

Identifying the Distinct Cognitive Phenotypes in Multiple Sclerosis

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 Supplemental content

IMPORTANCE Cognitive impairment is a common and disabling feature of multiple sclerosis (MS), but a precise characterization of cognitive phenotypes in patients with MS is lacking.

OBJECTIVES To identify cognitive phenotypes in a clinical cohort of patients with MS and to characterize their clinical and magnetic resonance imaging (MRI) features.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cross-sectional study consecutively screened clinically stable patients with MS and healthy control individuals at 8 MS centers in Italy from January 1, 2010, to October 31, 2019. Patients with MS and healthy control individuals who were not using psychoactive drugs and had no history of other neurological or medical disorders, learning disability, severe head trauma, and alcohol or drug abuse were enrolled.

MAIN OUTCOMES AND MEASURES Participants underwent a neurological examination and a cognitive evaluation with the Rao Brief Repeatable Battery and Stroop Color and Word Test. A subgroup of participants also underwent a brain MRI examination. Latent profile analysis was used on cognitive test z scores to identify cognitive phenotypes. Linear regression and mixed-effects models were used to define clinical and MRI features of each phenotype.

RESULTS A total of 1212 patients with MS (mean [SD] age, 41.1 [11.1] years; 784 women [64.7%]) and 196 healthy control individuals (mean [SD] age, 40.4 [8.6] years; 130 women [66.3%]) were analyzed in this study. Five cognitive phenotypes were identified: preserved cognition (n = 235 patients [19.4%]), mild-verbal memory/semantic fluency (n = 362 patients [29.9%]), mild-multidomain (n = 236 patients [19.5%]), severe-executive/attention (n = 167 patients [13.8%]), and severe-multidomain (n = 212 patients [17.5%]) involvement. Patients with preserved cognition and mild-verbal memory/semantic fluency were younger (mean [SD] age, 36.5 [9.8] years and 38.2 [11.1] years) and had shorter disease duration (mean [SD] 8.0 [7.3] years and 8.3 [7.6] years) compared with patients with mild-multidomain (mean [SD] age, 42.6 [11.2] years; mean [SD] disease duration, 12.8 [9.6] years; $P < .001$), severe-executive/attention (mean [SD] age, 42.9 [11.7] years; mean [SD] disease duration, 12.2 [9.5] years; $P < .001$), and severe-multidomain (mean [SD] age, 44.0 [11.0] years; mean [SD] disease duration, 13.3 [10.2] years; $P < .001$) phenotypes. Severe cognitive phenotypes prevailed in patients with progressive MS. At MRI evaluation, compared with those with preserved cognition, patients with mild-verbal memory/semantic fluency exhibited decreased mean (SE) hippocampal volume (5.42 [0.68] mL vs 5.13 [0.68] mL; $P = .04$), patients with the mild-multidomain phenotype had decreased mean (SE) cortical gray matter volume (687.69 [35.40] mL vs 662.59 [35.48] mL; $P = .02$), patients with severe-executive/attention had higher mean (SE) T2-hyperintense lesion volume (51.33 [31.15] mL vs 99.69 [34.07] mL; $P = .04$), and patients with the severe-multidomain phenotype had extensive brain damage, with decreased volume in all the brain structures explored, except for nucleus pallidus, amygdala and caudate nucleus.

CONCLUSIONS AND RELEVANCE This study found that by defining homogeneous and clinically meaningful phenotypes, the limitations of the traditional dichotomous classification in MS can be overcome. These phenotypes can represent a more meaningful measure of the cognitive status of patients with MS and can help define clinical disability, support clinicians in treatment choices, and tailor cognitive rehabilitation strategies.

JAMA Neurol. 2021;78(4):414-425. doi:10.1001/jamaneurol.2020.4920
Published online January 4, 2021.

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Cognitive impairment is a common and disabling manifestation of multiple sclerosis (MS), affecting patients' performance in everyday activities, behavior, and quality of life. It may be detected in the earliest stages of disease, such as a clinically¹ and radiologically isolated syndrome.²

Numerous magnetic resonance imaging (MRI) studies aimed at exploring the pathophysiological features of cognitive impairment in MS have been conducted. The earliest ones showed an association between cognitive deficits and higher brain lesion load,³ whereas subsequent work highlighted the importance of lesion location in strategic white matter (WM) regions,⁴ WM microstructural damage,⁵ gray matter (GM) lesions,⁶ cortical⁷ and deep⁸ GM atrophy,⁵ and abnormal patterns of cerebral activation.⁹

However, most clinical and MRI studies were based on a dichotomous classification of cognitive functioning, namely, preserved vs impaired cognition. The inevitable consequence in published studies was the inclusion of heterogeneous groups of patients with variable cognitive profiles, preventing a clear assessment of neuroanatomical substrates and personalized rehabilitation strategies.

A promising approach was introduced by Leavitt et al,¹⁰ who identified 3 cognitively homogeneous subgroups of patients with MS that were defined as cognitive phenotypes: isolated memory impairment, isolated information processing speed impairment, and combined deficits in processing speed and memory. Nevertheless, deficits in other cognitive domains have been reported in MS,^{11,12} and this classification was based on the dichotomous definition of impairment for each domain, not considering patients with mildly decreased cognitive performance.¹³

The definition of cognitive phenotypes may represent a step toward personalized treatment approaches and toward improving understanding of the pathophysiological mechanism of MS-related cognitive changes.

Against this background, we conducted a cross-sectional study with the aims of (1) identifying cognitive phenotypes in a clinical cohort of patients with MS, including the whole spectrum of disease subtypes, and (2) characterizing their clinical and MRI features. We used an unbiased, data-driven approach on neuropsychological data by applying latent profile analysis (LPA).¹⁴ For the characterization of MRI features, we selected highly reproducible and well-validated MRI metrics of MS-related brain damage.

Methods

Approval of this cross-sectional study was received from the local ethical standards committees on human experimentation of each participating center. Written informed consent was obtained from all participants before study enrollment.

Of the 1370 patients with MS and the 200 healthy control individuals consecutively screened from 8 Italian MS Centers (Azienda Ospedaliero-Universitaria (AOU) Careggi, Florence; San Raffaele Hospital, Milan; Policlinico Le Scotte, Siena; AOU Policlinico Vittorio Emanuele, Catania; AOU di Padova, Padova; Gallarate Hospital, Varese; Azienda Socio Sanitaria

Key Points

Question Given the heterogeneity of cognitive function in patients with multiple sclerosis (MS), can distinct cognitive phenotypes be identified for clinical and research purposes?

Findings In this cross-sectional study of 1212 patients with MS and 196 healthy control individuals, 5 cognitive phenotypes (preserved cognition, mild-verbal memory/semantic fluency, mild-multidomain, severe-executive/attention, and severe-multidomain) were identified by using a data-driven approach to cognitive evaluations. Each phenotype was characterized by specific clinical and magnetic resonance imaging features.

Meaning Findings of this study suggest that this new categorization of cognitive deficits in MS may integrate the Expanded Disability Status Scale score in defining clinical disability, support clinicians in treatment choices, and help tailor cognitive rehabilitation strategies.

Territoriale Spedali Civili Brescia, Brescia; and Policlinico di Bari, Bari) from January 1, 2010, to October 31, 2019, we enrolled 1212 clinically stable patients with MS and 196 healthy control individuals who were not using psychoactive drugs and had no history of other neurological or medical disorders, learning disability, severe head trauma, and alcohol or drug abuse. We excluded patients with MS who had relapses or corticosteroid use within 4 weeks preceding a neuropsychological assessment.¹⁰

Neuropsychological and Neurological Evaluation

All study participants underwent a neuropsychological evaluation with the Rao Brief Repeatable Battery¹⁵ and the Stroop Color and Word Test (SCWT).¹⁶ The Brief Repeatable Battery evaluates the most frequently impaired cognitive domains in MS, incorporating tests of verbal learning and memory (Selective Reminding Test [SRT]), including Long-term Storage, Consistent Long-term Retrieval, and delayed recall; visual or spatial learning and memory (10/36 Spatial Recall Test [SPART]) and its delayed recall; complex attention and information processing speed (Paced Auditory Serial Addition Test [PASAT] and Symbol Digit Modalities Test [SDMT]); and verbal fluency on semantic stimulus (Word List Generation [WLG]). The SCWT¹⁶ evaluates complex attention and aspects of executive functioning, such as cognitive interference inhibition.

