RESEARCH PAPER

Cerebellar lobule atrophy and disability in progressive MS

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ABSTRACT

Objective To investigate global and lobular cerebellar volumetries in patients with progressive multiple sclerosis (MS), testing the contribution of cerebellar lobular atrophy to both motor and cognitive performances.

Methods Eighty-two patients with progressive MS and 46 healthy controls (HC) were enrolled in this cross-sectional study. Clinical evaluation included motor and cognitive testing: Expanded Disability Status Scale, cerebellar Functional System score, Timed 25-Foot Walk Test, 9-Hole Peg Test (9-HPT), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test–Revised (BVMT) and California Verbal Learning Test II (CVLT). Cerebellar volumes were automatically obtained using the Spatially Unbiased Infratentorial Toolbox. A hierarchical multiple linear regression analysis was performed to assess the relationship between MRI variables of supratentorial and cerebellar damage (grey matter fraction, T2 lesion volume, metrics of cerebellar atrophy and cerebellar lesion volume) and motor/ cognitive scores.

Results Patients with MS exhibited lower cerebellar volumes compared with HC. Regression analysis showed that cerebellar metrics accounted for extra variance in both motor and cognitive performances, with cerebellar lesion volume, cerebellar Lobules VI, Crus I and VIIIa atrophy being independent predictors of 9-HPT, SDMT, BVMT and CVLT performances.

Conclusions Atrophy of specific cerebellar lobules explains different aspects of motor and cognitive disability in patients with progressive MS. Investigation of cerebellar involvement provides further insight into the pathophysiological basis of clinical disability in progressive MS.

INTRODUCTION

Progressive multiple sclerosis (MS), which encompasses both primary progressive (PP) and secondary progressive (SP) forms,[1] is characterised by gradually worsening disability, mainly presenting as myelopathy, and also as progressive hemiparesis, ataxia, visual dysfunction and cognitive impairment.[2] Pathological features of progressive MS, in comparison with the relapsing phenotype, are greater axonal loss, cortical demyelination and presence of meningeal inflammatory aggregates.[3] Although no pathognomonic MRI marker has been identified, patients with progressive MS show extensive cortical involvement, deep grey matter (GM) atrophy, spinal cord injury and widespread cerebellar pathology.[2 4]

The occurrence of cerebellar atrophy in MS, especially in patients with progressive MS, is well established,[4–11] and cerebellar involvement strongly contributes to both motor and cognitive disability,[12 13] but specific investigations of the relationship between cerebellar volume loss and clinical disability in progressive MS are lacking.

Cerebellar functional topography has been explored in several neuroimaging studies,[14] and clinical correlates of specific cerebellar lobule damage have been reported in neurodegenerative disease,[15 16] including MS.[17–20] A recent study showed a correlation between anterior and posterior cerebellum atrophy and motor/cognitive impairment in a group of patients with MS, including a small subgroup of patients with SP.[21] However, to the best of our knowledge, no data are available regarding the possible contribution of atrophy of specific cerebellar lobules to the development of motor/cognitive deficits in patients with progressive MS. Therefore, the aim of our study was to investigate global and lobular cerebellar volumetries in a relatively large group of patients with progressive MS and to determine whether atrophy of specific lobules corresponds to particular clinical features, in order to expand the current knowledge about cerebellar physiopathology in progressive MS.

METHODS

Subjects

Eighty-two patients with progressive MS and 46 healthy controls (HC) (mean age 48.6±10.0 years; range 28–66 years; M/F:22/24) were prospectively enrolled in the study from two different centres, as part of a shared project, from October 2016 to February 2017. Sixty-one of the 82 patients were enrolled at the Icahn School of Medicine at Mount Sinai, whereas the remaining 21 were enrolled at the University of Naples 'Federico II'. None of the HC presented any condition that could affect the CNS. All patients included in the analysis presented either a PP or an SP phenotype (n=47 (57.3%) and n=35 (42.7%), respectively). Inclusion criteria for patients with MS were as follows: age between

