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Regional cerebellar atrophy in multiple sclerosis patients with different levels of fatigue and cognitive impairment

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Background

Cognitive impairment (CI) and fatigue are common debilitating conditions in multiple sclerosis (MS), but their neural mechanisms and brain damage patterns remains poorly understood. CI and primary fatigue in MS have been associated with partially overlapping regions of cortical and deep gray matter (DGM) atrophies[1,2]. However, it is possible that those symptoms are consequence of dysrupted networks that involve other brain areas, including brainstem and cerebellum.

Cerebellum damage is traditionally associated with coordination and movement disorders. More recently, it was discovered cerebellar connections that are critical to cognition, emotion and associative functions[3]. However, the association between regional cerebellum atrophy cognitive impairment (CI) and fatigue in MS remains poorly understood. Furthermore, it remains unclear wether are overlapping or specific patterns of cerebellum atrophy when CI occur alone or combined.

Objective

This study aims to assess segmented cerebellum atrophy in pwMS with different levels of CI and fatigue.

Methods

Cross-sectional study including 266 people with MS (pwMS) and 96 healthy controls (HC).

MRI assessement: whole-brain 3T scanner

Cognitive assessment: 7 domains

Fatigue: Checklist Individual Strength (CIS-20)

Anxiety and depression: Hospital Anxiety and Depression Scale (HADS-A and HAD-D)

Classification of pwMS:

Cognitively impaired (CI): z-score ≤ -1.5 in 2 or more domais

High-fatigue: CIS-20 socre > 76

4 groups: CPLF = cognitively preserved low fatigue, CPHF = cognitively preserved high fatigue, CILF = cognitively impaired low fatigue, CIHF = cognitively impaired high fatigue

Cerebellum regional atrophy: Lesion-filled 3DT1 -> automatic parcellation in 23 regions (figure 1)

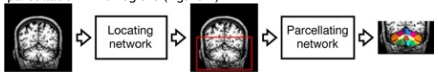

Figure 1. Flowchart of ACAPULCO The cerebellum is parcellated using two CNNs: the locating network identifies a bounding box around the cerebellum, and the parcellating network labels the regions within this bounding box.

Results

Table 1. Demographic characteristics, disease related variables, cognitive performance, fatigue, anxiety and depression scores in the groups

	HCs (n=81)	CPLF (n=78)	CPHF (n=66)	CILF (n=55)	CIHF (n=67)	*p*
Age	47.5 (9.6)	46.8 (10.6)	47.5 (10.0)	51.0 (11.7)	52.0 (11.2)	0.009
Sex female %	59	74	79	34	63	0.049
RRMS		68 (87.2%)	52 (78.8%)	41 (74.55%)	37 (55.2%)	<0.001
SPMS		7 (8.9%)	11 (16.7%)	7 (12.7%)	22 (32.8%)	
PPMS		3 (3.8%)	3 (4,6%)	7 (12.7%)	8 (11.9%)	
EDSS		2.5 (2-3.5)	3.0 (2.5-4)	3.5 (2.5-6)	4.0 (3-6)	<0.001
Avg Cog	-0.02 (0.47)	-0.18 (0.45)	-0.22 (0.50)	-1.50 (0.94)	- 1.62 (0.84)	<0.001
CIS	35 (28-49)	51 (37-66)	97 (83-106)	62 (47-70)	90 (84-105)	<0.001
HADS-A	3 (2-5)	3 (2-5)	5 (3-7)	3 (2-6.5)	4 (3-8)	0.003
HADS-D	1 (0-2)	1 (0.5-2.5)	4 (1.5-7)	2 (1-3.25)	5 (2-7)	<0.001

Age is expressed in years (standard deviation); Average cognition (Avg Cog) is expressend in z-score mean (standard deviation); EDSS, CIS, HADS-A (anxiety) and HADS-D are expressed in median (interquartile range)

The cerebellum volumes were significantly reduced in 10 cortical regions and corpus medullaris in pwMS vs HC. The cortical regions were symmetrical (left and right and the volumes were merged and represented bellow (figure 2 and 3)

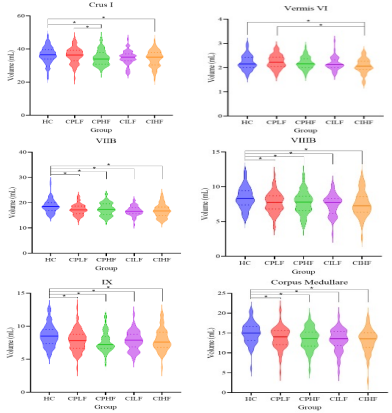

Figure 2. Cerebellar regional volumes for each group in milliliters (mL.) Volumes from all regions that significantly differed between the five groups: Crus I, Vermis VI, Corpus Medullare, lobule VIIIB, VIIIB and IX. Pairwise comparison differences considered significant when p<0.05.

*<0.05

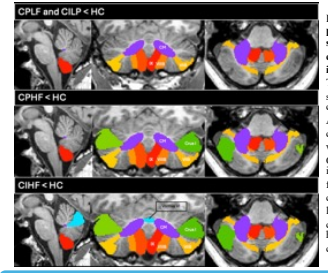

Figure 3. Anatomic locations of significant regional cerebellum atrophy in MS groups vs HC The segments with significant atrophy compared to HC. Abbreviations: CIHF: cognitively impaired with high fatigue; CILP: cognitively impaired without low fatigue; CPLF: cognitively preserved low fatigue; CPHF: cognitively preserved high fatigue; CM: corpus medullaris.

Conclusions

Fatigue and cognitive impairment are frequent in pwMS, affecting 50% and 45.8% of the pwMS, respectively, in this study. Those conditions can occur independently or combined.

The group with combined cognitive impairment and fatigue has a higher frequency of progressive MS.

All MS groups have reduced cerebellum volumes, compared to HC, affecting mainly the posterior lobe and corpus medullaris.

High fatigue levels = more atrophy in Crus I.

Combined cognitive impairment and high-fatigue = more atrophy in Vermis VI.

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