Our neuropsychologists (B.G., C.N., C.G.C., P. Grossi, M.R., C.S., and R.G.V.) participated in a common training session, in which test administration and scoring procedures were clarified and agreed on. Corrected scores for age, sex, and education according to normative values¹⁷ were standardized on the basis of healthy control individuals, obtaining *z* scores for each cognitive test. Fatigue was assessed using the Fatigue Severity Scale (score range: 1-7 for each item, with the highest score indicating greater fatigue severity),¹⁸ and depression was evaluated using the Montgomery-Åsberg Depression Scale (score range: 0-60, with the highest score indicating more severe depression).¹⁹

All patients underwent a same-day neurological examination with the Expanded Disability Status Scale (EDSS; score

range: 0-10, with higher scores indicating more severe clinical disability²⁰ and definition of clinical subtype.²¹ Given the high number of relapsing-remitting patients with MS, we classified these patients into early (duration <5 years) and late (duration ≥5 years) groups.²²

MRI Data Acquisition and Data Analysis

Two of the 8 involved MS centers (San Raffaele Hospital in Milan and Quantitative Neuroimaging Laboratory of the University of Siena) also performed brain MRI examination at the time of neuropsychological evaluation on 172 patients with MS and 50 healthy control individuals. By using a 3-T scanner, we acquired 3-dimensional T1-weighted (3-DT1) and dual-echo sequences. The complete acquisition protocol is available in the eMethods in the Supplement.

The T2-hyperintense lesion volumes were measured on proton density images, using a local thresholding, semiautomated segmentation technique (Jim 8 software; Xinapse Systems). Normalized brain volume, normalized WM volume, normalized GM volume, and normalized cortical GM volume were measured on lesion-filled²³ 3-DT1-weighted images using SIENAX software (SIENA; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>). Automated segmentation of the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens was performed on lesion-filled²³ 3-DT1-weighted images using FMRIB Integrated Registration and Segmentation Tool software (FIRST; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>).²⁴ The volume of these structures was multiplied by the head-normalization factor derived from SIENAX. Given the symmetry of right and left deep GM nuclei, we calculated the mean corresponding volumes across hemispheres before the statistical analysis.⁸

Statistical Analysis

To identify cognitive phenotypes, we performed LPA^{14,25} on cognitive test *z* scores. Latent profile analysis is a flexible, person-centered, and model-based clustering technique. We used it for the data-driven, probabilistic identification of neuropsychologically homogeneous subgroups of patients with MS, which we defined as cognitive phenotypes. In addition, LPA is based on specific mixture models²⁵ that analyze the joint distribution of a set of continuous observed variables (neuropsychological test *z* scores in this study) as a function of a finite and mutually exclusive and exhaustive number of unobserved components (mixtures) using a latent categorical variable or profile.^{26,27} In this study, the latent variable was a profile of cognitive functioning in patients with MS. It should be noted that LPA does not necessitate any a priori categorization of the observed variables or indicators, thus facilitating a more granular examination of heterogeneity within and between latent-level groupings.^{25,28}

A major advantage of applying LPA is the possibility to estimate profile-specific means, variances, and covariances of the observed variables.²⁸ An important step of LPA is the selection of the best-fitting model. Models with 1 to 6 profiles were run. For the optimal number of classes, we inspected the bootstrap likelihood ratio test, bayesian information criterion, and integrated completed likelihood in line with Nyl-

und et al²⁹ and Scrucca et al.³⁰ After selecting the best-fitting model, we classified each patient with MS into one of the cognitive phenotypes (latent profiles) on the basis of their phenotype membership probabilities estimated directly from the model.^{25,31-33} To test the accuracy of the probabilistic estimations in attributing a cognitive phenotype to each patient, we performed a 10-fold cross-validation.

Cognitive phenotypes were named according to tests in which patient performance was substantially lower compared with that of healthy control individuals and according to current knowledge about test interpretation. The names we used to label different cognitive phenotypes are amenable to changes in future developments. A mean *z* score threshold lower than -1.5 was used to distinguish severely from mildly decreased performance.

Between-group comparisons of demographic and clinical parameters were performed using age- and sex-adjusted linear regression models or nonparametric tests as appropriate; normal distribution was assessed by visual inspection and Kolmogorov-Smirnov test. Patients with and without an MRI assessment were compared in terms of demographic, clinical, and neuropsychological variables to assess the representativeness of the entire study cohort. To characterize the MRI features of each cognitive phenotype, we adopted linear mixed-effects models.

Statistical significance was corrected for multiple comparisons (Bonferroni method), and the threshold for statistical significance was set at corrected 2-sided *P* < .05. To provide a measure of effect size for the comparisons performed, we estimated Cohen *d*, Cliff Δ , and Cramer *V* as appropriate. Statistical analysis was performed with R software, version 3.6.1, with packages mclust, tidyLPA, and lme4 (R Foundation for Statistical Computing). Data analysis was conducted between November 20, 2019, and April 15, 2020.

Results

A total of 1212 patients with MS (mean [SD] age, 41.1 [11.1] years; 784 women [64.7%] and 428 men [35.3%]) and 196 healthy control individuals (mean [SD] age, 40.4 [8.6] years; 130 women [66.3%] and 66 men [33.7%]) were analyzed in this study. Compared with healthy control individuals, patients with MS did not differ in mean (SD) age, sex, and years of education (12.5 [3.4] years vs 12.2 [3.8]; *P* = .38). The clinical subtypes of the patients with MS were as follows: early relapsing-remitting (*n* = 396), late relapsing-remitting (*n* = 652), secondary progressive (*n* = 108), and primary progressive (*n* = 56). **Table 1** summarizes the main demographic characteristics and clinical features of study participants.

Cognitive Phenotypes

Using LPA, we found that a 5-profile model was the best-fitting one (eTable 1 in the Supplement). A Brier score of 0.05 was obtained at the 10-fold cross-validation analysis. Five cognitive phenotypes (eFigure in the Supplement) were identified: (1) preserved cognition comprised 235 patients (19.4%) who showed no substantial difference from healthy control in-

Table 1. Main Demographic and Clinical Characteristics of Participants in the Study

Characteristic	Mean (SD) [range]		P value
	Healthy control individuals	Patients with MS	
Total No.	196	1212	NA
Age, y	40.4 (8.6) [20.2-60.9]	41.1 (11.1) [18.0-77.2]	.38
Female sex, No. (%)	130 (66.3)	784 (64.7)	.87
Male sex, No. (%)	66 (33.7)	428 (35.3)	.87
EDSS score, median (range)	NA	2.0 (0.0-8.5)	NA
Disease duration, y	NA	10.5 (9.0) [0.20-55.2]	NA
Age at onset, y	NA	29.8 (9.9) [7.0-68.9]	NA
Education, y	12.5 (3.4) [5.0-19.0]	12.2 (3.8) [5.0-24.0]	.38
FSS score	NA	14.9 (17.4) [1.0-63.0]	NA
MADRS score	NA	10.1 (9.3) [0.0-59.0]	NA

Abbreviations: EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MS, multiple sclerosis; NA, not applicable.