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18 and 70 years, MS diagnosis fulfilling the revised McDonald criteria,[22] progressive phenotype[1] and Expanded Disability Status Scale (EDSS) score ≤7.0. Patients, in order to be classified as PP, had to present clinical progression (confirmed over a period of at least 1 year), in absence of prior exacerbations, whereas to be classified as SP, they had to present clinical progression (confirmed over a period of at least 1 year) after conversion from a RR course. Exclusion criteria were as follows: coexistence of any other systemic condition, diagnosis of psychiatric disorders, contraindications to undergo an MRI scan, pregnancy, history of head trauma, alcoholism, drug addiction or neurological disorders other than MS. At screening visit, 54 patients (65.9%) were under immunomodulatory treatment with the following drugs: glatiramer acetate (n=15, 18.3%), dimethyl fumarate (n=9, 11.0%), teriflunomide (n=6, 7.3%), fingolimod (n=10, 12.2%), natalizumab (n=4, 4.9%), interferon β−1a (n=3, 3.7%), interferon β−1b (n=3, 3.7%), alemtuzumab (n=2, 2.4%), rituximab (n=1, 1.2%) or ocrelizumab (n=1, 1.2%).

Written informed consent was obtained from all participants before the beginning of the study procedures, according to the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai and by the 'Carlo Romano' ethics committee for biomedical activities of 'Federico II', University of Naples. Clinical examination was performed within 1 week from the MRI scan by an experienced neurologist. Motor functions were assessed with the EDSS, Timed 25-Foot Walk Test (T25FW) and 9-Hole Peg Test (9-HPT).

Cognitive status was tested through the administration of the Brief International Cognitive Assessment of Multiple Sclerosis (BICAMS) battery, which includes the following tests: Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test - Revised (BVMT) and California Verbal Learning Test II (CVLT).

A complete list of the demographic and clinical information of all patients with MS included in the study is reported in table 1.

MRI data acquisition and processing

All images were acquired using 3T MRI scanners at both centres (Siemens Skyra and Siemens Trio, Siemens Medical Systems, Erlangen, Germany). The standardised MR acquisition protocol included a three-dimensional magnetization prepared rapid gradient-echo T1-weighted sequence (224 sagittal slices, TE=2.47 ms, TR=3000 ms, TI=1000 ms, voxel size=1.0×1.0× 1.0 mm^3) for the volumetric analysis and a T2-weighted sequence (TE=63.0–101.0 ms, TR=2500–8000 ms) used for the quantification of the T2-weighted lesion volume for the entire brain (LV) and the cerebellum (CLV).

The analysis of MRI data was done centrally at Mount Sinai Hospital by experienced observers, blinded to the subjects' identities.

For all patients, T2-weighted hyperintense lesions were segmented by one experienced observer using a semiautomatic segmentation technique (Jim 7, Xinapse Systems, Northants, UK), deriving both LV and CLV.

For all subjects included in the analysis, lesion-filled 3D T1-weighted images were segmented into GM, white matter (WM) and CSF using the segmentation tool implemented in the Statistical Parametric Mapping (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm). For each subject, intracranial volume (ICV) was computed as the sum of GM, WM and CSF for normalisation purposes. Furthermore, as an index of supratentorial brain atrophy, GM fraction (GMF) was computed as (brain GM volume − cerebellar GM volume)/ICV.

Cerebellar volumes were calculated on lesion-filled 3D T1-weighted images using the Spatially Unbiased Infratentorial Toolbox (SUIT) version 3.2, implemented in SPM12.

Briefly, cerebellum and brainstem were identified and isolated automatically, and a mask was automatically generated by calculating the probability of each voxel belonging to one of these structures. Each obtained mask was visually inspected and manually adjusted in four subjects. Next, the isolated cerebellum was aligned to the SUIT atlas template via an affine transformation (for the linear part of the normalisation) and a non-linear transformation using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra. The individual cerebellum was therefore resliced in the atlas space, modulating in order to grant volume preservation. Finally, by applying an inverse transformation matrix derived from the previous coregistration step, the SUIT atlas was aligned to the native subject space (figure 1), and lobular volumes were computed as the sum of their hemispheric and vermian portions. Anterior and posterior cerebellar volumes were also calculated as the sum of lobules I–V and VI–X.[21]

Statistical analysis

Normal distribution of all variables was preliminary probed via Shapiro-Wilk test; variables showing a significantly skewed

