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ORIGINAL ARTICLE

Cognitive function in primary and secondary progressive multiple sclerosis: A multiparametric magnetic resonance imaging study

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Abstract

Background and purpose: The differences in cognitive function between primary progressive and secondary progressive multiple sclerosis (MS) remain unclear. We compared cognitive performance between primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS), and explored the structural and functional magnetic resonance imaging (MRI) correlates of their cognitive functions.

Methods: Seventy-five healthy controls and 183 MS patients (60 PPMS and 123 SPMS) underwent 3.0-T MRI. MS patients were administered the Brief Repeatable Battery of Neuropsychological Tests; cognitive domain *z*-scores were calculated and then averaged to obtain a measure of global cognition. Using hierarchical linear regression analysis, the contribution of lesion volumes, normalized brain volumes, white matter (WM) fractional anisotropy (FA) and mean diffusivity abnormalities, and resting state (RS) functional connectivity (FC) alterations to global cognition in PPMS and SPMS was investigated.

Results: PPMS and SPMS had similar *z*-scores in all investigated cognitive domains. Poor global cognitive function was associated with decreased FA of the medial lemniscus ($\Delta R^2 = 0.11$, $p = 0.011$) and lower normalized gray matter volume ($\Delta R^2 = 0.29$, $p < 0.001$) in PPMS, and with decreased FA of the fornix ($\Delta R^2 = 0.35$, $p < 0.001$) and lower normalized WM volume ($\Delta R^2 = 0.05$; $p = 0.034$) in SPMS.

Conclusions: PPMS and SPMS had similar neuropsychological performance. Cognitive dysfunction in PPMS and SPMS was related to distinct patterns of structural MRI abnormalities and involvement of different WM tracts, whereas RS FC alterations did not contribute to explaining their global cognitive functioning.

KEYWORDS
executive function, memory, MRI, multiple sclerosis

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INTRODUCTION

Cognitive deficits are reported to be more frequent and severe in patients with progressive multiple sclerosis (MS) compared to those with a relapsing–remitting disease course [1]. However, it remains controversial whether patients with primary progressive MS (PPMS) and secondary progressive MS (SPMS) have similar frequency and patterns of cognitive dysfunction [1–4].

A number of cross-sectional investigations found higher prevalence of cognitive impairment in patients with SPMS (55%–86%) than those with PPMS (53%–73%) [1, 2], and PPMS patients were reported to perform significantly better on tasks involving visuospatial abilities [1], working memory [2], and verbal fluency [1].

In the past few years, a body of evidence has suggested that progressive MS phenotypes have a similar degree of cognitive dysfunction [4, 5]. A large nationwide study detected comparable measures of cognitive function between PPMS and SPMS (45% and 46% were classified as cognitively impaired, respectively) [3].

Several factors can contribute to explain discrepancies among studies, including the use of different neuropsychological assessments and matching biases, as SPMS and PPMS often differ in terms of age, disease duration, and physical disability [1, 3].

The application of advanced magnetic resonance imaging (MRI) techniques has contributed to identification of the substrates associated with cognitive dysfunction in progressive MS. T2-hyperintense lesions [6] and gray matter (GM) atrophy [7] have been correlated with the presence and severity of cognitive deficits in both PPMS and SPMS. T1-hypointense lesions [8], GM integrity [9], and microstructural alterations to the interhemispheric callosal pathways [10] have been related to cognitive dysfunction in PPMS, whereas microstructural damage of specific white matter (WM) tracts such as the corpus callosum, fornix, superior longitudinal fasciculus, and forceps major have been shown to play a crucial role in explaining cognitive deficits in SPMS [11, 12].

Resting state (RS) functional MRI (fMRI) studies have demonstrated different patterns of recruitment of cognitively related networks according to the stage of the disease [13]. At the beginning of MS, increased RS functional connectivity (FC) within these networks has been interpreted as a compensatory mechanism limiting the consequences of disease-related structural damage, whereas at later stages a reduced RS FC has been associated with worse cognitive performance [13, 14].

Only a limited number of studies have explored the MRI correlates of cognitive impairment in both PPMS and SPMS patients [2, 15]. In most available studies, a single or a few MRI techniques have been applied. It is arguable that a multiparametric approach, combining structural and functional MRI techniques, might contribute to improving the understanding of the mechanisms associated with cognitive deficits in PPMS and SPMS, allowing identification of shared and distinctive features of these disease clinical phenotypes.

In this study, we administered the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [16] to a large sample of progressive MS patients to compare the cognitive performance between PPMS and SPMS. We then combined different MRI modalities to explore the structural and functional substrates of cognitive dysfunction in the two progressive phenotypes of MS.

METHODS

Ethics committee approval

Approval was received from the local ethical standards committee on human experimentation, and written informed consent was obtained from all subjects prior to study participation.