Table 2. Mean z Scores of Cognitive Tests for Cognitive Phenotypes

Phenotype	Mean (SD) z score					
	SRT	SPART	SCWT	SDMT	PASAT	WLG
Preserved cognition	0.29 (0.58)	-0.01 (0.61)	0.02 (0.28)	0.75 (1.13)	0.22 (0.78)	0.06 (0.81)
Mild-verbal memory/semantic fluency	-0.59 (0.85)	-0.22 (0.93)	-0.18 (0.89)	-0.14 (0.86)	-0.44 (0.99)	-1.29 (0.71)
Mild-multidomain	-1.26 (0.72)	-0.25 (0.90)	-0.75 (1.11)	-1.01 (1.09)	-0.58 (1.11)	-0.16 (1.06)
Severe-executive/attention	-1.10 (1.04)	-0.33 (1.30)	-2.51 (3.24)	-1.29 (1.46)	-2.19 (1.48)	-1.06 (1.32)
Severe-multidomain	-1.55 (1.21)	-1.22 (0.52)	-1.89 (2.07)	-2.26 (1.16)	-2.51 (1.17)	-2.09 (0.77)

Abbreviations: PASAT, Paced Auditory Serial Addition Test; SCWT, Stroop Color and Word Test; SDMT, Symbol Digit Modalities Test; SPART, Spatial Recall Test; SRT, Selective Reminding Test; WLG, Word List Generation.

individuals; (2) mild-verbal memory/semantic fluency comprised 362 patients (29.9%) who showed only mildly decreased performance in SRT (mean [SD] z score, -0.59 [0.85]; Cohen $d = -0.69$; 95% CI, -0.89 to -0.50; $P < .001$) and WLG (mean [SD] z score, -1.29 [0.71]; Cohen $d = -1.41$; 95% CI, -1.89 to -1.39; $P < .001$) compared with healthy control individuals; (3) mild-multidomain comprised 236 patients (19.5%) who showed mildly decreased performance in SRT (mean [SD] z score, -1.26 [0.72]; Cohen $d = -1.68$; 95% CI, -1.92 to -1.44; $P < .001$), SDMT (mean [SD] z score, -1.01 [1.09]; Cohen $d = -0.96$; 95% CI, -1.18 to -0.74; $P < .001$), SCWT (mean [SD] z score, -0.75 [1.11]; Cohen $d = -0.68$; 95% CI, -0.90 to -0.47; $P < .001$), and PASAT (mean [SD] z score, -0.58 [1.11]; Cohen $d = -0.56$; 95% CI, -0.77 to -0.35; $P < .001$) compared with healthy control individuals; (4) severe-executive/attention comprised 167 patients (13.8%) who showed severely decreased performance in SCWT (mean [SD] z score, -2.51 [3.24]; Cohen $d = -1.72$; 95% CI, -1.95 to -1.48; $P < .001$) and PASAT (mean [SD] z score, -2.19 [1.48]; Cohen $d = -1.83$; 95% CI, -2.10 to -1.57; $P < .001$) and mildly decreased performance in SRT (mean [SD] z score, -1.10 [1.04]; Cohen $d = -1.17$; 95% CI, -1.41 to -0.93; $P < .001$), SPART (mean [SD] z score, -0.33 [1.30]; Cohen $d = -0.29$; 95% CI, -0.51 to -0.07; $P = .03$), SDMT (mean [SD] z score, -1.29 [1.46]; Cohen $d = -1.02$; 95% CI, -1.25 to 0.78; $P < .001$), and WLG (mean [SD] z score, -1.06 [1.32]; Cohen $d = -0.90$; 95% CI, -1.13 to 0.66; $P < .001$) compared with healthy control individuals; and (5) severe-multidomain comprised 212 patients (17.5%) who showed severely decreased performance in SRT (mean [SD] z score, -1.55 [1.21]; Cohen $d = -1.36$; 95% CI, -1.60 to -1.13; $P < .001$), SCWT (mean [SD]

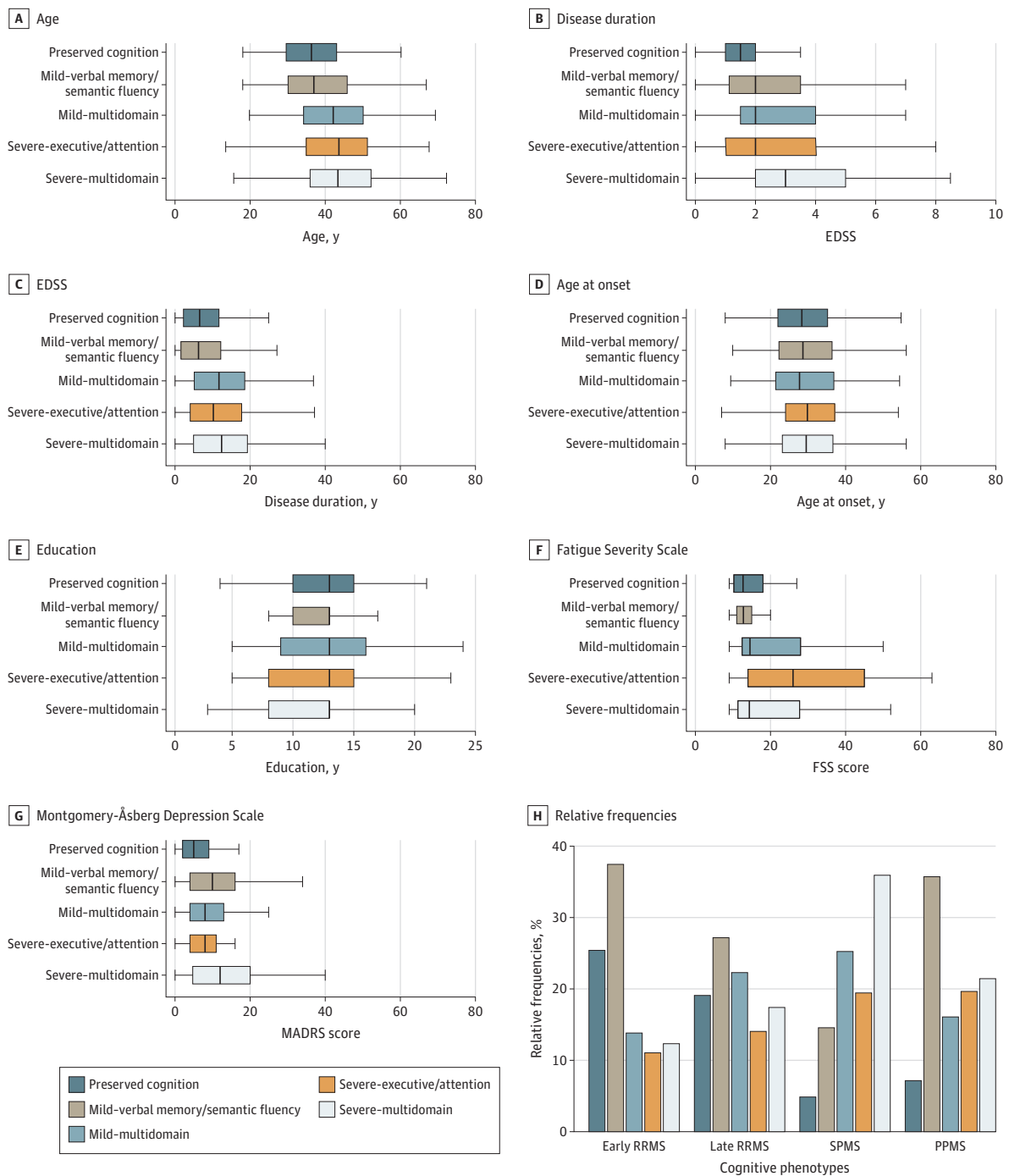
z score, -1.89 [2.07]; Cohen $d = -1.10$; 95% CI, -1.32 to -0.87; $P < .001$), SDMT (mean [SD] z score, -2.26 [1.16]; Cohen $d = -2.06$; 95% CI, -2.31 to 1.80; $P < .001$), PASAT (mean [SD] z score, -2.51 [1.17]; Cohen $d = -2.48$; 95% CI, -2.75 to -2.20; $P < .001$), and WLG (mean [SD] z score, -2.09 [0.77]; Cohen $d = -2.40$; 95% CI, -2.67 to -2.12; $P < .001$) and mildly decreased performance in SPART (mean [SD] z score, -1.22 [0.52]; Cohen $d = -1.71$; 95% CI, -1.95 to -1.46; $P < .001$) compared with healthy control individuals. Table 2 summarizes the neuropsychological features of each cognitive phenotype.

Clinical Features of Cognitive Phenotypes

Statistically significant differences were found when comparing clinical and demographic features among cognitive phenotypes, as summarized in Figure 1 and eTable 2 in the Supplement. In particular, patients with the preserved cognition and mild-verbal memory/semantic fluency phenotypes had similar age (mean [SD] age, 36.5 [9.8] years and 38.2 [11.1] years) and disease duration (mean [SD] duration, 8.0 [7.3] years and 8.3 [7.6] years), but they were younger and had a shorter disease duration compared with the patients with the other phenotypes such as the mild-multidomain (mean [SD] age, 42.6 [11.2] years; mean [SD] disease duration, 12.8 [9.6] years; $P < .001$), severe-executive/attention (mean [SD] age, 42.9 [11.7] years; mean [SD] disease duration, 12.2 [9.5] years; $P < .001$), and severe-multidomain (mean [SD] age, 44.0 [11.0] years; mean [SD] disease duration, 13.3 [10.2] years; $P < .001$) phenotypes.