Table 1	Patients demographics and clinical variables			
	MS (n=82)	PP-MS (n=47)	SP-MS (n=35)	p Value*
Age (mean±SD)	52.6±10.0 (range 29–69)	52.6±11.1 (range 31–69)	52.6±8.5 (range 29–66)	0.73
Sex (M/F)	31/51	20/27	11/24	0.57
DD (mean±SD)	13.1±9.6	10.1±7.1	17.1±11.0	**0.003**
EDSS (median)	5.8 (range 1.0–7.0)	4.5 (range 1.0–6.5)	6.0 (range 2.0–7.0)	0.15
FS (median)	2.0 (range 0–4.0)	2.0 (range 0–4.0)	2.0 (range 0–4.0)	0.74
T25FW (mean±SD)	12.3±10.4	9.9±6.7	15.9±13.6	0.02
9-HPT (mean±SD)	33.3±20.5	33.4±22.9	33.0±16.6	0.51
SDMT (mean±SD)	42.1±15.8	39.4±14.9	46.0±16.4	**0.001**
BVMT (mean±SD)	17.4±8.1	16.1±8.2	19.7±7.6	0.41
CVLT (mean±SD)	50.3±13.8	49.4±13.5	51.6±14.2	0.09
Years of education	15.1±3.7	15.4±3.6	14.7±3.6	0.43

Ages and DD are expressed in years.

*p Values for the PP-MS vs SP-MS comparison. Significant differences between the two groups are reported in bold.

9-HPT, 9-Hole Peg Test; BVMT, Brief Visuospatial Memory Test–Revised; CVLT, California Verbal Learning Test II; DD, disease duration; EDSS, Expanded Disability Status Scale; FS, cerebellar functional system; MS, multiple sclerosis; PP-MS, primary progressive multiple sclerosis; SDMT, Symbol Digit Modalities Test; SP-MS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk Test.
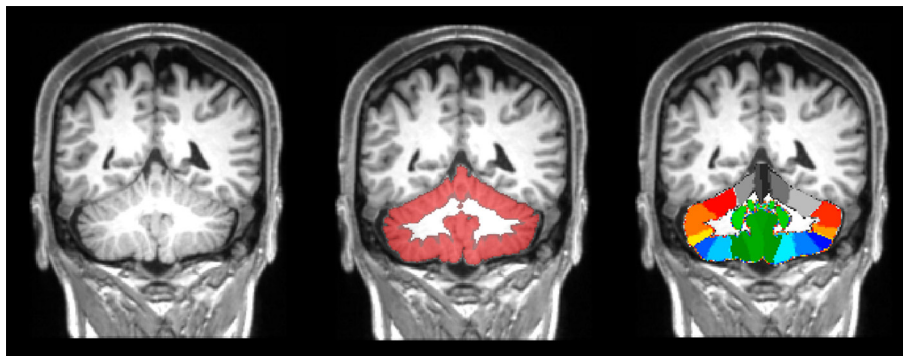
Figure 1 Lesion-filled T1-weighted coronal reconstruction of a 57-year-old male patient with MS. In the middle, the isolated cerebellar grey matter in red obtained by SUIT is superimposed to the T1-weighted image. On the right, the SUIT cerebellar atlas aligned in the native subject space.

distribution (DD, T25FW, 9-HPT and LV) were normalised by log-transformation for the subsequent analyses.

Group differences for demographic variables (age, sex, DD and years of education) were probed by Student's t-test analysis (for age, DD and educational level) and by χ^2 test (for sex), with a significance level set at p<0.0125, Bonferroni corrected for multiple comparisons (0.05/4, as the number of tested demographic variables).

Differences between MS subgroups in motor variables were tested via generalised linear model (GLM), including the effect of DD in the model, with a significance level of p<0.0125, Bonferroni corrected for multiple comparisons (0.05/4, as the number of tested motor scores). Similarly, differences between these two groups in cognitive tests were probed via multivariate GLM, including DD, level of education and a variable to take into account the different country of origin as covariates, with significance level set at p<0.016 after Bonferroni correction for multiple comparisons (0.05/3, as the number of tested cognitive scores).

Group differences in MRI metrics (GMF, LV and CLV) were tested by ANOVA analysis, including DD as covariate when testing differences between MS subgroups, with significance level set at p<0.016, Bonferroni corrected for multiple comparisons (0.05/3, as the number of tested MRI metrics).