Participants

We recruited 183 MS patients (60 PPMS and 123 SPMS) and 75 age- and sex-matched healthy controls (HC). Inclusion criteria were age ≥ 18 years, Italian native language, right handedness, and no previous history of neurological (other than MS for patients) or psychiatric disorders. MS patients were enrolled from the Neuroimaging Research Unit of IRCCS San Raffaele Scientific Institute, Milan, Italy. HC were mainly recruited among the spouses of patients and by word of mouth. To be included, patients with MS had to have a diagnosis of MS according to the 2017 revised McDonald criteria.

Clinical and neuropsychological assessment

Within 48 h from the MRI acquisition, all MS patients underwent a complete neurological examination, with rating on the Expanded Disability Status Scale (EDSS) [17].

Experienced neuropsychologists administered the BRB-N, which assesses verbal memory (Selective Reminding Test [SRT] long-term storage, SRT consistent long-term retrieval, and SRT delayed recall), visuospatial memory (10/36 Spatial Recall Test and delayed recall), attention and processing speed (Symbol Digit Modalities Test, Paced Auditory Serial Addition Test 3″ and 2″), and semantic verbal fluency (Word List Generation) [16]. Fatigue was also assessed through the Modified Fatigue Impact Scale [18].

Age-, sex-, and education-adjusted scores were calculated based on normative data, and *z*-scores were obtained for each cognitive test [16]. A *z*-score for each cognitive domain was subsequently calculated by averaging the *z*-scores of corresponding tests: *z*-verbal memory, *z*-visuospatial memory, *z*-attention/processing speed, and *z*-verbal fluency. Then, a global *z*-cognitive function score (*z*-BRB-N), corresponding to the mean *z*-score obtained from the abovementioned cognitive domains, was calculated [19]. Patients who scored below the 5th percentile of the normative sample on tests that explore at least two different cognitive domains were classified as cognitively impaired [5].

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MRI acquisition

Each subject underwent a brain MRI scan performed using two 3.0-T scanners (Scanner 1: Achieva; Scanner 2: Ingenia; Philips Medical Systems). Images acquired using the Achieva scanner included the following scans: (i) 200 sets of T2*-weighted echo-planar imaging sequence for RS fMRI, (ii) dual-echo turbo spin echo, (iii) three-dimensional (3D) T1-weighted fast field echo, and (iv) pulsed-gradient spin echo echo-planar imaging with sensitivity encoding (acceleration factor = 2) and diffusion gradients applied in 35 non-collinear directions.

Images acquired using the Ingenia scanner included: (i) 320 sets of T2*-weighted echo-planar imaging sequence for RS fMRI, (ii) 3D fluid attenuated inversion recovery, (iii) 3D T2-weighted sequence, (iv) 3D T1-weighted turbo field echo, and (v) axial pulsed-gradient spin echo single shot diffusion-weighted echo-planar imaging (see Appendix S1).

Conventional MRI analysis

T2-hyperintense lesion masks and their lesion volume (LV), normalized brain volume (NBV), normalized GM volume (NGMV), normalized WM volume (NWMV), and normalized deep GM volume (NDGMV; i.e., the sum of the normalized volumes of bilateral thalamus, caudate, putamen, pallidum, amygdala, and accumbens) were calculated (see Appendix S1).

Tract-based spatial statistics analysis

Preprocessing of diffusion-weighted images included correction for off-resonance (Scanner 2)—eddy current distortions and movements (http://white.stanford.edu/mrdiff [Scanner 1]; eddy tool, FMRIB Software Library [FSL] [20] [Scanner 2]). The diffusion tensor (DT) was estimated by linear regression on diffusion-weighted imaging data at $b = 900\,s/mm^2$ (Scanner 1) or $b = 700/1000\,s/mm^2$ (Scanner 2) [21]. Then, maps of fractional anisotropy (FA) and mean diffusivity (MD) were derived.

Tract-based spatial statistics (TBSS) analysis was used for voxelwise analysis of whole brain WM DT MRI measures (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). In detail, individual FA images were nonlinearly registered to the FMRIB58_FA atlas [22] provided within FSL and averaged. The resulting mean FA image was thinned to create a WM tract "skeleton," which was thresholded at FA > 0.2 to include only WM voxels.

Individual subjects' FA values were projected onto this group skeleton by searching perpendicularly from the skeleton for maximum FA values. Maximum FA values were chosen to restrict the analysis to the center of WM tracts (where maximum FA values are found), rather than considering voxels at the edge of tracts, which may suffer from partial volume effects. The individual registration and projection vectors obtained during the above-described process were also applied to MD data and lesion masks coregistered to b0 image. Nineteen regions, part of a combined atlas (Johns Hopkins University [JHU] WM Labels-2 mm and JHU ICBM-Tracts-maxprob-thr25-2 mm) and listed in Table S1, were overlaid on skeletonized FA maps from patients and HC to calculate average values in each region. Given the similar behavior of right and left tract values, left and right WM tracts were averaged.

