CEREBELLAR CONTRIBUTION TO MOTOR AND COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS PATIENTS: A SUB-REGIONAL STRUCTURAL MRI ANALYSIS

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INTRODUCTION and PURPOSE

The cerebellum plays a role in a wide variety of complex behaviors.

Our aim is to investigate the role of cerebellar sub-regions on motor and cognitive performance in multiple sclerosis (MS) patients.

METHODS

We recruited 95 consecutive right-handed MS patients and 32 sex-matched healthy controls (HC) (**Table 1**).

Table 1. Main demographic, clinical and MRI measures from all subjects.

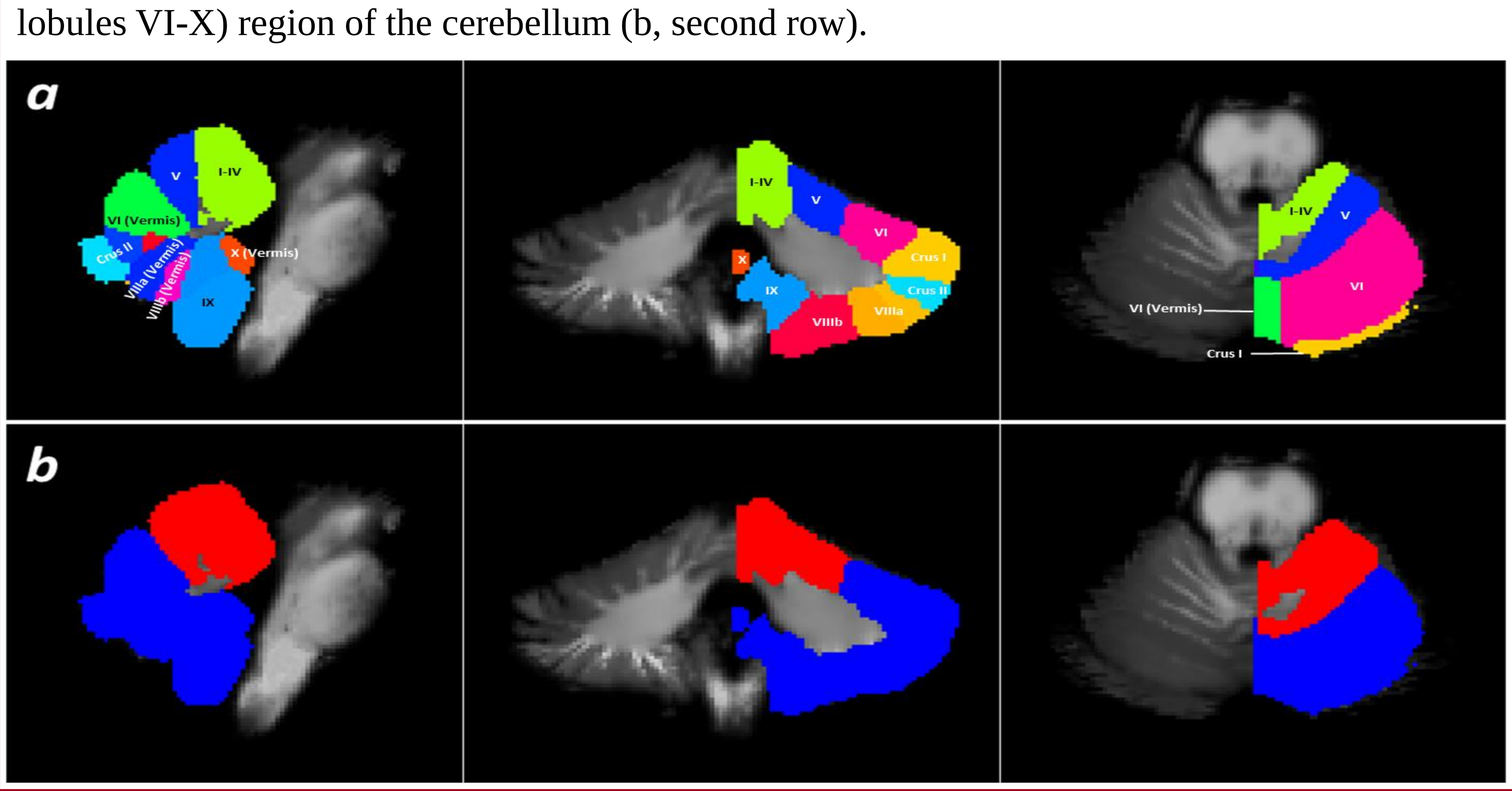
Variable	HC	MS	RRMS	BMS	SPMS	p value[a]	p value[b]
n	32	95	52	20	23	-	-
Mean age (SD), years	39.6 (8.4)	45.2 (10.7)	43.3 (11.2)	42.6 (7.8)	51.9 (9.1)	0.6	0.1
Females / Males	14/18	57/38	34/18	9/11	14/9	0.1	<0.001
Median disease duration, years (range)	-	14.6 (0-42)	8.2 (0-34)	18.4 (15-26)	19.6 (3-42)	-	<0.001