Group differences in terms of cerebellar volumes were tested via multivariate GLM, including the effect of ICV, in order to account for head size, with a significance level set at p<0.004, Bonferroni corrected for multiple comparisons (0.05/13, as the number of tested cerebellar volumes). When comparing MS subgroups, DD was entered as additional covariate. In order to explore the potential influence of scanner differences on the between-group comparison, we run a post hoc analysis on volumetric measures entering scanner type as fixed factor and disease duration, EDSS and, where appropriate, ICV as covariates of no interest. Because none of the explored metrics (GMF, total cerebellar volume as well as anterior cerebellar volume/anterior lobular volumes and posterior cerebellar volume/posterior lobular volumes) were significantly different between the two study sites (p>0.05), scanner type was not entered as covariate in the final group comparison.

Finally, the relationship between cerebellar volumes and clinical scores was investigated via hierarchical multiple linear regression analysis. For all models, the first block included the demographic variables (age, sex and DD), and the second and the third blocks included brain MR metrics (GMF and LV) and cerebellar MR metrics, entered in a stepwise order. Different models were tested, using alternatively anterior cerebellar volume/

anterior lobular volumes as input for predicting motor scores and posterior cerebellar volume/posterior lobular volumes as input for predicting cognitive scores. In the models predicting cognitive performance, years of education was entered as additional variable in the first block. Models were considered significant for p<0.007, Bonferroni corrected for multiple comparisons (0.05/7, as the number of tested clinical variables); within each significant model, independent predictors were considered significant for p<0.05.

All analyses were carried out using Statistical Package for Social Science (SPSS V.20.0).

RESULTS

Demographic and clinical assessment

Patients with HC and MS did not differ for age and sex (p=0.10 and p=0.11, respectively).

Results of the demographic and clinical assessment analyses are reported in table 1.

PP-MS and SP-MS groups did not show any significant differences in terms of demographic variables other than a longer DD in the SP group (p=0.0003).

Although no differences were present between PP-MS and SP-MS in terms of motor variables, patients with PP-MS showed worse performances compared with SP-MS for SDMT (p=0.001) when testing cognitive status, whereas no other differences emerged for the BMVT and CVLT.

MRI volumetric analysis

A complete list of the MRI volumetric analysis, with the respective p values, is reported in table 2.

The entire MS population showed a reduction in GMF compared with HC (p<0.0001), whereas no differences emerged for any of the tested MRI metrics (GMF, LV nor CLV) between the MS subgroups.

All cerebellar volumes (global, anterior and posterior cerebellar volumes, as well as individual lobular volumes) were significantly lower in patients with MS in comparison with HC (p<0.004), with the only exception of Crus II and Lobule IX volumes that did not survive the multiple comparison correction (p=0.01), and Lobule X, in which mean values were lower in patients with MS compared with HC but did not reach the statistical significance (p=0.06). When comparing MS subgroups, no differences emerged between patients with PP-MS in comparison with patients with SP-MS.

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Table 2 MRI metrics for all subjects included in the analysis

	HC (n=46)	MS (n=82)	PP-MS (n=47)	SP-MS (n=35)	p Value*	p Value†
GMF (mean±SD)	0.39±0.03	0.36±0.05	0.36±0.05	0.35±0.05	**<0.0001**	0.86
LV (mean±SD)	n.a.	9.3±12.7	7.9±10.1	11.0±15.5	n.a.	0.27
CLV (mean±SD)	n.a.	0.2±0.2	0.2±0.2	0.2±0.2	n.a.	0.72
Global cerebellar volume	141.24±19.79	132.64±16.53	132.12±14.40	133.33±19.23	**0.001**	0.50
Anterior cerebellar volume	26.27±3.68	24.79±2.73	24.73±2.58	24.86±2.95	**0.001**	0.65
Posterior cerebellar volume	114.98±16.2	107.85±13.96	107.38±11.99	108.47±16.41	**0.002**	0.48
Lobules I–IV volume	13.73±1.97	13.01±1.39	12.98±1.34	13.05±1.48	**0.001**	0.74
Lobule V volume	12.53±1.73	11.78±1.37	11.75±1.28	11.81±1.50	**0.001**	0.58
Lobule VI volume	24.13±3.10	22.80±2.81	22.60±2.60	23.06±3.09	**0.002**	0.22
Crus I volume	29.06±4.09	27.15±3.66	26.87±3.21	27.53±4.21	**0.001**	0.21
Crus II volume	20.34±3.18	19.12±2.72	19.19±2.30	19.04±3.22	0.01	0.90
Lobule VIIb volume	11.06±1.71	10.31±1.51	10.32±1.26	10.29±1.80	**0.003**	0.98
Lobule VIIIa volume	11.68±1.81	10.95±1.52	10.96±1.32	10.93±1.78	**0.004**	0.79
Lobule VIIIb volume	9.35±1.43	8.67±1.20	8.64±1.04	8.70±1.41	**0.001**	0.54
Lobule IX volume	7.66±1.20	7.21±1.06	7.17±0.91	7.26±1.24	0.01	0.46
Lobule X volume	1.71±0.23	1.65±0.18	1.64±0.18	1.65±0.20	0.06	0.36

Volumes (in millilitres) are expressed as mean ±SD deviation.