Patients with the severe-multidomain phenotype had higher physical disability compared with those with other

Figure 1. Clinical and Demographic Features of Clinical Phenotypes



A-G, Boxplots are represented for each phenotype. H, The histograms show the relative frequencies as percentages of cognitive phenotype within clinical phenotypes from left to right: early relapsing-remitting multiple sclerosis

(RRMS), late RRMS, secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS). EDSS indicates Expanded Disability Status Scale.

phenotypes (median [range] EDSS score, 3.0 [0.0-8.0]; $P \leq .001$). Patients with preserved cognition (median [range] EDSS score, 1.5 [0.0-7.0]; $P < .001$) had lower physical disability compared with those with the mild-verbal memory/semantic fluency (median [range] EDSS score, 2.0 [0.0-7.5]; $P < .001$), mild-multidomain (median [range] EDSS score, 2.0 [0.0-8.0];

$P < .001$), severe-executive/attention (median [range] EDSS score, 2.0 [0.0-8.0]; $P = .001$), and severe-multidomain (median [range] EDSS score, 3.0 [0.0-8.0]; $P < .001$) phenotypes.

Regarding mean (SD) years of education, a difference was found only between the mild-multidomain and the severe-executive/attention phenotypes (12.6 [3.9] years vs 11.5 [4.2]

years; $P = .04$). Patients with the severe-executive/attention phenotype had higher mean (SD) Fatigue Severity Scale scores (22.4 [19.4]) compared with those in the other phenotype groups such as preserved cognition (14.2 [15.3]; $P = .002$), mild-verbal memory/semantic fluency (11.1 [15.5]; $P < .001$), mild-multidomain (17.2 [18.5]; $P = .05$), and severe-multidomain (15.5 [18.7]; $P = .01$). Higher mean (SD) Montgomery-Åsberg Depression Scale scores were found in the severe-multidomain (13.8 [11.0]) vs preserved cognition (7.7 [9.5]; $P = .01$) and severe-executive/attention (8.3 [5.5]; $P = .02$) phenotypes and in the mild-verbal memory/semantic fluency vs preserved cognition (11.9 [10.0] vs 7.7 [9.5]; $P = .04$) phenotypes.

In intersecting cognitive phenotypes and clinical subtypes, we observed a progressive decrease in the relative frequencies of preserved cognition and mild-verbal memory/semantic fluency phenotypes from early relapsing-remitting MS (25% and 38%) to late relapsing-remitting MS (19% and 27%) and then to secondary progressive MS (5% and 15%) clinical subtypes. At the same time, we found a parallel increase of the relative frequencies of mild-multidomain (14% in early relapsing-remitting, 22% in late relapsing-remitting, and 25% in secondary progressive MS), severe-executive/attention (11% in early relapsing-remitting, 14% in late relapsing-remitting, and 19% in secondary progressive MS), and severe-multidomain (12% in early relapsing-remitting, 18% in late relapsing-remitting, and 36% in secondary progressive MS) phenotypes. The primary progressive MS subtype showed a distinct distribution of cognitive phenotypes, with a higher prevalence of patients with the mild-verbal memory/semantic fluency (36%) followed by the severe-multidomain (21%), severe-executive/attention (20%), and mild-multidomain (16%) phenotypes and with only a small percentage of patients with preserved cognition (7%).

MRI Features of Cognitive Phenotypes

Participants undergoing MRI did not differ from the entire study cohort in terms of demographic, clinical, and neuropsychological variables (data not shown). **Table 3** and **Figure 2** summarize the MRI features of each cognitive phenotype. Compared with healthy control individuals, those with preserved cognition showed significantly lower mean (SE) thalamic volume (10.39 [0.28] mL vs 9.69 [0.28] mL; $P = .005$). A shared pattern of damage was observed when comparing patients with the mild-verbal memory/semantic fluency, mild-multidomain, and severe-executive/attention phenotypes with healthy control individuals (mean [SD] brain volume, 1532.61 [31.39] mL) with lower normalized brain volume (mild-verbal memory/semantic fluency: 1493.63 [30.85] mL, $P = .03$; mild-multidomain: 1469.94 [31.52] mL, $P = .001$; and severe-executive/attention: 1479.23 [33.10] mL, $P = .03$), normalized GM volume (mild-verbal memory/semantic fluency: 733.70 [38.86] mL, $P = .01$; mild-multidomain: 715.71 [39.08] mL, $P = .002$; and severe-executive/attention: 725.78 [39.63] mL, $P = .01$), normalized cortical GM volume (mild-verbal memory/semantic fluency: 672.04 [35.26] mL, $P = .02$; vs mild-multidomain: 662.59 [35.48] mL, $P = .005$; and severe-executive/attention: 665.35 [36.01] mL, $P = .02$), thalamic volumes (mild-verbal memory/semantic fluency: 9.62 [0.27]

mL, $P = .001$; mild-multidomain: 9.31 [0.28] mL, $P < .001$; and severe-executive/attention: 9.35 [0.31] mL, $P = .001$), and putamen volumes (mild-verbal memory/semantic fluency: 6.00 [0.25] mL, $P = .03$; mild-multidomain: 5.95 [0.25] mL, $P = .01$; and severe-executive/attention: 5.94 [0.27] mL, $P = .04$).

In addition, compared with healthy control individuals, those with the mild-verbal memory/semantic fluency phenotype were characterized by lower nucleus accumbens (mean [SE] volume, 0.74 [0.16] mL vs 0.66 [0.16]; $P = .04$) and hippocampal volume (mean [SE] volume, 5.58 [0.68] mL vs 5.13 [0.68]; $P = .03$), those with the severe-executive/attention phenotype were characterized by lower hippocampal volume (mean [SE] volume, 5.10 [0.69] mL; $P = .006$), and those with the mild-multidomain phenotype were characterized by lower caudate volume (mean [SE] volume, 5.39 [0.81] mL vs 5.06 [0.81] mL; $P = .05$). Compared with patients with preserved cognition, those with mild-verbal memory/semantic fluency only showed statistically significantly lower hippocampal volume (mean [SE] volume, 5.42 [0.68] mL vs 5.13 [0.68] mL; $P = .02$); those with the mild-multidomain phenotype were characterized by lower normalized cortical GM volume (mean [SE] volume, 687.69 [35.40] mL vs 662.59 [35.48] mL; $P = .04$), whereas those with severe-executive/attention were characterized by higher T2 lesion volume (mean [SE] volume, 51.33 [31.15] mL vs 99.69 [34.07] mL; $P = .04$).

Patients with severe-multidomain phenotype had extensive and severe brain damage. Compared with healthy control individuals, these patients showed lower mean (SE) volumes in all of the analyzed brain structures except for nucleus pallidus and amygdala (normalized brain volume: 1423.67 [32.77] mL, $P < .001$; GM volume: 703.70 [39.51] mL, $P < .001$; cortical GM volume: 646.36 [35.89] mL, $P < .001$; WM volume: 718.99 [68.45] mL, $P < .001$; thalamic volume: 8.72 [0.30] mL, $P < .001$; caudate volume: 4.87 [0.81], $P = .004$; putamen volume: 5.68 [0.26] mL, $P < .001$; accumbens volume: 0.55 [0.16] mL, $P < .001$; and hippocampal volume: 5.09 [0.69] mL, $P = .002$). Compared with those with preserved cognition, patients with the severe-multidomain phenotype showed the same differences except for the caudate nucleus.

Discussion

In this cross-sectional study, we propose a classification of cognitive functions in patients with MS that is based on the identification of distinct cognitive phenotypes. We applied LPA to neuropsychological data from a large cohort of patients with MS and characterized MRI features using well-validated assessment tools. This approach allowed us to identify the latent variables replacing single test measures, which can be affected by multiple cognitive functions, and to capture the shared variance across cognitive tests, likely reflecting purer measures of cognitive domains. Moreover, by using z scores rather than a dichotomous classification, we found that the cognitive function was more properly represented as a continuum.