Median EDSS (range)	-	2.5 (1.0-8.0)	2.0 (1.0-6.0)	1.5 (1.0-3.0)	6.5 (3.0-8.0)	-	<0.001
Mean education, years (SD)	16.9 (2.6)	13.5 (3.5)	13.8 (3.7)	14.4 (2.4)	12.6 (3.9)	<0.001	0.5
Mean Inv Right 9-HPT (SD)	0.04 (0.008)	0.04 (0.01)	0.04 (0.009)	0.04 (0.008)	0.03 (0.01)	0.06	0.1
Mean SDMT (SD)	-	43.8 (13)	46.8 (13)	45.8 (8)	34.8 (11)	-	0.003
Mean PASAT3 (SD)	-	36.5 (12)	36.6 (12)	38.5 (11)	34.4 (15)	-	0.6
Mean T2 LV, mL (SD)	-	11.3 (14)	9.5 (13)	9.6 (7)	17.3 (18)	-	0.5
Mean infratentorial T2 LV, mL (SD)	-	0.4 (0.5)	0.3 (0.5)	0.3 (0.3)	0.5 (0.5)	-	0.7
Mean NBV, mL (SD)	1496 (55)	1405 (70)	1406 (74)	1395 (64)	1411 (69)	<0.001	0.6
Mean GMV, mL (SD)	810 (35)	749 (40)	753 (40)	742 (31)	747 (47)	<0.001	0.6
Mean WMV, mL (SD)	686 (33)	655 (41)	653 (43)	652 (42)	663 (38)	0.02	0.6
Mean Tot Cerebell Vol, mL (SD)	131 (3)	127 (5)	127 (4)	128 (3)	123 (5)	0.2	0.5
Mean Ant Cerebell Vol, mL (SD)	17 (1)	17 (1)	17(1)	17 (1)	16 (1)	0.1	0.02
Mean Post Cerebell Vol, mL (SD)	113 (3)	109 (4)	110 (4)	110 (2)	107 (4)	0.08	0.02

