 shows the effects on the neural activity of the two brain features characterizing the autistic phenotype. First, the lower number of PC in ASD influences the earlier greater activation of DN (see **Figure 4**) and consequently the earlier greater activation of M1, from which is calculated the CR (see Equation 4). Comparing the activation times of the two groups, we can also see an earlier (and greater) activation in those of the ASD group, particularly in M1, from which is calculated the peak latency (see Equation 5). For these neural dynamics, in the ASD group, the percentage of CRs is higher, and the CR signal reaches the peak faster than the control group. For both ASD and control groups, **Figure 7** also shows that after a few sessions (**Figures 7A,C**), the LTD processes lead to getting a tangible inhibition of only the PCm belonging to the motor pathway. In contrast, the PCc of the cognitive pathway becomes inhibited only with the progression of learning (**Figures 7B,D**). The M1 activity is initially mainly supported by the motor pathway and then also by the cognitive path. Thus, mPFC (cognitive path) exerts only a modulatory influence on the M1 activity only after a few repetitions and not from the beginning. In this way, the model suggests possible neural dynamics underlying the involvement of PFC in associative learning processes found in empirical experiments (Nardone et al., 2019). The model also suggests that the neural processes supporting the mPFC involvement in DEBC could be influenced by both the greater functional connectivity between DN and mPFC (simulated by the lower DNc-mPFC delay parameter) and the reduced connectivity with M1 (simulated by the higher DNm-M1 delay parameter) (Allen et al., 2005; Habas, 2010; Bostan et al., 2013).

4. DISCUSSION

The simulations run with the model show that the autistic brain features reproduced by the model, namely the reduced number of Purkinje cells and the hyper-connectivity of the cerebellum with sensory and motor cortex, are critical to explaining the experimental data about DEBC learning in ASD. In particular, the higher ASD CR learning rate found from real children study (Sears et al., 1994) and replicated by the computational model (**Figure 3**) could be due to a reduced number of Purkinje cells. The consequence of this loss is more powerful disinhibition of the dentate nucleus (**Figures 4**, **7**), which in turn facilitates the associative learning processes along the motor pathway of the model in ASD. Note how the associative learning processes operating within the cognitive pathway and mainly involving the mPFC-M1 circuits, critically contributes to the gradual improvement of CR acquisition for both ASD and control groups. Therefore, the cognitive pathway becomes more involved with learning, as shown in the **Figure 7**. Interestingly, this latter result agrees with recent data supporting the involvement of PFC in DEBC (Nardone et al., 2019) and suggests a possible neural mechanism on how PFC could contribute to associative learning processes.

The result about lower peak latency found in experiments with real children (Sears et al., 1994; Oristaglio et al., 2013; Welsh and Oristaglio, 2016) and reproduced by the model (**Figure 5**) mainly depends on the hyper-connection of the cerebellum with sensory and motor cortex. In the model, the effects of this hyper-connection are reproduced manipulating the connection delay parameter, affecting the signal transmission speed between different neural populations. There is a higher transmission rate in the connections between the areas where CS and US originate and the cerebellum, so the latter receives sensory input earlier in the ASD group than in the control group (**Figure 6**). Similarly, the hyper-connectivity between the dentate nucleus belonging to the motor pathway and the motor area allows a fast M1 uploading in the ASD group compared to the control group.

Building on these results, new methodologies could be devised to act on these neural processes, for example, to manipulate the degree of hyper-connectivity. In this respect, transcranial magnetic stimulation (Demirtas-Tatlidede et al., 2013) or transcranial direct current stimulation (D'Urso et al., 2015) can be applied as therapeutic modalities in ASD subjects to reduce the effects of hyper-connectivity and to modulate synaptic plasticity. Besides, hyper-connectivity could be manipulated through drug treatments, such as Memantine, NMDA receptor antagonist, that have already tested in ASD to restore the imbalance between excitation and inhibition (Ghaleiha et al., 2013; Uzunova et al., 2014). All of these methodologies could be incorporated into future versions of the model to test their effectiveness.

4.1. Related Works

Several theories underlying ASD have been formulated over the years (Fakhoury, 2015), and some of them support our model (Belmonte et al., 2004; Baron-Cohen et al., 2009; Markram and Markram, 2010). Our hypothesis is in line with the numerous studies related to the abnormal cerebellum (Hampson and Blatt, 2015) and its hyper-connectivity with the sensory and motor cortex in ASD (Khan et al., 2015; Oldehinkel et al., 2019).