Table 3. Estimated Marginal Means of Magnetic Resonance Imaging Features of Cognitive Phenotypes

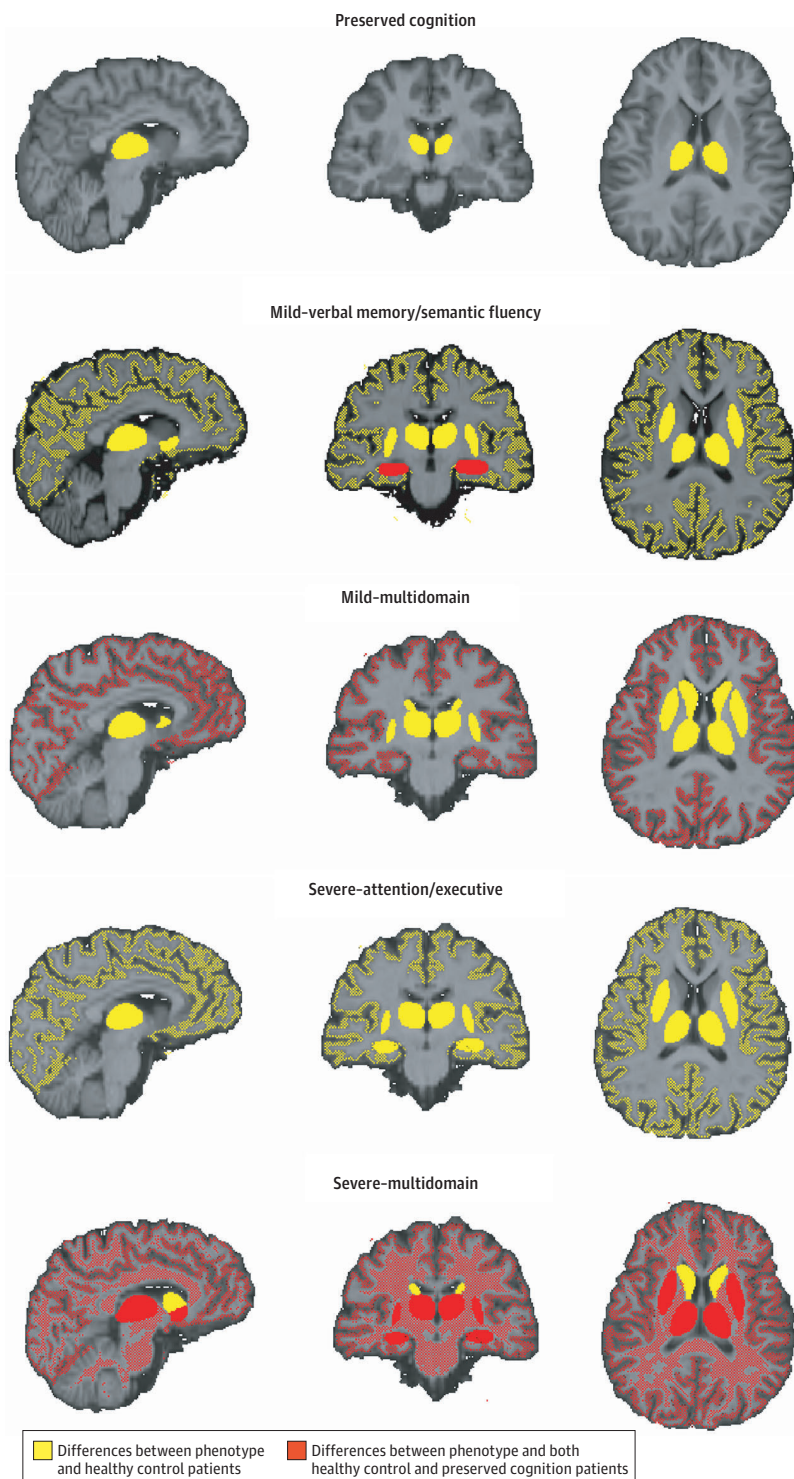
Variable	Mean (SE), mL		P value vs HC ^a	Mild- verbal memory/semantic fluency, mean (SE), mL	P value ^a		Mild-multidomain, mean (SE), mL	P value ^a		Severe-executive/attention, mean (SE), mL	P value ^a		Severe-multidomain, mean (SE), mL	P value ^a	
	HC	PC			vs HC	vs PC		vs HC	vs PC		vs HC	vs PC		vs HC	vs PC
No.	50	39	NA	49	NA	NA	37	NA	NA	22	NA	NA	24	NA	NA
T2LV	NA	51.33 (31.15)	NA	75.99 (30.49)	NA	.23	76.29 (31.56)	NA	.15	99.69 (34.07)	NA	.04	133.70 (33.56)	NA	<.001
NBV	1532.61 (31.39)	1502.55 (31.27)	.13	1493.63 (30.85)	.03	.63	1469.94 (31.52)	.001	.11	1479.23 (33.10)	.03	.31	1423.67 (32.77)	<.001	.001
NGMV	764.07 (39.02)	749.69 (39.00)	.25	733.70 (38.86)	.01	.18	715.71 (39.08)	.002	.04	725.78 (39.63)	.01	.12	703.70 (39.51)	<.001	.002
NCGMV	698.93 (35.42)	687.69 (35.40)	.36	672.04 (35.26)	.02	.19	662.59 (35.48)	.005	.04	665.35 (36.01)	.02	.13	646.36 (35.89)	<.001	.005
NWMV	765.72 (68.22)	752.90 (68.22)	.39	759.16 (68.15)	.59	.59	743.06 (68.25)	.06	.51	753.64 (68.51)	.51	.94	718.99 (68.45)	<.001	.02
NThalV	10.39 (0.28)	9.69 (0.28)	.005	9.62 (0.27)	.001	.78	9.31 (0.28)	<.001	.13	9.35 (0.31)	.001	.22	8.72 (0.30)	<.001	.001
NCaudV	5.39 (0.81)	5.14 (0.81)	.15	5.17 (0.81)	.15	.95	5.06 (0.81)	.05	.65	5.16 (0.81)	.24	.95	4.87 (0.81)	.004	.15
NPutav	6.39 (0.25)	6.08 (0.25)	.09	6.00 (0.25)	.03	.70	5.95 (0.25)	.01	.54	5.94 (0.27)	.04	.54	5.68 (0.26)	<.001	.05
NPallV	2.23 (0.08)	2.23 (0.08)	.97	2.27 (0.08)	.78	.78	2.20 (0.08)	.78	.78	2.17 (0.09)	.78	.78	2.05 (0.09)	.17	.17
NAmygV	1.84 (0.10)	1.74 (0.10)	.33	1.82 (0.09)	.96	.41	1.82 (0.10)	.96	.41	1.82 (0.10)	.96	.43	1.69 (0.10)	.27	.73
NAccuV	0.74 (0.16)	0.69 (0.16)	.22	0.66 (0.16)	.04	.54	0.67 (0.16)	.10	.82	0.67 (0.17)	.17	.83	0.55 (0.16)	<.001	.009
NHippV	5.58 (0.68)	5.42 (0.68)	.25	5.13 (0.68)	.03	.02	5.32 (0.68)	.06	.51	5.10 (0.69)	.006	.06	5.09 (0.69)	.002	.05

Abbreviations: HC, healthy control individuals; LV, lesion volume; NA, not applicable; NAccuV, normalized accumbens volume; NAmygV, normalized amygdala volume; NBV, normalized brain volume; NCaudV, normalized caudate volume; NCGMV, normalized cortical gray matter volume; NGMV, normalized gray matter volume; NHippV, normalized hippocampal volume; NPallV, normalized pallidum volume; NPutav, normalized putamen

volume; NThalV, normalized thalamic volume; NWMV, normalized white matter volume; PC, patients with preserved cognition.

^a P values were adjusted for multiple comparisons (Bonferroni method).

Figure 2. Magnetic Resonance Imaging Features of Cognitive Phenotypes



To improve the readability of the study and the interpretation of results, we named cognitive phenotypes according to patients' performance at neuropsychological tests. Although current knowledge does not allow for a complete understanding of the meaning of these phenotypes, their definition represents a starting point for future studies.

By using MRI, we were able to identify neuroanatomical substrates for each phenotype, substantiating the data-driven cognitive findings with a biological basis. Given that volume loss in a specific GM region reflects demyelination and loss of neurons, synaptic trees, and supporting cells,³⁴ the finding of lower volume in a region with known functional

relevance^{9,35} in a given phenotype can represent an important biological validation of the data-driven classification.