*p Values for the HC vs MS comparison. Significant differences between the two groups are reported in bold.

†p Values for the PP-MS vs SP-MS comparison. Significant differences between the two groups are reported in bold.

CLV, cerebellar lesion volume; GMF, supratentorial grey matter fraction; HC, healthy controls; LV, whole brain lesion volume; MS, multiple sclerosis; n.a., not applicable; PP-MS, primary progressive multiple sclerosis; SP-MS, secondary progressive multiple sclerosis.

Correlations between cerebellar volumes and clinical disability

Scatterplots of the relationships between cerebellar lobular atrophy and clinical variables are shown in figure 2, whereas a complete list of regression analysis results are reported in tables 3 and 4.

Regression models exploring the relation between EDSS/cerebellar FS score, demographical and MRI variables did not identify any significant predictor.

The regression model exploring the relationship between T25FW, demographical and MRI variables (GMF, LV, CLV and anterior cerebellar volume) explained 15.0% of the variance in T25FW (p=0.028, not significant when correcting for multiple comparisons), with 6.9% of the variance explained by cerebellar metrics, and the anterior cerebellar volume as the only independent predictor (p=0.024). A nearly identical regression model, with anterior cerebellar lobules volume entered in the third block, explained 15.5% of the variance in T25FW (p=0.024, not significant when correcting for multiple comparisons), with 7.4% of the variance explained by cerebellar metrics, and Lobules I–IV volumes as the only independent predictor (p=0.019).

The regression model exploring the relationship between 9-HPT, demographical and MRI variables (GMF, LV, CLV and anterior cerebellar volume) explained 33.4% of the variance in 9-HPT (p<0.0001), with 13.1% of the variance explained by cerebellar metrics, and CLV as an independent predictor (p=0.001).

The regression model exploring the relationship between SDMT, demographical and MRI variables (GMF, LV, CLV and posterior cerebellar volume) explained 30.6% of SDMT variance (p<0.001) with 5.6% of the variance explained by cerebellar metrics, and the posterior cerebellar volume as an independent predictor (p=0.024). When replacing the posterior cerebellar volume with the volume of individual posterior cerebellar lobules, 38.3% of the variance in SDMT was explained (p=0.0001), with 4.7% of the total variance explained by cerebellar metrics, and Lobule VI/Crus I as independent predictors (p=0.029 and p=0.001, respectively).

The regression model exploring the relationship between BVMT, demographic and MRI variables (GMF, LV, CLV and posterior cerebellar volume) accounted for 32.2% of BVMT variance (p<0.001), with 4.3% of the variance explained by cerebellar metrics, and the posterior cerebellar volume as an independent predictor (p=0.046). When replacing the posterior cerebellar volume with the individual posterior cerebellar lobules volume, 33.5% of the variance in BVMT was explained (p<0.0001), with 5.7% of the total variance explained by cerebellar metrics, and Lobule VIIIa volume as an independent predictor (p=0.022).

Although posterior cerebellar volume did not independently predict CVLT, the regression model exploring the predictive role of individual cerebellar lobules explained 28.9% of CVLT variance (p=0.001), with 5.5% of the variance explained by cerebellar metrics, and Crus I volume as an independent predictor (p=0.026).

DISCUSSION

To the best of our knowledge, this is the first study that explores the contribution of specific cerebellar lobule volumes to clinical impairment in patients with progressive MS.