RS fMRI analysis

After preprocessing, RS FC was assessed using independent component analysis (see Appendix S1).

The visual inspection of the spatial patterns, a frequency analysis of the spectra of the estimated independent components, and a template-matching procedure allowed removal of components clearly related to motion-related artifacts and physiological noise, and selection of nine components of interest: one sensorimotor network [23], one basal ganglia network [24], two default mode networks (DMN I and II) [25], one executive control network [26], one salience network [26], and one left and one right working memory network [25]. For each network, global network mean RS FC *z*-score (mean *z*-score of voxels within the familywise error-corrected mask of the network) was computed and extracted using the Marsbar toolbox.

Statistical analysis

Statistical analysis was performed using R-4.0.3 and SPSS software (version 22.0). Between-group comparisons of demographic characteristics and neuropsychological *z*-scores were assessed with the Chi-square test (qualitative variables) or the Mann–Whitney *U*-test/two-sample *t*-test/linear models, according to normality assumption (quantitative variables).

Between-group voxelwise differences in FA, MD, and lesions were tested using a permutation-based inference for nonparametric statistical thresholding (the "randomize" program within FSL) and two-sample *t*-tests with age, sex, and disease duration as covariates. T2-hyperintense WM lesion masks were included as voxelwise covariate in TBSS analyses to focus only on normal-appearing WM. A correlation analysis between lesions and *z*-BRB-N was also performed in PPMS and SPMS. The number of permutations was set to 5000. A p-value < 0.05 (familywise error-corrected for multiple comparisons) using the threshold-free cluster enhancement option in the "randomize" tool was set.

White matter tract DT-derived measures and RS FC *z*-scores were compared between HC and MS patients as well as between PPMS and SPMS patients using age-, sex-, and scanner number-adjusted linear models. Disease duration was included as covariate in linear models assessing the differences between PPMS and SPMS.

Hierarchical regression analysis was performed to select the independent predictors of cognitive status (*z*-BRB-N) in PPMS and SPMS, separately. We used a within-block stepwise approach: Block

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1 included demographic and clinical variables (age, sex, disease duration, and education); Block 2 comprised all MRI measures that significantly differed between HC and MS patients. For all analyses, statistical significance was set at $p < 0.05$.

All analyses were performed on the whole sample and separately on subjects acquired on Scanner 1 to assess the influence of the scanner hardware on the obtained results (i.e., validation analysis).

RESULTS

Demographic, clinical, and neuropsychological features

PPMS and SPMS had similar sex distribution, age, years of education, EDSS, and level of fatigue. Compared to PPMS, SPMS patients had longer disease duration ($p = 0.001$; Table 1).

Nineteen PPMS (31.6%) and 53 SPMS (43.1%) patients were classified as cognitively impaired ($p = 0.19$). No significant differences in *z*-BRB-N and cognitive domains *z*-scores were found between PPMS and SPMS (Table 1).

MRI findings

Compared with HC, MS patients had lower NBV, NGMV, NWMV, and NDGMV (Table 2).

TBSS revealed decreased FA and increased MD in the entire WM skeleton in MS patients compared to HC (Figure 1). Similarly, in the WM tract analysis, MS patients showed decreased FA and increased MD in all WM tracts analyzed (Table S2).

Compared to PPMS, SPMS had higher frequency of T2-hyperintense WM lesions in the corpus callosum, left superior corona radiata, left anterior corona radiata, bilateral posterior corona radiata, right superior longitudinal fasciculus, and bilateral inferior longitudinal fasciculus (Figure S1).

In RS FC analysis, compared to HC, MS patients showed decreased RS FC within the sensorimotor network, DMN I, and salience network (Table 3).

TABLE 1 Main demographic, clinical, and neuropsychological characteristics of the subjects included in the study.