ASD subjects could show deficits in long-range connectivity with cortical sites, producing, in turn, impairments in cognitive functions coordination (Courchesne, 1997; Fatemi et al., 2002; Verly et al., 2014). Recent genetic (Gharani et al., 2004) and MRI-behavior correlation (Akshoomoff et al., 2004; Kates et al., 2004) studies suggest that cerebellar abnormality may play a more central role in ASD than previously thought. The reduction in Purkinje cell numbers would release the deep cerebellar nuclei from inhibition, producing abnormally strong physical connectivity

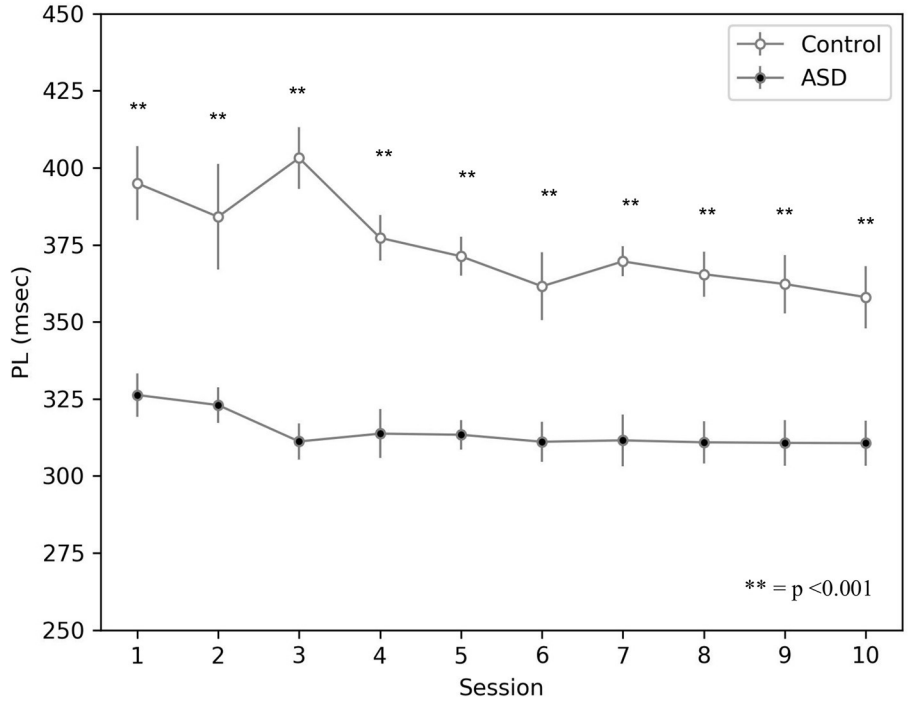

FIGURE 5 | Peak latency response during DEBC by simulation. Data obtained with groups of 15 simulated subjects over 10 training sessions. We compared the PL of subjects of the two groups, as the average of each session. The distribution does not respect the assumptions for the use of parametric tests. Applying the Mann-Whitney *U*-test to all sessions, the difference is significant for all sessions $p < 0.001$.

