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Superior Cerebellar Peduncle Atrophy Predicts Cognitive Impairment in Relapsing Remitting Multiple Sclerosis Patients with Cerebellar Symptoms: A DTI Study

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Abstract

Background: Using Diffusion Tensor Imaging (DTI), we tested the hypothesis that cerebellar abnormalities in fractional anisotropy (FA) may be involved in cognitive dysfunctions in Relapsing-Remitting (RR)-Multiple Sclerosis (MS).

Objective: The aim of our study was to investigate the microstructural integrity in MS of regions that connect in both feedforward and feedback pathways to cortical areas, i.e., Superior Cerebellar Peduncles (SCP), Middle Cerebellar Peduncles (MCP), Dentate nuclei (DN) and Thalamus (Th).

Patients and methods: We studied 46 patients with RR-MS (21 with cerebellar signs and 25 without) and 23 normal subjects. All subjects underwent cognitive testing.

Results: In patients with a cerebellar phenotype, cognitive performance in all considered domains was from moderately to strongly related ($p<0.05$) to abnormalities of SCP ($r=0.119$ to 0.735) and Thalamus ($r=0.477$ to 0.602).

Discussion: Our study showed an important correlation between cognitive testing and FA values of SCP and thalamus in cerebellar MS patients. We found not only the involvement of thalamus but also of SCP that is an important link between cerebellar nuclei and thalamus, suggesting that a disconnection is present also out of the thalamus. These results suggest that SCP and thalamic damage is a clinically relevant biomarker of the neurodegenerative cerebellar process in MS.

Keywords: Multiple sclerosis; Cerebellar symptoms; DTI; Thalamus; Superior cerebellar peduncle; Middle cerebellar peduncle; Cognitive impairment

Introduction

The presence of cognitive dysfunctions in Multiple Sclerosis (MS) has been well described as one of the most common co-morbidities [1-3], with a prevalence ranging from 45% to 65% [4]. The most affected cognitive domains in MS are memory, visuospatial perception, executive functions, attention and information processing speed [5].

Although the cerebellum has been traditionally associated with motor control, recently a growing body of clinical and experimental evidences has suggested that it may be also involved in non-motor functions [6-8]. In fact, it has been shown that cerebellar abnormalities, e.g. lesions, are associated with cognitive impairment as measured by neuropsysiological tests [9]. Thus, evidences suggest that the cerebellum has an important role in monitoring sensory information and providing adaptation of both motor and non-motor functions to perform contextually relevant behaviours [10,11].

The cognitive role of the cerebellum is mainly due to its strong connections with several higher-level cortical regions, such as with the controlateral cerebral hemispheres in both feed forward and feedback directions. The feed forward loop (Figure 1 in blue) connects cortical areas via middle cerebellar peduncle (MCP) with deep cerebellar nuclei, including the dentate nucleus (DN) (afferent pathway). The feedback loop (Figure 1 in orange) connects the deep cerebellar nuclei with motor cortex, via the superior cerebellar peduncle (SCP), the red nucleus and the thalamus (Th) (efferent pathway) [12,13].

Disconnections of the fibers to the thalamus, negatively involve the limbic circuitry avoiding the mediation and regulation of many cognitive functions [14,15]. Although many studies have shown a strong association between thalamic atrophy and cognitive function [16-18], no one focused on its microstructural changes, as well as on abnormalities of MCP, SCP and DN, and on their relationships to cognitive functions in MS.

Diffusion tensor imaging (DTI) is one of the most sensitive methods for detecting subtle alterations of white matter [19] (WM) by evaluating the directional movement of water molecules in the brain. Analysis of DTI images could indeed distinguish between regions where fibers present a strong alignment from those with a lower coherence. Diffusion properties are summarized by several indices, in particular by fractional anisotropy (FA) that refers to the degree to which diffusion is direction-dependent. FA is used to quantify the changes in WM microstructure, which might be related to development or progression of a specific disease [20].