Abbreviations: RR=Relapsing-Remitting; BMS=Benign MS; SP=Secondary Progressive; SD=Standard Deviation; LV=Lesion Volume; NBV=Normalized Brain Volume; GMV=Gray Matter Volume; WMV=White Matter Volume; Tot=Total; Ant=Anterior; Post=Posterior; Cerebell Vol=Cerebellar Volume. p-value[a] = Mann-Whitney test for the comparison between HC *vs* MS patients (as a whole); p-value[b] = Kruskal-Wallis test for the comparison between MS phenotypes.

Cerebellar analysis was performed on the high resolution 3D-T1-weighted brain images using the SUIT tool from SPM12. The 28 cerebellar lobules were merged to obtain the volume of the anterior (lobules I-V) and posterior (lobules VI-X) cerebellar regions (**Figure 1**).

Figure 1. T1-weighted scan of a representative MS patient transformed into the atlas space with the SUIT atlas overlapped.

The different colours show the lobular parcellation (a, first row). According to Stoodley et al. (2010), lobules were merged to obtain the anterior (red, lobules I-V) and the posterior (blue, lobules VI-X) region of the cerebellum (b, second row).



For all subjects, we obtained normalized brain volumes and 9-Hole Peg Test (9-HPT). MS patients also underwent a clinical and cognitive evaluation, including the EDSS, SDMT and PASAT.

Multivariate linear regression models assessed the relationships between MRI measures and motor/cognitive scores.

RESULTS

Secondary progressive (SP) MS patients showed significant lower cerebellar volumes compared to HC. In the whole MS group, we found:

- positive correlation between motor performance and cerebellar volumes, mostly in the anterior region (lobules I-V) (p=0.001 for EDSS; p=0.01 for 9-HPT) (**Figure 2a-b**);
- positive correlation between cognitive performance and cerebellar volumes, mostly in the posterior-inferior region (lobules VI-X) (p<0.001 for SDMT; p=0.006 for PASAT) (**Figure 2b-c**).

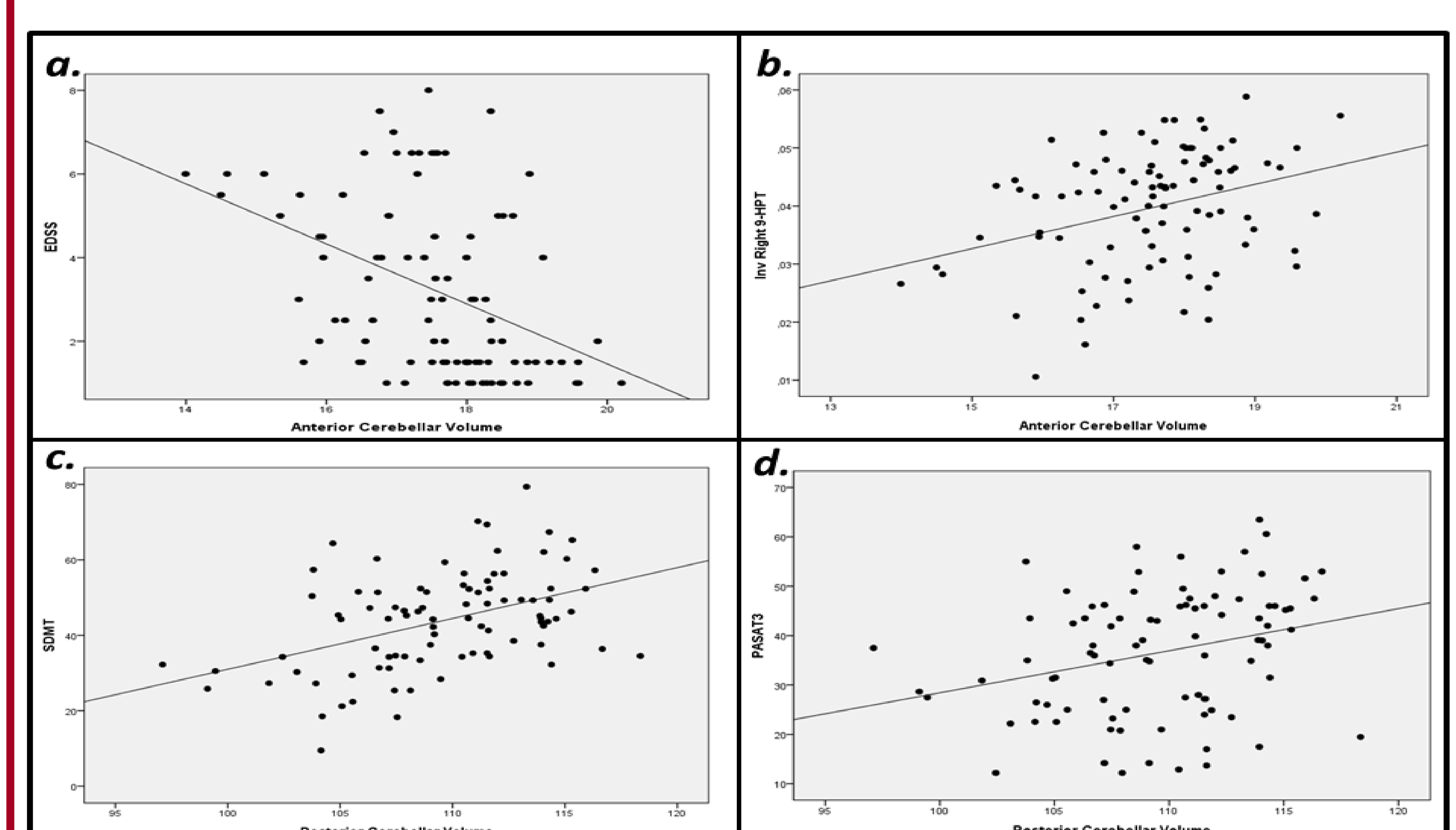
Final multivariate models included T2 lesion volume (LV) and anterior cerebellar volume as independent predictors of motor performance, and T2-LV and posterior cerebellar volume as independent predictors of cognitive performance (**Table 2**).