Different elements contribute to clinical disability in progressive MS, including GM volume loss, spinal cord atrophy, T2-weighted lesion burden and cerebellar damage.[2][4] Among these, brain atrophy plays a central role in the development of both motor and cognitive impairments.[23–27] As highlighted by most of the studies focused on cerebellar volumetry,[4][7][9][10][21] GM volume loss is not only limited to supratentorial structures. Similar to what has been hypothesised for deep GM nuclei involvement, cerebellar damage could be determined by the occurrence of both focal lesions and damage to its afferent and efferent connections with all major components of the CNS (cerebrum, basal ganglia, diencephalon, limbic system, brainstem and spinal cord).[2][28]

The cerebellum plays a central role in brain function due to its involvement in motor tasks and non-motor functions.
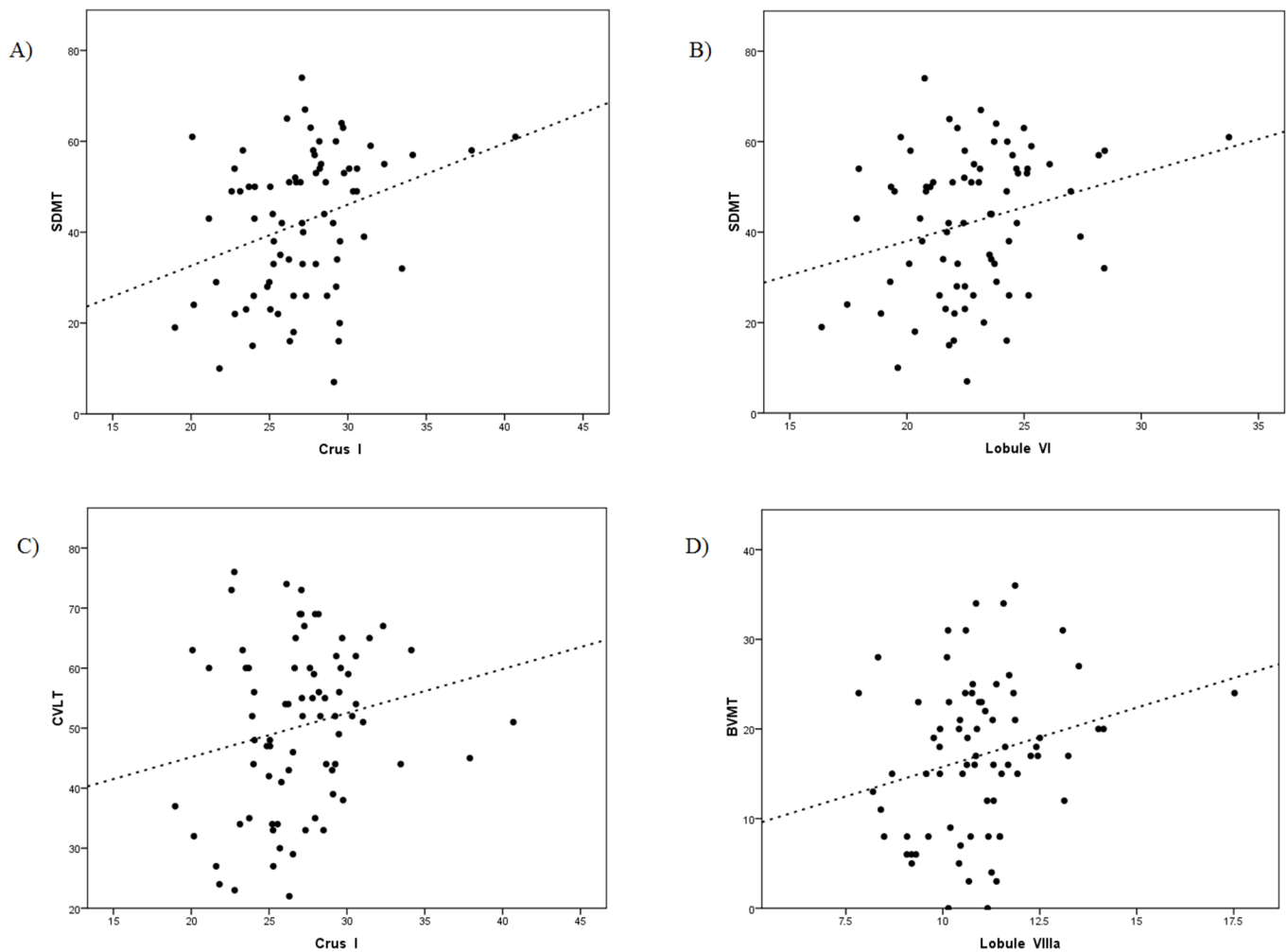
Figure 2 Scatterplots of the correlations between Symbol Digit Modalities Test (SDMT) scores, Crus I (A) and Lobule VI (B) volumes, respectively; between California Verbal Learning Test II (CVLT) scores and Crus I volume (C) and between Brief Visuospatial Memory Test (BVMT) scores and Lobule VIIIa volume (D) in the Multiple Sclerosis group.