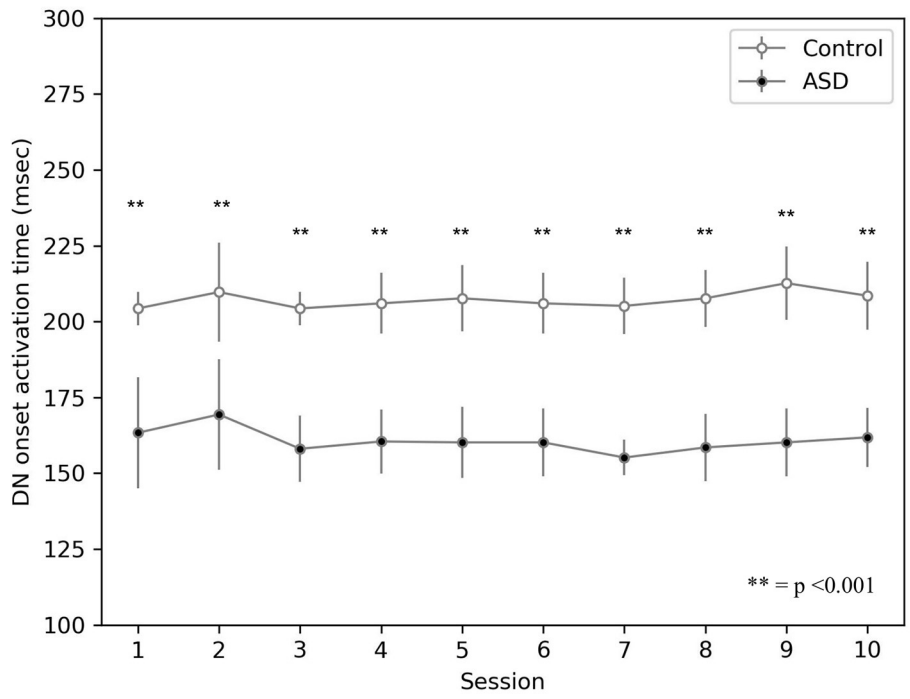

FIGURE 6 | Average timing firing rate of dentate nuclei (both DNm and DNc) during DEBC. Data obtained with groups of 15 simulated subjects over 10 training sessions. We compared the DN timing firing rate of subjects of the two groups, as the average of each session. The distribution does not respect the assumptions for the use of parametric tests. Applying the Mann-Whitney *U*-test to all sessions, the difference is significant for all sessions $p < 0.001$.

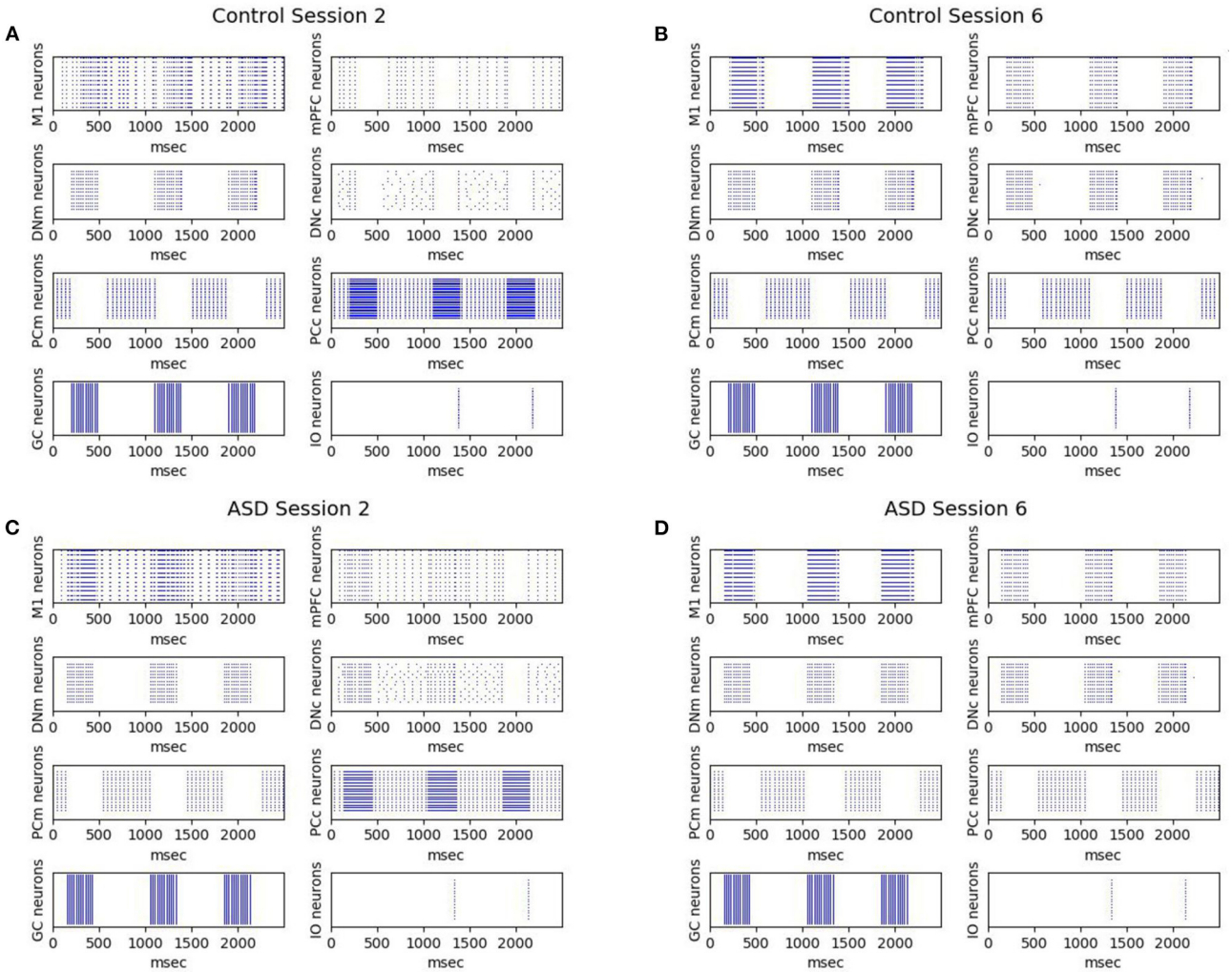

FIGURE 7 | Neurons activation during DEBC simulation. Data obtained during session 2 **(A,C)** and session 6 **(B,D)**, respectively by the control group **(A,B)** and the ASD group **(C,D)**.The comparison between **(A,B)** and **(C,D)** shows robust and rapid activation of M1 in the ASD group rather than in the control group.

and potentially abnormally weak computational connectivity along the cerebello-cortical circuit (Belmonte et al., 2004).