Characteristic	HC, $n = 75$	MS, $n = 183$	p: HC vs. MS	PPMS, $n = 60$	SPMS, $n = 123$	p: PPMS vs. SPMS
Demographic and clinical variables						
Women/men, *n* (%)	42 (56)/33 (44)	102 (56)/81 (44)	1.00[a]	29 (48)/31 (52)	73 (60)/50 (40)	0.21[a]
Mean age, years (SD)	48.2 (10.8)	50.6 (9.8)	0.10[b]	52.6 (10.6)	49.6 (9.2)	0.06[b]
Median education, years (IQR)	–	13.0 (8.0–13.0)	–	12.5 (8.0–13.0)	13.0 (8.0–13.0)	0.18[c]
Median disease duration, years (IQR)	–	17.4 (11.8–23.0)	–	**12.7 (6.7–18.6)**	**17.0 (13.0–25.0)**	**0.001**[c]
Median EDSS (IQR)	–	6.0 (5.5–6.5)	–	6.0 (5.0–6.5)	6.0 (5.5–6.5)	0.80[c]
Mean MFIS (SD)	–	41.1 (16.3)	–	39.5 (19.3)	42.0 (14.3)	0.44[b]
Subjects scanned with S1/S2, *n* (%)	62 (83)/13 (17)	155 (85)/28 (15)	0.82[a]	51 (85)/9 (15)	104 (84)/19 (16)	1.00[a]
Cognitive performance						
Cognitively impaired subjects, *n* (%)	–	72 (39.3)	–	19 (31.6)	53 (43.1)	0.19[a]
Mean *z*-BRB-N (SD)	–	−1.0 (1.1)	–	−1.0 (1.2)	−1.1 (1.0)	0.77[d]
Mean *z*-verbal memory (SD)	–	−1.3 (1.1)	–	−1.3 (1.1)	−1.3 (1.1)	0.83[d]
Mean *z*-visuospatial memory (SD)	–	−1.0 (1.0)	–	−1.0 (1.0)	−1.0 (1.0)	0.51[d]
Mean *z*-attention/processing speed (SD)	–	−1.2 (1.3)	–	−1.0 (1.3)	−1.3 (1.3)	0.34[d]
Mean *z*-verbal fluency (SD)	–	−0.8 (1.1)	–	−0.7 (1.2)	−0.8 (1.1)	0.46[d]

Note: Unless otherwise specified, data are presented as mean (95% confidence interval). Bold text indicates a statistically significant result ($p < 0.05$).

Abbreviations: BRB-N, Brief Repeatable Battery of Neuropsychological Tests; EDSS, Expanded Disability Status Scale; HC, healthy controls; IQR, interquartile range; MFIS, modified fatigue impact scale; MS, multiple sclerosis; PPMS, primary progressive MS; S, scanner; SPMS, secondary progressive MS; *z*, *z*-score.

[a]Chi-square test.

[b]Two-sample *t*-test.

[c]Mann–Whitney *U*-test.

[d]Disease duration-adjusted linear models.

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TABLE 2 Main magnetic resonance imaging characteristics of healthy subjects and patients with MS.

Characteristic	HC, $n=75$	MS, $n=183$	p: HC vs. MS	Statistically significant covariates	PPMS, $n=60$	SPMS, $n=123$	p: PPMS vs. SPMS	Statistically significant covariates
Median T2-LV, mL	**0.3 (0.0–2.8)**	**13.2 (11.6–14.8)**	**<0.001**[a]	Scanner number	11.7 (8.3–15.0)	14.0 (11.8–16.3)	0.13[b]	Disease duration; scanner number
Median T1-LV, mL	**0.2 (0.0–2.3)**	**9.5 (8.1–10.8)**	**<0.001**[a]	–	8.2 (5.3–11.0)	10.2 (8.3–12.2)	0.33[b]	Disease duration
Mean NBV, mL	**1532 (1512–1552)**	**1443 (1430–1455)**	**<0.001**[c]	Age	1451 (1428–1475)	1432 (1417–1448)	0.19[d]	Age; disease duration
Mean NGMV, mL	**694 (681–708)**	**632 (624–640)**	**<0.001**[c]	Age; scanner number	640 (624–657)	625 (614–636)	0.15[d]	Age; disease duration; scanner number
Mean NWMV, mL	**801 (790–812)**	**775 (769–782)**	**<0.001**[c]	Age; scanner number	778 (764–791)	774 (765–783)	0.64[d]	Scanner number
Mean NDGMV, mL	**52 (51–53)**	**45 (44–46)**	**<0.001**[c]	Sex; scanner number	46 (45–48)	45 (44–46)	0.09[d]	Disease duration; scanner number

Note: Bold text indicates a statistically significant result ($p<0.05$).

Abbreviations: HC, healthy controls; LV, lesion volume; MS, multiple sclerosis; NBV, normalized brain volume; NDGMV, normalized deep gray matter volume; NGMV, normalized gray matter volume; NWMV, normalized white matter volume; PPMS, primary progressive MS; SPMS, secondary progressive MS.

[a]Age-, sex-, and scanner-adjusted linear models performed on log scale.

[b]Age-, sex-, disease duration-, and scanner-adjusted linear models performed on log scale.

[c]Age-, sex-, and scanner-adjusted linear models.

[d]Age-, sex-, disease duration-, and scanner-adjusted linear models.