In addition to the modulation of four main cognitive domains (executive functions, language and verbal memory, spatial tasks and emotions),[29 30] the cerebellum contributes to the control and estimation of future motor activation for movement coordination purposes.[31] Current data, supported by a meta-analysis of the available neuroimaging studies,[14] prove that the cerebellum shows a functional dichotomy, with the anterior lobe mainly related to sensorimotor activities and the posterior lobe predominantly involved in higher-level cognitive tasks, in particular Lobules VI and VII.[32] Evidence suggests that Lobule VI and Crus I could be functionally involved in different cognitive domains, showing activation during working memory tasks when testing executive functions and in emotion processing.[32]

Although the relationship between cerebellar atrophy and clinical disability in MS has been acknowledged in several studies,[7 9 21] the functional dichotomy and the contribution of specific lobules have been rarely explored in MS and never investigated in the progressive population, where cerebellar involvement is a predominant feature. A recent publication has reported, in a cohort of patients with MS, including a relatively small group of SP-MS, a correlation between anterior and posterior cerebellar subregions and motor and cognitive impairment, respectively.[21] The specific contribution of each lobule to the development of the clinical impairment has been recently

explored in a large and heterogeneous group of MS subjects, including clinically isolated patients with syndrome as well as patients with MS with 15 years of DD, revealing a direct correlation between specific lobular volumes (especially Lobule VI) and impairment in information processing speed.[18]

Our results confirm and expand these findings. Indeed, we found a reduction of both anterior and posterior cerebellar volumes in patients with progressive MS compared with HC, which is in line with what has been reported for the MS population by D'Ambrosio and colleagues.[21] Likewise, we found a significant contribution of different cerebellar metrics to motor and cognitive clinical outcomes in our group, thus confirming the impact of cerebellar atrophy on the clinical status of patients with MS and its aforementioned functional dichotomy.[13 21 32] Furthermore, atrophy of specific cerebellar lobules seems to predict different aspects of clinical disability. Specifically, atrophy of Lobules I–IV, but not Lobule V, contributes to T25FW performance. This result is in line with the known major role of the more anterior lobules (Lobules II and III, in particular) in lower limb movements control, in contrast to the preferential activation of the more posterior Lobules IV–VI for hand movements, as reported in fMRI and focal lesion studies.[33–36] 9-HPT performance was also influenced by cerebellar metrics, but mainly by cerebellar lesion load rather than atrophy. Although apparently

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Table 3 Results of the hierarchical multiple linear regression analysis when considering anterior and posterior cerebellar volumes

	Model					Independent predictors		
	R^2	R^2 change	F	DF	p Value	β	t Value	p Value
T25FW	0.150	0.069	2.903	4–66	0.028*			
Anterior cerebellum						−0.290	−2.309	0.024
9-HPT	0.334	0.131	6.714	5–67	<0.0001			
Sex						0.296	2.820	0.006
LV						0.241	2.138	0.036
CLV						0.437	3.630	0.001
SDMT	0.306	0.056	4.847	6–66	<0.001			
Years of education						0.138	2.984	0.004
Sex						−0.227	−2.033	0.046
LV						−0.296	−2.506	0.015
Posterior cerebellum						0.258	2.311	0.024
BVMT	0.322	0.043	5.138	6–65	<0.001			
Years of education						0.241	2.283	0.026
GMF						0.477	4.348	<0.0001
Posterior cerebellum						0.222	2.036	0.046
CVLT	0.234	0.082	4.148	5–68	0.002			
Years of education						0.346	3.185	0.002
GMF						0.312	2.702	0.009

*Not significant after Bonferroni correction.