Table 2. Correlation analysis between clinical scores (EDSS, Inv Right 9-HPT, SDMT, PASAT3) and MRI parameters in MS patients.

Variable	Covariate	Spearman rho	p-value	Multivariate Analysis		
				R^2	Beta	p-Value
EDSS	T2 LV	0.26	0.01	0.253	0.237	**0.01**
	NBV	-0.01	0.9			
	GMV	-0.08	0.4			
	WMV	0.06	0.5			
	Infratentorial T2 LV	0.33	0.001			
	Tot Cerebell Vol	-0.30	0.004			
	Ant Cerebell Vol	-0.33	0.001		-0.320	**0.003**
	Post Cerebell Vol	-0.25	0.01			
Inv Right 9-HPT	T2 LV	-0.24	0.01	0.208		
	NBV	0.20	0.04			
	GMV	0.15	0.1			
	WMV	0.19	0.05			
	Infratentorial T2 LV	-0.29	0.005			
	Tot Cerebell Vol	0.25	0.01			
	Ant Cerebell Vol	0.26	0.01		0.264	**0.02**
	Post Cerebell Vol	0.21	0.04			
SDMT	T2 LV	-0.51	<0.001	0.358	-0.382	**<0.001**
	NBV	0.19	0.06			
	GMV	0.18	0.08			
	WMV	0.16	0.1			
	Infratentorial T2 LV	-0.32	0.002			
	Tot Cerebell Vol	0.46	<0.001			
	Ant Cerebell Vol	0.35	0.001			
	Post Cerebell Vol	0.44	<0.001		0.251	**0.01**
PASAT3	T2 LV	-0.29	0.006	0.135	-0.235	**0.03**
	NBV	-0.04	0.6			
	GMV	-0.07	0.5			
	WMV	0.01	0.9			
	Infratentorial T2 LV	-0.17	0.1			
	Tot Cerebell Vol	0.29	0.007			
	Ant Cerebell Vol	0.15	0.1			
	Post Cerebell Vol	0.29	0.006		0.238	**0.05**

Abbreviations: LV=Lesion Volume; NBV=Normalized Brain Volume; GMV=Gray Matter Volume; WMV=White Matter Volume; Tot=Total; Ant=Anterior; Post=Posterior; Cerebell Vol=Cerebellar Volume.

Figure 2. Correlation scatterplots from the whole MS group between: (a) volumes of the anterior cerebellar regions and EDSS score (r=-0.33; p=0.001); (b) volumes of the anterior cerebellar regions and inverted right hand 9-HPT score (r=0.26; p=0.01); (c) volumes of the posterior cerebellar regions and SDMT score (r=0.44; p<0.001); and (d) volumes of the posterior cerebellar regions and (PASAT3 score (r=0.29; p=0.006).



Abbreviations: EDSS=Expanded disability Status Scale; 9-HPT=9-Hole Peg Test SDMT=Symbol Digit Modalities Test; PASAT=Paced Auditory Serial Addition Test.

CONCLUSIONS

Cerebellar volumetric abnormalities contribute to explain motor and cognitive performance in MS patients.

Consistently with functional mapping studies, cerebellar posterior-inferior volume accounted for variance in cognitive measures, whereas anterior cerebellar volume accounted for variance in motor performance, supporting the assessment of cerebellar damage at sub-regional level.

DISCLOSURES

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