The aim of this study was to investigate a group of patients affected by relapsing-remitting multiple sclerosis with (RR-MSc) and without (RR-MSnc) cerebellar signs, in order to determine the alteration of FA in the Th, MCP, SCP and DN and their correlation to cognitive functions, as assessed by neuropsysiological tests. In particular, we examined two hypotheses:

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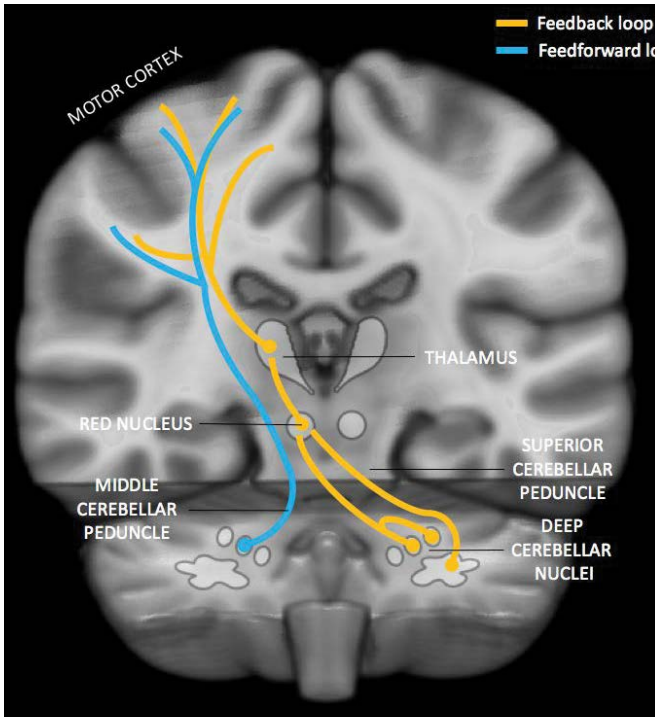

Figure 1: Schematic representation on the MNI standard T1-weighted of the feed forward loop (in blue) that connects cortical areas via middle cerebellar peduncle (MCP) with deep cerebellar nuclei, including the dentate nucleus (DN) (afferent pathway) and of the feedback loop (in orange) that connects the deep cerebellar nuclei with motor cortex, via th superior cerebellar peduncle (SCP), the red nucleus and the thalamus (Th) (efferent pathway).

1) FA values of Th, MCP, SCP and DN are lower in RR-MSc patients compared with RR-MSnc and with healthy controls;

2) Thalamic, MCP, SCP and DN FA values are correlated to cognitive impairment.

Materials and Methods

Participants

Our sample initially consisted of 46 patients with relapsing-remitting multiple sclerosis according to McDonald and Polman criteria [20]. All subjects were recruited from the Neurology Unit of the University "Magna Graecia" of Catanzaro. Patients' inclusion criteria were:

(1) No clinical relapses and steroid treatment at least one month prior to study enter [21];

(2) No concomitant therapy with antidepressant or psychoactive drugs;

(3) No evidence of dementia as assessed by the Mini Mental State Examination [22] (MMSE>24, cut-off value compared with normative data corrected for gender, age and education [23]);

(4) Expanded Disability Status Scale (EDSS) [24] score from 0 to 5;

(5) No history of psychiatric problems, according to the Structured Clinical Interview of the DSM-IV [25]. All patients were clinically evaluated by two neurologists (PV, SB), blind to any other result and with over 15 years of experience in MS. The clinical assessment also included the Fatigue Severity scale (FSS) [26].

From the initial cohort, 21 MS patients with predominant cerebellar symptoms (RR-MSc) were selected (mean age: 33.04 ± 5.04; males: 13; mean disease duration: 108.6 ± 64.7 months; median EDSS: 3.57 ± 0.8). In the RR-MSc group, the most common manifestations were gait ataxia and dysmetria, followed by tremor and dysdiadochokinesis and nystagmus.