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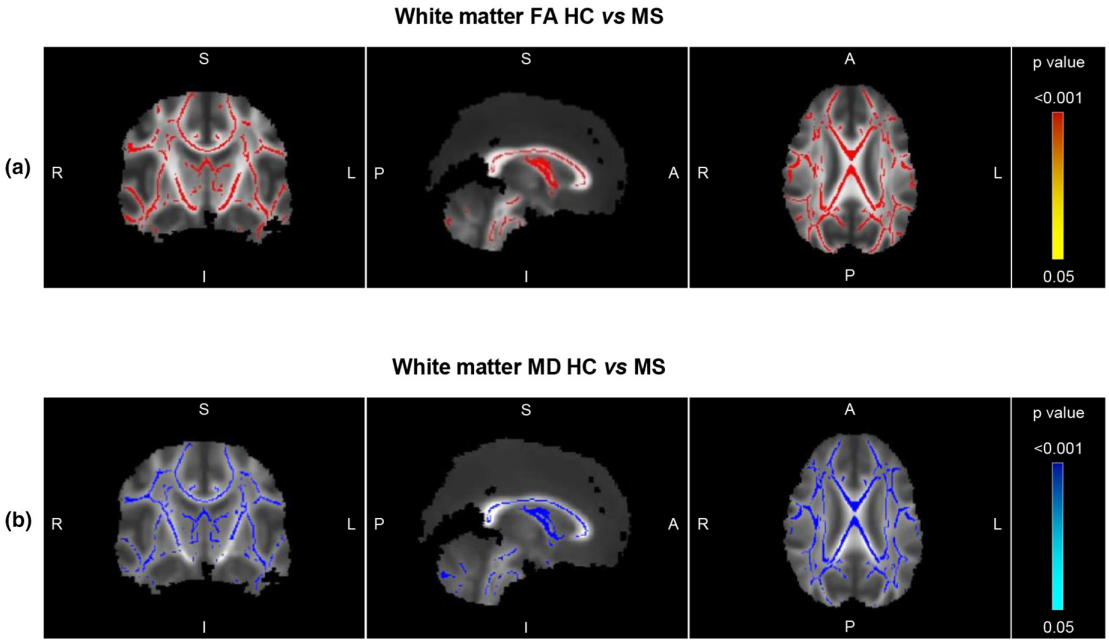

FIGURE 1 Voxelwise differences in fractional anisotropy (FA) and mean diffusivity (MD) values between healthy controls (HC) and multiple sclerosis (MS) patients. (a) Image shows clusters of voxels with significant (red for *p*-value, familywise error [FWE]-corrected) decreased FA in MS patients compared to HC. Background image is the mean FA map derived from all subjects. (b) Image shows clusters of voxels with significant (blue for *p*-value, FWE-corrected) increased MD in MS patients compared to HC. Background image is the mean FA map derived from all subjects. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

TABLE 3 Average *z*-scores of resting state functional connectivity for each group in all selected resting state networks.

Network	HC, $n=75$	MS, $n=183$	*p*: HC vs. MS	PPMS, $n=60$	SPMS, $n=123$	*p*: PPMS vs. SPMS
Sensorimotor network	**1.67 (0.40)**	**1.49 (0.44)**	**0.005**[a]	1.42 (0.39)	1.53 (0.46)	0.07[b]
DMN I	**1.61 (0.26)**	**1.51 (0.28)**	**0.01**[a]	1.46 (0.30)	1.53 (0.27)	0.19[b]
R-working memory network	1.17 (0.14)	1.12 (0.18)	0.06[a]	1.12 (0.20)	1.12 (0.17)	0.76[b]
Executive network	0.98 (0.17)	0.98 (0.18)	0.70[a]	1.00 (0.20)	0.98 (0.17)	0.45[b]
DMN II	1.07 (0.19)	1.02 (0.23)	0.14[a]	1.00 (0.27)	1.03 (0.20)	0.56[b]
Salience network	**1.01 (0.17)**	**0.93 (0.19)**	**0.003**[a]	0.91 (0.21)	0.93 (0.18)	0.74[b]
Working memory network	0.96 (0.16)	0.95 (0.19)	0.69[a]	0.90 (0.19)	0.97 (0.19)	0.84[b]
Basal ganglia network	0.85 (0.16)	0.82 (0.17)	0.20[a]	**0.86 (0.17)**	**0.79 (0.17)**	**0.005**[b]
L-working memory network	1.16 (0.20)	1.12 (0.20)	0.36[a]	1.11 (0.23)	1.13 (0.20)	0.85[b]

Note: Unless otherwise specified, data are presented as mean (SD). Bold text indicates a statistically significant result ($p<0.05$).

Abbreviations: DMN, default mode network; HC, healthy controls; L, left; MS, multiple sclerosis; PPMS, primary progressive MS; R, right; SPMS, secondary progressive MS.

[a]Age-, sex-, and scanner-adjusted linear models.

[b]Age-, sex-, disease duration-, and scanner-adjusted linear models.

PPMS and SPMS patients had similar T2-LV, T1-LV, NBV, NGMV, NWMV, and NDGMV (Table 2).