We identified a first phenotype, preserved cognition, that was characterized by preserved functioning in all cognitive tests. This phenotype, prevailing in the early stages of the disease, included patients with shorter disease duration and less severe disability compared with other phenotypes. As for MRI features, patients in this group only showed lower thalamic volume compared with healthy control individuals. Given the well-known thalamic involvement in cognitive functioning,³⁶ there are a few explanations for the findings. Real-world cognitive deficits that were not assessed in the neuropsychological battery (eg, multitasking and word-finding tasks) may account for the lower thalamic volume. Otherwise, patients with higher cognitive reserve may be clustered in this phenotype, thus exhibiting normal cognitive performance despite mild thalamic damage.³⁷ Future research on patients with MS that evaluates real-world cognitive abilities and their cognitive reserve using advanced MRI techniques for thalamic analysis and segmentation^{38,39} could help clarify the role of thalamic damage in patients with preserved cognition. In this study, we did not assess the premorbid intelligence quotient as a proxy for the participant's cognitive reserve.

A second phenotype, mild-verbal memory/semantic fluency, was characterized by mildly decreased performance in SRT and WLG. The data-driven cosegregation of decreased performance in verbal learning and memory and in semantic fluency⁴⁰ was likely associated with impaired common semantic clustering strategies^{41,42} and lexical access modalities.⁴³ In line with this explanation, the MRI data in this study showed hippocampal atrophy as a potential pathological substrate. Hippocampal damage (both in terms of atrophy and abnormal functional connectivity)^{44,45} was associated with decreased performance in verbal learning and memory^{45,46} and in semantic fluency.^{47,48} In future studies, a detailed examination of cognitive functions,^{49,50} together with MRI analysis of hippocampal subfields⁵¹ and connections,⁵² may better characterize the neural basis of this phenotype. On the other hand, the lack of processing speed impairment in these patients seems to challenge the notion that slowed processing speed can always underlie memory difficulties in MS.⁵³

A third phenotype, mild-multidomain, showed mildly decreased cognitive performance in SRT, SCWT, SDMT, and PASAT. These tests can recruit different cortically oriented cognitive functions that may be interconnected with each other. Cortical atrophy turned out to be the distinctive MRI feature of this phenotype, in line with previous findings⁵⁴ of decreased neocortical volumes in patients with MS with mild cognitive impairment. Moreover, lower neocortical volume was associated with a worse performance on tests of verbal memory, attention/concentration, and verbal fluency in MS.^{54,55} The relative frequency of mild-multidomain phenotype increased from early to late relapsing-remitting and secondary progressive MS, and it was also high in patients with primary progressive MS. These results are consistent with previous reports of cortical atrophy in progressive MS.^{56,57} Future MRI studies should focus on cortical thickness estimation at the vertex level⁵⁸ and on cerebral activation³⁵ to as-

sess the precise patterns of cortical damage, possibly corresponding to specific cognitive networks.

A fourth phenotype, severe-executive/attention, was characterized by decreased performance in all tests, with more severe involvement in the PASAT and SCWT. Patients with this phenotype are likely to have a severe impairment of attention and aspects of executive functions, such as cognitive interference inhibition. This impairment may also justify, at least in part, the decreased performance in the remaining tests.⁵⁹ This phenotype was characterized by higher fatigue scores compared with all of the other groups. Fatigue was previously associated with lower performance in attentive⁶⁰ and executive tasks.⁶¹ At MRI assessment, patients with severe-executive/attention compared with those with preserved cognition had a higher WM lesion load. Given the preferential location close to the ventricles of WM lesions in MS, a high lesion burden may play a major role in both impaired cognition⁶² and higher fatigue levels^{63,64} by disrupting long-range WM connections, which are also located close to the ventricles.^{65,66} Long-range connections have been associated with attention and executive functioning,^{67,68} and a higher lesion burden was associated with worse performance at SCWT and PASAT in patients with MS.⁶⁷⁻⁷² Long-range connections also have been associated with the pathophysiological mechanism of MS-related fatigue,^{63,64,73} and a higher lesion burden was associated with higher fatigue levels in MS.^{63,64} Future studies should further investigate the role of regional WM microstructural integrity as a possible neural substrate of this cognitive phenotype.

A fifth phenotype, severe-multidomain, was characterized by severely decreased performance in all cognitive tests. This phenotype was more frequent in the late stages of MS, corresponding to end-stage cognitive failure in the study population. However, the phenotype was also represented in patients with short disease duration and low physical disability, underscoring the importance of cognitive assessment of patients with MS from the early disease stages. These patients had severe brain atrophy on MRI, involving all explored tissue compartments, which mirrored the extensive cognitive impairment. Patients with severe-multidomain phenotype also experienced severe depressive symptoms, which is consistent with the association between depression and difficulties in working memory,⁷⁴ executive functioning,⁷⁵ and information processing speed.⁷⁶

The findings of this study may have several implications for clinical management and decision-making. This categorization of cognitive features could help in planning rehabilitative strategies⁷⁷⁻⁸³ tailored to subgroups of cognitively homogeneous patients. This categorization could be particularly relevant to patients with mildly impaired profiles who may be the ideal candidates for rehabilitative treatments because they may have higher brain plasticity resources.⁸⁴⁻⁸⁷ Moreover, a recent meta-analysis provided some evidence supporting the potential advantage of disease-modifying drugs for patient cognitive outcome.^{88,89} Transition to a more severe phenotype may support the clinical decisions on changes in the pharmacological treatment.⁹⁰⁻⁹²

Use of these cognitive phenotypes can also represent a step forward in research, allowing a better selection of candidates

for cognitive rehabilitation trials as well as fostering future studies on the pathophysiological mechanism of cognitive changes in MS by using more advanced MRI techniques and deep learning approaches.

Limitations

This study has several limitations. First, the cross-sectional design did not allow us to describe the time-dependent association and evolution of phenotypes over time. Second, the study was based on a clinical sample, which may not be entirely representative of the general MS population. Third, although commonly used in MS clinical and research settings, the Brief Repeatable Battery and SCWT did not provide a finer-grained assessment of cognitive functions. Fourth, only a subgroup of

participants underwent MRI examination at the time of the neuropsychological evaluation.

Conclusions

The data-driven cognitive phenotypes presented in this study can overcome the limitations of the traditional dichotomous classification in MS and have the potential to represent a more meaningful measure of the cognitive status of patients with MS. This new categorization of cognitive deficits may integrate the EDSS score in defining clinical disability, support clinicians in treatment choices, and help tailor cognitive rehabilitation strategies.

ARTICLE INFORMATION

Accepted for Publication: October 30, 2020.

Published Online: January 4, 2021.

doi:10.1001/jamaneurol.2020.4920

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Author Contributions: Dr De Meo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs De Meo and Portaccio equally contributed to the article. **Concept and design:** De Meo, Ruano, Goretti, Simone, Amato.

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Statistical analysis: De Meo, Bonacchi.

Obtained funding: Goretti.

Administrative, technical, or material support: De Meo, Goretti, Mattioli, De Stefano.

Supervision: De Meo, Portaccio, Giorgio, Patti, Gallo, Ghezzi, Amato.

Other: Simone.

Conflict of Interest Disclosures: Dr Portaccio reported receiving personal fees from Biogen, Merck Serono, Genzyme, and Teva outside the submitted work. Dr Ruano reported receiving grants from Biogen and personal fees from Roche and Novartis outside the submitted work. Prof Patti reported receiving grants from RELOAD Onlus Association, University of Catania, Biogen, and Merck; personal fees from Almirall, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Roche, Sanofi, and Teva outside the submitted work; and grants from Federazione Italiana Sclerosi Multipla during the conduct of the study. Dr Rocca reported receiving personal fees from Biogen Idec, Novartis, Genzyme, Sanofi, Teva, Merck-Serono, Roche, Celgene, and Bayer outside the submitted work. Prof De Stefano reported receiving personal fees from Immunic Therapeutics, Sanofi Genzyme, Teva, and Biogen as well as grants and personal fees from Merck Serono and Novartis Pharma outside the submitted work. Prof Filippi reported receiving personal fees from Bayer, Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme, Takeda, and Teva Pharmaceutical Industries; receiving grants from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries, and Roche outside the submitted work; and being editor in chief of *Journal of Neurology*. Prof Amato reported receiving grants and personal fees from Merck, Biogen, Sanofi Genzyme, Roche, Teva, and Novartis outside the submitted work. No other disclosures were reported.