These patients were matched for clinical variables with 25 MS patients without any cerebellar dysfunction (RR-MSnc) (mean age: 33.28 ± 7.8; males: 9; mean disease duration: 75.04 ± 59.9 months; median EDSS: 2.1 ± 0.66). Twenty-three healthy volunteers (mean age: 33.04 ± 4.8; males: 9) with no previous history of neurological/psychiatric diseases and with normal MRI of the brain were matched for demographic variables with MS patients. Exclusion criteria were known psychiatric disorders clinically significant depression or fatigue, and drug or alcohol abuse. All participants gave written informed consent, which was approved by the Ethical Committee of the University 'Magna Graecia' of Catanzaro, according to the Helsinki Declaration.

Neuropsychological assessment

All patients completed an extensive battery of neuropsychological tests [27], administered by an experienced clinical neuropsychologist blinded to clinical results (CC). The neuropsychological tests assessed were:

(a) STROOP-Color/Color Word

(b) WLG (Word List Generation)

(c) LTS (Long Term Storage)

(d) SDMT (Symbol Digit Modalities Test)

(e) CLTR (Consistent Long Term Retrieval); SPART-I/D (Spatial Recall Test Immediate/Delayed); BDI II (Beck Depression Inventory II)

(f) STAI-Y1/Y2. None of the subjects had been previously exposed to this neuropsychological evaluation. Finally, global cognitive function was tested using the Mini Mental State Examination (MMSE). Results were compared with Italian published normative values [28,29].

MRI acquisition

Subjects' MRI was acquired according to our routine protocol by a 3 T scanner with an 8-channel head coil (Discovery MR-750, General Electric, Milwaukee, WI, USA). The protocol included:

(a) whole-brain T1-weighted scan MRI scanning (SPGR; TE/TR=3.7/9.2 ms, flip angle 12°, voxel-size 1 × 1 × 1 mm^3)

(b) Conventional T2-weighted

(c) diffusion-weighted volumes, acquired by using spin-echo echo-planar imaging (TE/TR=87/10,000 ms, bandwidth 250 KHz, matrix size 128 × 128, 80 axial slices, voxel size 2.0 × 2.0 × 2.0 mm^3) with 27 equally distributed orientations for the diffusion-sensitizing gradients at a b-value of 1,000 s/mm^2. Particular care was taken to restrain the subject's movements with cushions and adhesive medical tape. Moreover, before further processing, we visually checked the images to exclude all scans with artifacts, largely caused by subject motion.

MRI/DTI analysis and ROI tracing

Hyperintensities (MS lesions) were manually segmented on T2-w

patients' images by an expert neurologist (G.N.) and supra-tentorial and infra-tentorial lesion volumes were calculated using a semi-automated technique with the Jim v6.0 software (Xinapse System, Leicester, UK) [30].

Diffusion images were first converted from DICOM to NifTI format by using the script *dcm2nii* from the MRIcron tool (http://www.mccauslandcenter.sc.edu/mricro/mricro/index.html). The FMRIB's v5.0 (Oxford Centre for Functional MRI of the Brain· www.fmrib.ox.ac.uk/fsl/) Diffusion Toolbox (FDT) was used for correcting eddy currents distortions and motion artifacts. The non-diffusion-weighted images (b=0) were skull stripped using the FMRIB's brain extraction tool (*bet*) and used to mask all diffusion-weighted images. A diffusion-tensor model was fitted at each voxel using Diffusion Toolkit (*dtifit*), generating FA maps for each subject.

The left and right SCP (Figure 2a), MCP (Figure 2b) and ventrolateral (VL) thalamus were manually outlined on T1-w images, while DN was delineated on T2-w (Figure 2c), using the software Jim 6.0. In particular, about T1-w images, regions of interest (ROIs) were delineated in single image (1 mm thick), and the areas ranged from 12 mm^2 for the SCP (smallest structure) to 98 mm^2 for the VL thalamus (largest structure).

About DN, after its segmentation, T2 images were then aligned to the T1 using a non-linear registration and this transformation was then applied on DN ROIs using the FMRIB's tools.

Finally, for extracting the average FA values within the boundaries of each ROI, FA maps were registered on the T1 images, using a full-affine (correlation ratio cost function) transformation.