Our model agrees with the *Intense World Theory* (Markram and Markram, 2010), suggesting that hyper-sensitivity could result from a processing difference at various sensory levels. This difference could include the density or sensitivity of sensory receptors, inhibitory and exhibitory neurotransmitter imbalance, or neural processing speed. Besides, Belmonte and colleagues suggested that local range neural overconnectivity in posterior, sensory parts of the cerebral cortex are responsible for the hyper-sensoriality in people with ASD (Belmonte et al., 2004). Studies investigating the sensory profile have revealed sensory abnormalities in over 90% of children with ASD (Kern et al., 2006; Leekam et al., 2007; Tomchek and Dunn, 2007).

Furthermore, numerous studies report abnormal perception in ASD in different sensory channels (Bertone et al., 2003; Cascio et al., 2008; Jrvinen-Pasley et al., 2008). In particular, ASD showed hyper-sensitivity to vibrotactile stimulation in the *tactile* modality (Blakemore et al., 2006) and superior pitch processing in the *auditory* modality (Mottron et al., 1999; Bonnel et al., 2003). In addition, recent works support the imbalance of excitation and inhibition in the neocortex in ASD (Hussman, 2001; Casanova et al., 2003; Rubenstein and Merzenich, 2003), with excitation winning over inhibition. In particular, suppressed GABAergic inhibition and increased glutamatergic excitation (Uzunova et al., 2016).

The model proposed here does not reproduce some aspects, such as some neurotransmitter modulatory action (Goris et al., 2020) and the imbalance of excitation and inhibition in the neocortex (Hussman, 2001; Casanova et al., 2003). By contrast, the model successfully captures the evidence on the crucial role of the cerebellum and altered sensoriality in ASD and demonstrates that these features are critical to investigate abnormal EBC behavior in ASD.

5. CONCLUSION

Building on a computational modeling approach, this work proposes that two anatomic-physiological features of the autistic cerebellar-cortical network, the fewer number of Purkinje cells (Whitney et al., 2009; Skefos et al., 2014; Hampson and Blatt, 2015), and the hyper-connectivity between the cerebellum and sensory-motor network (Khan et al., 2015; Oldehinkel et al., 2019), are critical to explaining the neural mechanisms underlying the ASD abnormal behavior in DEBC. In more detail, the simulated subjects behavior is consistent with the experimental observations in real subjects (Sears et al., 1994; Oristaglio et al., 2013; Welsh and Oristaglio, 2016). Moreover, the biological plausibility of model allowed us to formulate hypotheses on the low-level neural mechanisms underlying DEBC and to explore the relationships between ASD brain neuroanatomy and altered behavior.

Notwithstanding these positive features, future works could improve the model in several ways. Among these, the introduction of more complex neuromodulatory mechanisms could provide additional information about the detailed neurobiological processes underlying ASD. In other words, an enhanced version of the model could directly simulate the action of noradrenaline, dopamine and acetylcholine (Lawson et al., 2017), manipulating, for example, the responsiveness of their associated receptors (Caligiore et al., 2019b). We can also investigate the role of the environment in ASD learning. In this respect, behavioral results show that performance in volatile environments is lower in participants with more autistic traits (Goris et al., 2020). Finally, the system-level hypothesis proposed by the model could be tested through new experiments. For example, it could be devised an experiment to compare the behavior of three groups: typical development, low and high functioning ASD children involved in DEBC and trace eyeblink conditioning (TEBC) tasks. In this way, it could be possible to investigate changes in the timing performance of CR acquired during trace and delay eyeblink conditioning in subgroups of ASD children. This investigation could be useful in studying the differences in response timing between ASD subgroups during DEBC and understanding why autistic functioning does not diverge from that of the control group during TEBC (Oristaglio et al., 2013; Welsh and Oristaglio, 2016).

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://github.com/ctnlab/cerebellum_autism_DEBC_model.

AUTHOR CONTRIBUTIONS

ET, PM, and DC: conceptualization, data curation, investigation, methodology, software, validation, writing–review, and editing. ET and PM: formal analysis and resource. DC: funding acquisition and project administration. PM and DC: supervision. ET and DC: writing–original draft. All authors contributed to the article and approved the submitted version.

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