REFERENCES

1. Zipoli V, Goretti B, Hakiki B, et al. Cognitive impairment predicts conversion to multiple

sclerosis in clinically isolated syndromes. *Mult Scler*. 2010;16(1):62-67. doi:10.1177/1352458509350311

2. Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. *Mult Scler*. 2016;22(2):250-253. doi:10.1177/1352458515591072

3. Rao SM, Leo GJ, Houghton VM, St Aubin-Faubert P, Bernardin L. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology*. 1989;39(2, pt 1):161-166. doi:10.1212/WNL.39.2.161

4. Kincses ZT, Ropele S, Jenkinson M, et al. Lesion probability mapping to explain clinical deficits and cognitive performance in multiple sclerosis. *Mult Scler*. 2011;17(6):681-689. doi:10.1177/1352458510391342

5. Preziosa P, Rocca MA, Pagani E, et al; MAGNIMS Study Group. Structural MRI correlates of cognitive impairment in patients with multiple sclerosis: a multicenter study. *Hum Brain Mapp*. 2016;37(4):1627-1644. doi:10.1002/hbm.23125

6. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Arch Neurol*. 2009;66(9):1144-1150. doi:10.1001/archneurol.2009.174

7. Steenwijk MD, Geurts JJ, Daams M, et al. Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant. *Brain*. 2016;139 (pt 1):115-126. doi:10.1093/brain/aww337

8. Damjanovic D, Valsasina P, Rocca MA, et al. Hippocampal and deep gray matter nuclei atrophy is relevant for explaining cognitive impairment in MS: a multicenter study. *AJNR Am J Neuroradiol*. 2017;38(1):18-24. doi:10.3174/ajnr.A4952

9. Benedict RHB, Amato MP, DeLuca J, Geurts JGG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol*. 2020;19(10):860-871. doi:10.1016/S1474-4422(20)30277-5

10. Leavitt VM, Tosto G, Riley CS. Cognitive phenotypes in multiple sclerosis. *J Neurol*. 2018; 265(3):562-566. doi:10.1007/s00415-018-8747-5

11. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol*. 2008;7(12):1139-1151. doi:10.1016/S1474-4422(08)70259-X

12. Leavitt VM, Lengenfelder J, Moore NB, Chiaravalloti ND, DeLuca J. The relative contributions of processing speed and cognitive

- load to working memory accuracy in multiple sclerosis. *J Clin Exp Neuropsychol*. 2011;33(5):580-586. doi:10.1080/13803395.2010.541427
13. Sumowski JF, Chiaravalloti N, Erlanger D, Kaushik T, Benedict RH, DeLuca J. L-amphetamine improves memory in MS patients with objective memory impairment. *Mult Scler*. 2011;17(9):1141-1145. doi:10.1177/1352458511404585
14. Miettunen J, Nordström T, Kaakinen M, Ahmed AO. Latent variable mixture modeling in psychiatric research—a review and application. *Psychol Med*. 2016;46(3):457-467. doi:10.1017/S0033291715002305
15. Bever CT Jr, Grattan L, Panitch HS, Johnson KP. The Brief Repeatable Battery of neuropsychological tests for multiple sclerosis: a preliminary serial study. *Mult Scler*. 1995;1(3):165-169. doi:10.1177/135245859500100306
16. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18(6):643-662. doi:10.1037/h0054651
17. Amato MP, Portaccio E, Goretti B, et al. The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population. *Mult Scler*. 2006;12(6):787-793. doi:10.1177/1352458506070933
18. Krupp LB, Tardieu M, Amato MP, et al; International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler*. 2013;19(10):1261-1267. doi:10.1177/1352458513484547
19. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389. doi:10.1192/bjp.134.4.382
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology*. 1983;33(11):1444-1452. doi:10.1212/WNL.33.11.1444
21. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-286. doi:10.1212/WNL.0000000000000560
22. Debernard L, Melzer TR, Van Stockum S, et al. Reduced grey matter perfusion without volume loss in early relapsing-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2014;85(5):544-551. doi:10.1136/jnnp-2013-305612
23. Chard DT, Jackson JS, Miller DH, Wheeler-Kingshott CA. Reducing the impact of white matter lesions on automated measures of brain gray and white matter volumes. *J Magn Reson Imaging*. 2010;32(1):223-228. doi:10.1002/jmri.22214
24. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011;56(3):907-922. doi:10.1016/j.neuroimage.2011.02.046
25. Oberski D. Mixture models: latent profile and latent class analysis. In: Kaptein M, Robertson J, eds. *Modern Statistical Methods for HCI*. Springer; 2016:275-287. doi:10.1007/978-3-319-26633-6_12
26. Blanken AE, Jang JY, Ho JK, et al. Distilling heterogeneity of mild cognitive impairment in the National Alzheimer Coordinating Center Database using latent profile analysis. *JAMA Netw Open*. 2020;3(3):e200413. doi:10.1001/jamanetworkopen.2020.0413
27. Iqbal K, Flory M, Khatoun S, et al. Subgroups of Alzheimer's disease based on cerebrospinal fluid molecular markers. *Ann Neurol*. 2005;58(5):748-757. doi:10.1002/ana.20639
28. Spurk D, Hirschi A, Wang M, Valero D, Kauffeld S. Latent profile analysis: a review and "how to" guide of its application within vocational behavior research. *J Vocat Behav*. 2020;120:103445. doi:10.1016/j.jvb.2020.103445
29. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. *Struct Equ Modeling*. 2007;14(4):535-569. doi:10.1080/10705510701575396
30. Scrucca L, Fop M, Murphy TB, Raftery AE. mclust 5: clustering, classification and density estimation using Gaussian finite mixture models. *R J*. 2016;8(1):289-317. doi:10.32614/RJ-2016-021
31. Woo SE, Jebb AT, Tay L, Parrigon S. Putting the "person" in the center: review and synthesis of person-centered approaches and methods in organizational science. *Organ Res Methods*. 2018;21(4):814-845. doi:10.1177/1094428117752467
32. Nagin D. *Group-Based Modeling of Development*. Harvard University Press; 2005. doi:10.4159/9780674041318
33. Berlin KS, Williams NA, Parra GR. An introduction to latent variable mixture modeling (part 1): overview and cross-sectional latent class and latent profile analyses. *J Pediatr Psychol*. 2014;39(2):174-187. doi:10.1093/jpepsy/jst084
34. Filippi M, Brück W, Chard D, et al; Attendees of the Correlation Between Pathological and MRI Findings in MS Workshop. Association between pathological and MRI findings in multiple sclerosis. *Lancet Neurol*. 2019;18(2):198-210. doi:10.1016/S1474-4422(18)30451-4
35. Rocca MA, Amato MP, De Stefano N, et al; MAGNIMS Study Group. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol*. 2015;14(3):302-317. doi:10.1016/S1474-4422(14)70250-9
36. Minagar A, Barnett MH, Benedict RHB, et al. The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. *Neurology*. 2013;80(2):210-219. doi:10.1212/WNL.0b013e31827b910b
37. Sumowski JF, Leavitt VM. Cognitive reserve in multiple sclerosis. *Mult Scler*. 2013;19(9):1122-1127. doi:10.1177/1352458513498834
38. Louapre C, Govindarajan ST, Gianni C, et al. Heterogeneous pathological processes account for thalamic degeneration in multiple sclerosis: insights from 7 T imaging. *Mult Scler*. 2018;24(11):1433-1444. doi:10.1177/1352458517726382
39. Johansen-Berg H, Behrens TE, Sillery E, et al. Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. *Cereb Cortex*. 2005;15(1):31-39. doi:10.1093/cercor/bhh105
40. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I: frequency, patterns, and prediction. *Neurology*. 1991;41(5):685-691. doi:10.1212/WNL.41.5.685
41. Pitteri M, Dapor C, Pisani AI, et al. Executive functioning affects verbal learning process in multiple sclerosis patients: behavioural and imaging results. *J Neuropsychol*. 2020;14(3):384-398. doi:10.1111/jnp.12198
42. Costa SL, DeLuca J, Costanza K, Chiaravalloti ND. Comparing the open trial—Selective Reminding Test results with the California Learning Verbal Test II in multiple sclerosis. *Appl Neuropsychol Adult*. 2019;26(5):488-496. doi:10.1080/23279095.2018.1448818
43. Kavé G, Sapir-Yogev S. Associations between memory and verbal fluency tasks. *J Commun Disord*. 2020;83:105968. doi:10.1016/j.jcomdis.2019.105968
44. van Geest Q, Hulst HE, Meijer KA, Hoyng L, Geurts JGG, Douw L. The importance of hippocampal dynamic connectivity in explaining memory function in multiple sclerosis. *Brain Behav*. 2018;8(5):e00954. doi:10.1002/brb3.954
45. Kern KC, Ekstrom AD, Suthana NA, et al. Fornix damage limits verbal memory functional compensation in multiple sclerosis. *Neuroimage*. 2012;59(3):2932-2940. doi:10.1016/j.neuroimage.2011.09.071
46. Rocca MA, Barkhof F, De Luca J, et al; MAGNIMS Study Group. The hippocampus in multiple sclerosis. *Lancet Neurol*. 2018;17(10):918-926. doi:10.1016/S1474-4422(18)30309-0
47. Catheline G, Amieva H, Dilharreguy B, et al. Semantic retrieval over time in the aging brain: structural evidence of hippocampal contribution. *Hippocampus*. 2015;25(9):1008-1016. doi:10.1002/hipo.22423
48. Sheldon S, Moscovitch M. The nature and time-course of medial temporal lobe contributions to semantic retrieval: an fMRI study on verbal fluency. *Hippocampus*. 2012;22(6):1451-1466. doi:10.1002/hipo.20985
49. Beatty WW. RBANS analysis of verbal memory in multiple sclerosis. *Arch Clin Neuropsychol*. 2004;19(6):825-834. doi:10.1016/j.acn.2003.12.001
50. Whiteside DM, Kealey T, Semla M, et al. Verbal fluency: language or executive function measure? *Appl Neuropsychol Adult*. 2016;23(1):29-34. doi:10.1080/23279095.2015.1004574
51. Hrybouski S, MacGillivray M, Huang Y, et al. Involvement of hippocampal subfields and anterior-posterior subregions in encoding and retrieval of item, spatial, and associative memories: longitudinal versus transverse axis. *Neuroimage*. 2019;191:568-586. doi:10.1016/j.neuroimage.2019.01.061
52. Llufríu S, Rocca MA, Pagani E, et al. Hippocampal-related memory network in multiple sclerosis: a structural connectivity analysis. *Mult Scler*. 2019;25(6):801-810. doi:10.1177/1352458518771838
53. Costa SL, Genova HM, DeLuca J, Chiaravalloti ND. Information processing speed in multiple sclerosis: past, present, and future. *Mult Scler*. 2017;23(6):772-789. doi:10.1177/1352458516645869
54. Amato MP, Bartolozzi ML, Zipoli V, et al. Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology*. 2004;63(1):89-93. doi:10.1212/01.WNL.0000129544.79539.D5
55. Benedict RH, Bruce JM, Dwyer MG, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Arch*