Statistical analysis

Statistical analysis was performed with R Statistical Software (R for Unix/Linux, v3.1, The R Foundation for Statistical Computing).

Sex distribution between groups was assessed using the χ^2 test. All between-group comparisons were carried out after checking for normality by means of the Shapiro-Wilk test. Normal variables were compared using the t-test or the one-way analysis of variance (ANOVA), followed, where necessary, by a pairwise t-test. Non-normal variables were compared by means of the Mann-Whitney U test or Kruskal-Wallis test followed by a pairwise Wilcoxon rank sum test. P-values were corrected according to Bonferroni. The significance of correlations between neuropsychological and MRI variables was tested using either Pearson's r or Spearman's ρ statistic, depending on the normality of measures.

Results

Participants

Table 1 summarizes the main demographic, clinical, and neuropsychological characteristics of the three different study groups. The sex distribution of patients was not statistically different among groups (Chi-squared p=0.951). No statistically significant differences were found among groups in age (p=0.98), education (p=0.16), disease duration (p=0.098) and FSS (p=0.78). EDSS was different between patient's groups, RR-MSc verses RR-MSnc ($p \leq 0.001$).

Neuropsychological assessment

For what concerns cognitive evaluation (Table 1), RR-MSc displayed significantly lower performances in attention (SDMT), Stroop C, Stroop CW, STAI Y1 and Y2, MMSE.