TBSS analysis showed no FA and MD differences between PPMS and SPMS patients, whereas in WM tract analysis, compared to PPMS, SPMS patients had decreased FA and increased MD values in the fornix, and higher MD values in the optic radiation and posterior corona radiata (Figure 2, Table S2).

Finally, compared to PPMS, SPMS patients showed decreased RS FC within the basal ganglia network (Table 3).

Regarding associations between MRI features and cognitive status, Table 4 summarizes the results of the hierarchical regressions analysis.

No significant correlations between *z*-BRB-N and lesion distribution were found in either PPMS or SPMS.

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In PPMS, lower NGMV ($p < 0.001$, $\Delta R^2 = 0.29$) and decreased FA of the medial lemniscus ($p = 0.01$, $\Delta R^2 = 0.11$) were selected as significant predictors of lower *z*-BRB-N (adjusted $R^2 = 0.36$).

In SPMS, decreased FA of the fornix ($p < 0.001$, $\Delta R^2 = 0.35$) and lower NWMV ($p = 0.03$, $\Delta R^2 = 0.05$) were associated with worse cognitive status (adjusted $R^2 = 0.37$).

Validation analysis

The subgroup of participants acquired on Scanner 1 consisted of 150 MS patients (51 PPMS and 99 SPMS) and 62 age- and sex-matched HC. PPMS and SPMS were similar for demographic, clinical, neuropsychological, and MRI variables, except for a longer disease duration in SPMS patients (Table S3).

TBSS analysis showed no FA and MD differences between PPMS and SPMS patients. Reduced FA in the optic radiation and increased MD in the superior cerebellar peduncle, corticospinal tract, and superior longitudinal fasciculus in SPMS were significant also in the WM tract analysis (Table S4).

PPMS and SPMS had similar RS FC within the investigated networks.

In PPMS, both lower NGMV ($p < 0.001$, $\Delta R^2 = 0.29$) and decreased FA of the medial lemniscus ($p = 0.01$, $\Delta R^2 = 0.11$) were confirmed to be significantly associated with lower *z*-BRB-N.

Hierarchical regression confirmed the prominent association of reduced FA in the fornix and worse cognitive status in SPMS

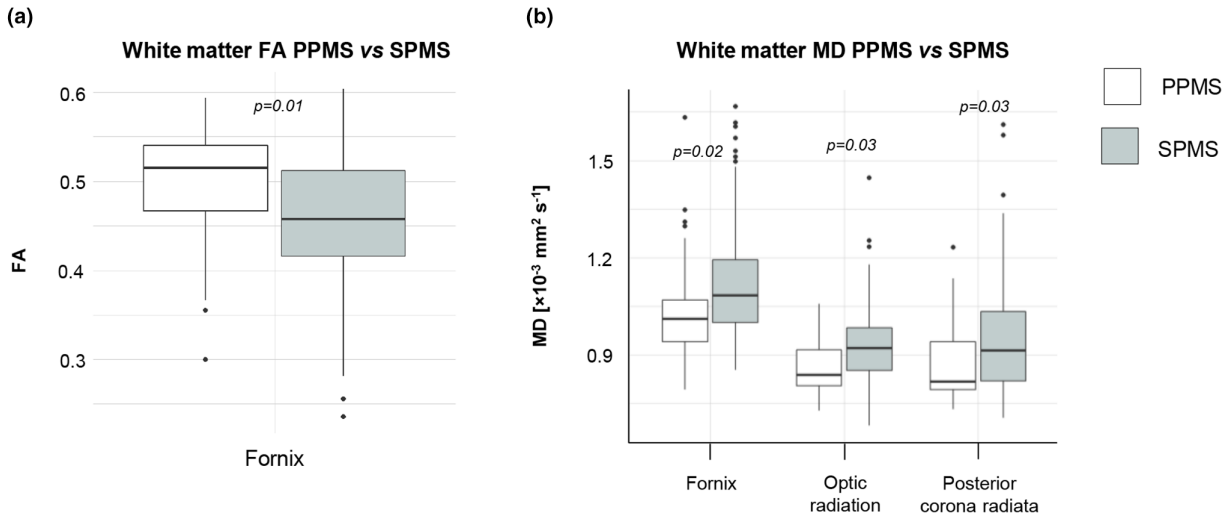

FIGURE 2 Comparisons of diffusion tensor metrics between primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS) patients. Boxplot of fractional anisotropy (FA) of the fornix (a) and mean diffusivity (MD) of the fornix, optic radiation, and posterior corona radiata (b) in PPMS and SPMS patients. Boxes show the first and third quartiles, with the line denoting the median. The upper whisker extends from the hinge to the largest value no further than 1.5 × interquartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 × IQR from the hinge. Data beyond the end of the whiskers are plotted individually.