9-HPT, 9-Hole Peg Test; BVMT, Brief Visuospatial Memory Test–Revised; CLV, cerebellar lesion volume; CVLT, California Verbal Learning Test II; GMF, grey matter fraction; LV, whole brain lesion volume; SDMT, symbol digit modalities test; T25FW, Timed 25-Foot Walk Test.

counterintuitive and not in line with previous evidences,[7 21] the lack of correlation between cerebellar volumes and 9-HPT scores has already been reported[8] and might be ascribed to the different association of cerebellar GM and WM volumes with manual motor performance. In particular, cerebellar WM volume, that preferentially correlates with hand dexterity,[37] has not been assessed in the present study. Finally, we have found no correlations between cerebellar atrophy and both EDSS and FS,

in line with most of the previous works which failed to find a correlation between these scores and cerebellar volumes,[8 10 11 38] probably due to the low specificity of these measures, that can be influenced by pyramidal involvement and fatigue.

When analysing the contribution of cerebellar lobules to cognitive status in patients with progressive MS, a preferential involvement of Crus I emerged above the other posterior cerebellar lobules as independent predictor of SDMT and CVLT

Table 4 Results of the hierarchical multiple linear regression analysis when considering cerebellar lobule volumes

	Model					Independent predictors		
	R^2	R^2 change	F	DF	p Value	β	t Value	p Value
T25FW	0.155	0.074	3.017	4–66	0.024*			
Lobules I–IV						−0.303	−2.398	0.019
9-HPT	0.334	0.131	6.714	5–67	<0.0001			
Sex						0.296	2.820	0.006
LV						0.241	2.138	0.036
CLV						0.437	3.630	0.001
SDMT	0.383	0.047	5.764	7–65	0.0001			
Years of education						0.356	3.469	0.001
LV						−0.397	−3.398	0.001
Crus I						0.765	3.337	0.001
Lobule VI						−0.545	−2.231	0.029
BVMT	0.335	0.057	5.456	6–65	<0.0001			
Years of education						0.242	2.317	0.024
GMF						0.478	4.399	<0.0001
Lobule VIIIa						0.250	2.350	0.022
CVLT	0.289	0.055	4.534	6–67	0.001			
Years of education						0.338	3.197	0.002
GMF						0.311	2.780	0.007
Crus I						0.242	2.278	0.026

*Not significant after Bonferroni correction.

9-HPT, 9-Hole Peg Test; BVMT, Brief Visuospatial Memory Test–Revised; CLV, cerebellar lesion volume; CVLT, California Verbal Learning Test II; GMF, grey matter fraction; LV, whole brain lesion volume; SDMT, Symbol Digit Modalities Test; T25FW, Timed 25-Foot Walk Test.

performances. In particular, SDMT scores were mainly predicted by Crus I, with a minor contribution of Lobule VI. This result is in line with the known major involvement of Crus I and Lobule VI in attention[28] and executive function,[14] and with the notion that processing speed is closely related to executive performance.[39] Similarly, Crus I contributes to CVLT performances, in agreement with recent findings in neurodegenerative cerebellar disease[15] and with the known physiological role of Crus I in verbal working memory encoding.[14] Finally, we confirmed the role of Lobule VIIIa in visual working memory encoding,[39] demonstrating its role as an independent predictor of BVMT scores. In addition to cerebellar damage, significant predictors of clinical disability in several models were LV and GMF, thus highlighting the importance of supratentorial brain involvement in motor and cognitive impairment determination.[26]

Some limitations should be considered. First, our study has a cross-sectional design and therefore only allows for a limited number of conclusions. Furthermore, our analysis focused on volumetric changes, without evaluating functional data. Therefore, future evaluations of the possible interactions between cerebellar atrophy and functional connectivity changes in patients with progressive MS are warranted to further elucidate the role of cerebellum in the development of MS clinical disability. Moreover, we did not evaluate cerebellar cortical lesions or disruption of normal appearing WM in these patients, which are known correlates of clinical disability in MS.[4 12] Finally, although the BICAMS battery has been validated in both US and Italy and we have taken into account the enrolment country as possible confounding factor when analysing the cognitive data, we cannot exclude a residual impact of the different language version of the batteries on our group comparison.

CONCLUSIONS

In conclusion, we proved that beyond the degree of impairment accounted for by supratentorial damage, atrophy of specific cerebellar lobules explains different aspects of motor and cognitive disability in progressive MS, thus suggesting that the investigation of cerebellar damage provides further insight into the physiopathological basis of clinical disability in progressive MS. Future studies, including a direct comparison of the possible different contribution of cerebellar lobule atrophy to clinical disability in different MS phenotypes, are warranted in order to clarify the contribution of cerebellar damage to disability accrual along the disease natural history.

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