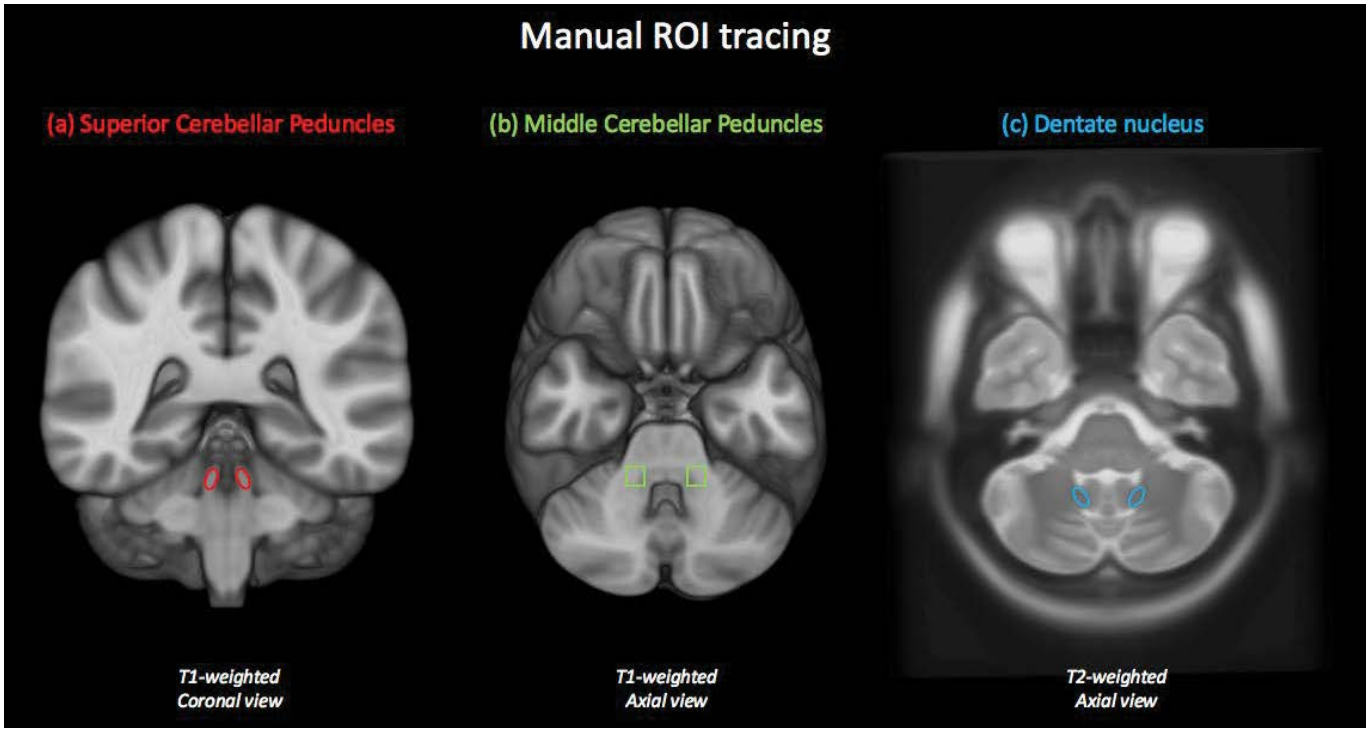

Figure 2: Segmentation of the ROIs constituting the feed forward and feedback pathways to cortical areas on MNI standard for visualization purpose.
(a) Delineation of the superior cerebellar peduncles.
(b) Delineation of the middle cerebellar peduncles.
(c) Delineation of the dentate nucleus.

Characteristics	RR-MSc (n=21)	RR-MSn (n=25)	CTRL (n=23)	p-Value
Clinical data				
Age (mean ± SD)	33.04 ± 5.4	33.28 ± 7.8	33.04 ± 4.89	0.98†
Gender (m)	13	9	9	0.951‡
Education (years)	12.04 ± 2.09	12.04 ± 3.8	13.69 ± 3.08	0.168‡
Duration of disease (mean ± SD)	108.61 ± 64.7	75.04 ± 59.9	_	0.098*
EDSS	3.57 ± 0.88	2.1 ± 0.66	_	<0.001*
FSS	3.56 ± 1.57	3.69 ± 1.67		0.78§
Neuropsychological data				
SDMT	32.4 ± 11.3	41.4 ± 11.9	47.5 ± 7.4	<0.001†
Stroop C	36.3 ± 10.4	41.4 ± 11.9	44.4 ± 8.1	<0.005‡
Stroop CW	15.6 ± 6.2	20.1 ± 6.1	20.8 ± 6.3	<0.015†
WLG	14.1 ± 3.9	16.1 ± 3.3	20.5 ± 4.3	<0.001†
LTS	36.8 ± 12.8	38.8 ± 10.4	41.1 ± 7.7	0.39†
CLTR	27.1 ± 14.3	29.9 ± 9.1	30.6 ± 7.7	0.51†
SPART I	17.1 ± 4.1	18.1 ± 5.2	18.9 ± 4.9	0.46†
SPART D	5.1 ± 1.5	5.7 ± 2.7	6.6 ± 2.1	0.09†
BDI II	11.09 ± 8.02	11.8 ± 10.1	8.7 ± 6.9	0.59‡
STAI Y1	42.9 ± 10.8	44.2 ± 9.6	34.3 ± 6.3	0.001‡
STAI Y2	43.1 ± 11.7	41.08 ± 11.5	35. ± 7.8	0.03†
MMSE	28.4 ± 1.7	29.5 ± 0.8	29.8 ± 0.4	0.001‡

Data are given as mean values (SD)
RR-MSc: Relapsing Remitting MS Patients with Cerebellar Symptoms; RR-MSnc: Relapsing Remitting MS Patients without Cerebellar Symptoms; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; SDMT: Symbol Digit Modalities Test; STROOP C: Color; STROOP CW: Color Word; WLG: Word List Generation; LTS Long Term Storage; CLTR Consistent Long Term Retrieval; SPART-I/D Spatial Recall Test Immediate/Delayed; BDI II: Beck Depression Inventory II: MMSE: Mini Mental State Examination
†One-way Anova; ‡ Kruskal Wallis; *Mann-Whitney test; § t test

Table 1: Demographic and clinical features in patients with multiple sclerosis.