TABLE 4 Hierarchical regression models assessing the predictors of global cognitive function score for PPMS and SPMS patients.

Dependent variable	Block	Significant IVs	Standardized β weights	R^2	R^2 change	*p*	Adjusted R^2
PPMS							
z-BRB-N	1	–	–	–	–	–	0.36
	2	NGMV	0.45	0.29	–	<0.001	
		Medial lemniscus FA	0.34	0.36	0.11	0.01	
SPMS							
z-BRB-N	1	–	–	–	–	–	0.37
	2	Fornix FA	0.53	0.35	–	<0.001	
		NWMV	0.22	0.39	0.05	0.03	

Abbreviations: BRB-N, Brief Repeatable Battery of Neuropsychological Tests; FA, fractional anisotropy; IV, independent variable; NGMV, normalized gray matter volume; NWMV, normalized white matter volume; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; *z*, *z*-score.

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($p < 0.001$, $\Delta R^2 = 0.23$), with the potential additional contribution of decreased FA in the medial lemniscus ($p = 0.004$, $\Delta R^2 = 0.08$).

DISCUSSION

To determine whether there are differences in frequency and pattern of cognitive dysfunction between PPMS and SPMS patients, we administered a comprehensive battery of neuropsychological tests [16]. We then combined different MRI modalities, specific for different disease-related pathological substrates, to identify the MRI variables associated with global cognitive functioning in PPMS and SPMS.

Patients with PPMS and SPMS had similar cognitive performance. Global cognitive functioning was negatively associated with lower NGMV and decreased FA of the medial lemniscus in PPMS, and with lower NWMV and decreased FA of the fornix in SPMS, the latter confirmed also in the validation analysis.

In our study, the overall prevalence of cognitive impairment in progressive MS patients investigated by the BRB-N was 39.3%, which is at the lower limit of the rates reported in previous studies, ranging from 37% to 86% [2–5]. The high degree of variability can be attributed to the differences in the sample characteristics, the cognitive assessment procedures, and the chosen cutoff scores [3]. In previous studies, cognitive impairment was most commonly defined as performing 2.0 SD below the normative mean on two tests [2, 4], whereas one study applied a more liberal criterion based on an impaired performance (a score below the 5th percentile) on a single test [3]. To reduce the risk of false positive results, we adopted a strict definition of cognitive impairment based on consensus recommendations: an age-, sex-, and education-adjusted score below the 5th percentile of the normative sample on tests that explore at least two cognitive domains [5].

In comparison with PPMS, the prevalence of severe cognitive impairment was higher in SPMS (31.7% vs. 41.3%), but the difference was not statistically significant. Our results are in line with a recent study [3] that found a similar frequency of cognitive dysfunction in the two progressive phenotypes of MS.

Domainwise comparison revealed that the composite scores for verbal memory, visuospatial memory, attention/processing speed, and verbal fluency were similar in PPMS and SPMS after controlling for disease duration. Previous works reported differences between PPMS and SPMS in performance on tests measuring information processing speed [27], attention [27], memory [1, 4, 27], and verbal fluency [1, 4]. However, in one study, patient groups were not matched for age, sex, and level of physical disability [1], and in others disease duration was considerably longer for patients with SPMS than for those with PPMS [4, 27].

Taken together, these results suggest that PPMS and SPMS share a similar pattern of cognitive impairment in terms of prevalence, severity, and affected domains. Our results do appear to be robust, considering that, despite SPMS patients having longer disease duration than PPMS patients, the two patient groups were matched for age, sex, education, physical disability, and level of fatigue, and no significant differences were found in terms of T2-LV, T1-LV, NBV, NGMV, NWMV, and NDGMV (including the thalamus).

Compared to HC, both PPMS and SPMS showed widespread brain damage in terms of LV, NBV, NGMV, NWMV, NDGMV, WM microstructural abnormalities, and RS FC alterations in the sensorimotor network, DMN, and salience network. In line with the results of previous DT MRI studies [15, 28], WM tract analysis revealed that SPMS patients exhibited more severe microstructural alterations in the fornix, optic radiation, and posterior corona radiata compared to PPMS. Moreover, SPMS had higher occurrence of T2 lesions in the corpus callosum, left superior corona radiata, left anterior corona radiata, bilateral posterior corona radiata, right superior longitudinal fasciculus, and bilateral inferior longitudinal fasciculus than PPMS. We also found a reduction of RS FC in the basal ganglia network in SPMS compared to PPMS, supporting the notion that different pathologic mechanisms might underlie MRI abnormalities and, consequently, clinical manifestations in these progressive phenotypes [29].

No significant association was found between cognitive status and lesion distribution in either PPMS or SPMS. This result was expected, as multiparametric MRI studies have consistently shown that WM lesions contribute to cognitive impairment only partially or together with damage to normal-appearing WM and GM [6].