Fractional anisotropy (mean ± SD)	RRMS with cerebellar signs (n=21)	RRMS without Cerebellar signs (n=25)	Controls (n=23)	Kruskal-Wallis p-value
Right Dentate Nucleus	0.318 ± 0.038	0.321 ± 0.033	0.344 ± 0.024	0.015
Left Dentate Nucleus	0.329 ± 0.032	0.330 ± 0.027	0.342 ± 0.020	0.2615
Right MCP	0.372 ± 0.068	0.401 ± 0.061	0.634 ± 0.017	0
Left MCP	0.368 ± 0.073	0.400 ± 0.050	0.635 ± 0.018	0
Right SCP	0.606 ± 0.034	0.654 ± 0.031	0.635 ± 0.017	0
Left SCP	0.658 ± 0.056	0.671 ± 0.045	0.633 ± 0.016	0.008
Right Thalamus	0.194 ± 0.024	0.234 ± 0.024	0.250 ± 0.022	0
Left thalamus	0.198 ± 0.026	0.233 ± 0.027	0.255 ± 0.039	0

Table 2: Fractional anisotropy mean values for each group and ROI and Kruskal-Wallis p-values.

About the STROOP-C test, RR-MSc patients performed significantly worse than controls, and compared to RR-MSnc patients they exhibited only a trend towards significance. About SDMT test, RR-MSc patients performed significantly worse than RR-MSnc patients.

MRI/DTI data

ANOVA revealed that there were significant differences in all ROIs except that in left DN. When we compared the patient's groups (RR-MSc verses RR-MSnc) we found significant differences in right ($p<0.001$) and left ($p=0.0030$) SCP, and in right ($p<0.0001$) and left ($p=0.0006$) Th, with RR-MSc showing lower FA values than RR-MSnc. Healthy controls showed higher FA values than RR-MSc and RR-MSnc in all ROIs except for left DN (never significant) and left Th (significant only in controls verses RR-MSc) (Table 2).

Correlation between MRI data and clinical performance

Regarding RR-MSnc, FA values of SCP, both left and right, significantly correlated ($p<0.05$) with STROOP-CW (respectively r=0.409 and r=0.638), while only left SCP correlated with LTS (r=0.487) and CLTR (r=0.515). Right MCP FA correlated inversely with SDMT (r=-0.494) and directly with STAI-Y2 (r=0.497). Left MCP positively correlated with LTS (r=0.433). No other significant correlations were detected between remaining ROIs and clinical values.

In RR-MSc group, FA values of SCP, both left and right, significantly correlated directly with SDMT (left r=0.522 and right r=0.119) and CLTR (left r=0.735 and right r=0.439). The right SCP negatively correlated with SPART-D (r=-0.462). FA values of bilateral thalami correlated directly with SDMT (left r=0.496 and right r=0.602). Right thalamus FA correlated positively with MMSE (r=0.477) and negatively FSS (r=-0.525), while the left one directly correlated with STROOP-C (r=0.539) and CLTR (r=0.567). Left MCP FA positively correlated with BDI II (r=0.502), STAI-Y2 (r=0.532) and MMSE (r=0.504). Right DN FA correlated directly with WLG (r=0.479) while left one positively with LTS (r=0.544) and negatively with FSS (r=-0.516). Total lesion load negatively correlated with SDMT (r=-0.467), STAI-Y1 (r=-0.557) and STAI-Y2 (r=-0.572).

Discussion

In this study, we found significant abnormalities of FA values in the SCP and thalamus of RR-MSc patients when compared with RR-MSnc patients and healthy subjects. MCP was only different between patients and controls, but not between MS sub-groups.

The SCP contains cerebellar efferent fibers that originate mainly in the dentate nucleus. The fibers cross the midline in the decussation of SCP and project via the red nucleus to the controlateral ventrolateral nucleus of the thalamus. A small group of SCP fibers projects to reticular and vestibular nuclei of the brainstem and this may represent the pathological basis of postural instability.

In precedent works [27-29,31,32], we demonstrated the involvement of the thalamus in the pathophysiological mechanisms of RR-MS as evidenced in other works [33-35]. In this study, we confirm with a DTI analyses, the involvement of the thalamus in RR-MS, but we found that the afferent and efferent pathways were involved when we compared both RR-MS groups with controls. On the contrary, we found a significant difference in SCP only, when we compared RR-MSc vs. RR-MSnc, with higher FA in RR-MSnc than RR-MSc. Moreover, the latter group showed significantly difference in EDSS values compared to RR-MSnc group.

The interruption of dentatothalamic and dentatorubral tracts (which run in the SCP) may play a role in determining motor dysfunction and determine the disability in patients with MS, particularly in RR-MSc patients. At the same time, the interruption of the MCP, composed by afferent fibers to the cerebellum, might contribute to the occurrence of cerebellar and brainstem symptoms in MS patients.

We speculate that not only the cerebellum atrophy may contribute to motor function and disability in MS patients, but also the afferent (MCP) and efferent (SCP) tracts. MCP and SCP revealed a significantly degree of alteration in both MS groups compared to controls, and in particular, SCP showed lower FA values when we compared MS groups among them. We conclude that the structural disconnection between the cerebellum and the cerebral hemispheres may contribute to cerebellar and brainstem symptoms. Our results are supported by neuroanatomical studies that have shown bidirectional pathways between the cerebellum and cortical structures involved not only in motor but also in cognitive regulation. More specifically, the cortex sends information to the cerebellum via pontine nuclei (and MCP), while the cerebellum sends information back to the cortical areas through dentatothalamic pathways [35] (and SCP).

About cognitive functions, it has been demonstrated that cerebellar lesions may contribute to determine not only the cerebellar motor syndrome but also the so-called "cerebellar cognitive affective syndrome" [36] that includes executive dysfunction, language deficits and impairment in spatial cognition.

In our study, we found that both SM groups showed worse performances than healthy controls in the Word List Generation (WLG) test, RR-MSc performed significantly worse than controls in the Stroop-C and Stroop CW test. Finally, only SDMT test was significantly different between RR-MSc patients and both RR-MSnc and healthy controls groups. The semantic verbal fluency, as assessed by WLG, is the most frequently impaired cognitive function at an early stage of MS, but it is less sensitive to the SDMT in identifying MS patients [36]. In the same work, authors demonstrated that fluency deficits appear to be correlated with greater neurological disability, disease duration and age [36].

About SDMT, in our precedent works [27-29,31,32], we demonstrated that:

a) RR-MS patients with cerebellar signs performed worse in the areas of attention (SDMT) and verbal fluency (COWAT) than individually matched MS patients without cerebellar damage [27].

b) Using a well-known working memory fMRI task (PASAT), widely employed to assess the functional integrity of the parieto-prefrontal network, RR-MSc patients displayed statistically significant low performances in SDMT and verbal fluency (WLG) [32].

c) An advanced structural neuroimaging analysis demonstrated that, with respect to controls, RR-MSnc patients were characterized by a specific atrophy of the bilateral thalami that became more widespread in the RR-MSc group. SDMT assesses information about processing speed, sustained attention and working memory, its neural network suggests the involvement of cortical and subcortical structures distributed throughout the brain, mainly involving the cerebellum.

In this study, we found a significantly correlation between not only thalami but also SCPs and SDMT in the RR-SMc group. This means that the neurodegenerative process involves the feedback loop that connects the deep cerebellar nuclei with cerebral areas, via the SCP (efferent pathway). These lesions determine cognitive deficits in executive functions as measured by SDMT only in RR-SMc patients and not in RR-SMnc patients, suggesting a more severe cognitive impairment in patients with cerebellar symptoms compared with patients without cerebellar dysfunction. Executive functions are a set of abilities whose primary mission consists in organizing information, planning, managing and problem-solving. DTI, which measures the random translational motion of water molecules in biologic tissues, provides unique information on white matter injury that may not be apparent with other MR modalities.

Conclusion

In conclusion, our study demonstrates that cognitive deficits are secondary to a disconnection among the efferent fibers (SCP) carrying information from the cerebellum through the midbrain and thalamus to the cortex. SCP region is crucial to understand the clinical and cognitive involvement in RR-MSc patients, confirming the cerebellum as a very important area in this pathology.

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