In PPMS, reduced NGMV accounted for a significant proportion of overall cognitive performance, suggesting that GM damage plays a crucial role in their cognitive dysfunction [7]. Despite the pathogenic mechanism responsible for cortical atrophy not being fully understood, several studies have found a correlation between patterns of reduced GM volume and impairment in processing speed, working memory, attention, verbal memory, and verbal fluency [30]. GM atrophy can be detected even at the earliest stages of PPMS and progresses more rapidly than WM atrophy. A histopathologic study identified neuroaxonal loss and neuronal shrinkage as the possible cause for cortical atrophy in PPMS, which appears to be independent from WM demyelination [31].

Consistent with previous research [14], decreased FA of the medial lemniscus was associated with worse global cognitive functioning in PPMS. The medial lemniscus pathway is essential for the analysis and integration of sensory motor information, and microstructural damage within this tract is likely to affect integration processes, resulting in poor performance in neuropsychological tests [14].

In SPMS patients, lower NWMV was significantly associated with worse cognitive status, supporting the notion that a reduction of WM volume influences the speed of mental processing [32]. The temporary storage and manipulation of new information demands rapid communication between different brain regions via WM tracts, which may decrease with disease progression [32]. However, regression analysis suggested that the integrity of the fornix might be the most critical anatomical correlate of cognitive functioning in SPMS. The fornix is the major hippocampal efferent pathway, and damage to this tract can cause episodic memory deficits in MS [33].

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Interestingly, measures derived from the analysis of RS FC were not present among the predictors of overall cognitive performance in either PPMS or SPMS. Previous studies suggest that increased RS FC may be present at early disease stage to compensate structural disease-related burden, whereas RS FC depletion takes place in later phases, contributing to a wide spectrum of clinical manifestations [34]. However, the extent of structural damage accumulation might limit our sensitivity to assess the role of specific RS FC alterations in cognitive dysfunction in progressive MS [35].

In PPMS and SPMS, distinct MRI abnormalities produced comparable levels of cognitive impairment. This suggests that different underlying neuropathological mechanisms may be responsible for the observed cognitive deficits in these two groups. Although there were no significant differences in the pattern of structural MRI alterations between PPMS and SPMS, subtle variations in the location or extent of damage could account for the differences in MRI predictors of global cognition. Furthermore, differences in the timing and progression of the disease could also contribute to the observed variability. Both demyelination and neurodegeneration are involved in the cognitive impairment observed in MS. However, the relative contribution of each of these mechanisms may differ between PPMS and SPMS.

This study is not without limitations. First, compared to PPMS, SPMS patients had longer disease duration. Matching these patients could be difficult, as in SPMS the disease starts with a recognizable relapsing–remitting course, which is followed by a secondary progressive phase, whereas PPMS patients miss the relapsing–remitting stage and start with uninterrupted progression from disease onset. Second, we did not administer specific scales for the assessment of depression and anxiety, which may influence cognitive performance in MS patients [6]. Third, the study is cross-sectional, thus not allowing evaluation of whether the observed MRI correlates are related to cognitive worsening. Fourth we adopted a strict definition of cognitive impairment that can neglect mild degrees of impairment. Finally, the selected demographical, clinical, and MRI variables were able to explain only 36% and 37% of variance of the overall cognitive performance in PPMS and SPMS, respectively. The inclusion of other variables such as cognitive reserve could have increased the proportion of variance accounted for [6].

In conclusion, this study represents the largest exploration of the cognitive performance discrepancies between PPMS and SPMS, employing multiparametric MRI techniques to elucidate the various substrates of impairment. Our findings indicate that the different disease courses of PPMS and SPMS do not seem to affect cognitive function in a detectably distinct manner; however, different structural substrates contribute to explain cognitive dysfunction in these clinical phenotypes of MS.

This implies that the same routine cognitive screening and monitoring should be performed for all patients with progressive MS. However, the different structural substrates of cognitive dysfunction in these phenotypes indicate a need for individualized diagnostic, treatment, and management approaches, as well as continued research into the underlying mechanisms of cognitive impairment in progressive MS.

AUTHOR CONTRIBUTIONS

Damiano Mistri: Formal analysis (equal); investigation (equal); writing–original draft (equal). **Laura Cacciaguerra**: Formal analysis (equal); investigation (equal); writing–original draft (equal). **Paola Valsasina**: Formal analysis (equal); writing–review & editing (equal). **Elisabetta Pagani**: Formal analysis (equal); writing–review & editing (equal). **Massimo Filippi**: Conceptualization (lead); supervision (lead); writing–review & Editing (equal). **Maria A. Rocca**: Conceptualization (lead); supervision (lead); writing–review & editing (equal).

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DATA AVAILABILITY STATEMENT

The anonymized dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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