- Neurol.* 2006;63(9):1301-1306. doi:10.1001/archneur.63.9.1301
56. Eijlers AJC, van Geest Q, Dekker I, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. *Brain.* 2018;141(9):2605-2618. doi:10.1093/brain/awy202
57. Eijlers AJC, Dekker I, Steenwijk MD, et al. Cortical atrophy accelerates as cognitive decline worsens in multiple sclerosis. *Neurology.* 2019;93(14):e1348-e1359. doi:10.1212/WNL.0000000000008198
58. Mainero C, Louapre C, Govindarajan ST, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. *Brain.* 2015;138(pt 4):932-945. doi:10.1093/brain/awv011
59. Sarter M, Givens B, Bruno JP. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Res Brain Res Rev.* 2001;35(2):146-160. doi:10.1016/S0165-0173(01)00044-3
60. Hanken K, Eling P, Hildebrandt H. Is there a cognitive signature for MS-related fatigue? *Mult Scler.* 2015;21(4):376-381. doi:10.1177/1352458514549567
61. Holtzer R, Foley F. The relationship between subjective reports of fatigue and executive control in multiple sclerosis. *J Neurol Sci.* 2009;281(1-2):46-50. doi:10.1016/j.jns.2009.02.360
62. Meijer KA, Steenwijk MD, Douw L, Schoonheim MM, Geurts JGG. Long-range connections are more severely damaged and relevant for cognition in multiple sclerosis. *Brain.* 2020;143(1):150-160. doi:10.1093/brain/awz355
63. Tedeschi G, Dinacci D, Lavorgna L, et al. Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability. *J Neurol Sci.* 2007;263(1-2):15-19. doi:10.1016/j.jns.2007.07.004
64. Sepulcre J, Masdeu JC, Gofii J, et al. Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways. *Mult Scler.* 2009;15(3):337-344. doi:10.1177/1352458508098373
65. Haider L, Zrzavy T, Hametner S, et al. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain.* 2016;139(pt 3):807-815. doi:10.1093/brain/awv398
66. Liu Z, Pardini M, Yaldizli Ö, et al. Magnetization transfer ratio measures in normal-appearing white matter show periventricular gradient abnormalities in multiple sclerosis. *Brain.* 2015;138(pt 5):1239-1246. doi:10.1093/brain/awv065
67. Foong J, Rozewicz L, Quaghebeur G, et al. Executive function in multiple sclerosis: the role of frontal lobe pathology. *Brain.* 1997;120(pt 1):15-26. doi:10.1093/brain/120.1.15
68. Pujol J, Vendrell P, Deus J, et al. The effect of medial frontal and posterior parietal demyelinating lesions on Stroop interference. *Neuroimage.* 2001;13(1):68-75. doi:10.1006/nimg.2000.0662
69. Camp SJ, Stevenson VL, Thompson AJ, et al. A longitudinal study of cognition in primary progressive multiple sclerosis. *Brain.* 2005;128(pt 12):2891-2898. doi:10.1093/brain/awh602
70. Arnett PA, Rao SM, Bernardin L, Grafman J, Yetkin FZ, Lobeck L. Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. *Neurology.* 1994;44(3, pt 1):420-425. doi:10.1212/WNL.44.3.Part_1.420
71. Nocentini U, Rossini PM, Carlesimo GA, et al. Patterns of cognitive impairment in secondary progressive stable phase of multiple sclerosis: correlations with MRI findings. *Eur Neurol.* 2001;45(1):11-18. doi:10.1159/000052083
72. Sperling RA, Guttmann CR, Hohol MJ, et al. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. *Arch Neurol.* 2001;58(1):115-121. doi:10.1001/archneur.58.1.115
73. Filippi M, Rocca MA, Colombo B, et al. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage.* 2002;15(3):559-567. doi:10.1006/nimg.2001.1011
74. Arnett PA, Higginson CI, Voss WD, Bender WI, Wurst JM, Tippin JM. Depression in multiple sclerosis: relationship to working memory capacity. *Neuropsychology.* 1999;13(4):546-556. doi:10.1037/0894-4105.13.4.546
75. Arnett PA, Higginson CI, Randolph JJ. Depression in multiple sclerosis: relationship to planning ability. *J Int Neuropsychol Soc.* 2001;7(6):665-674. doi:10.1017/S1355617701766027
76. Patel VP, Feinstein A. The link between depression and performance on the Symbol Digit Modalities Test: mechanisms and clinical significance. *Mult Scler.* 2019;25(1):118-121. doi:10.1177/1352458518770086
77. Amato MP, Goretti B, Viterbo RG, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult Scler.* 2014;20(1):91-98. doi:10.1177/1352458513501571
78. Charvet LE, Yang J, Shaw MT, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: results from a randomized controlled trial. *PLoS One.* 2017;12(5):e0177177. doi:10.1371/journal.pone.0177177
79. Pedullà L, Bricchetto G, Tacchino A, et al. Adaptive vs. non-adaptive cognitive training by means of a personalized app: a randomized trial in people with multiple sclerosis. *J Neuroeng Rehabil.* 2016;13(1):88. doi:10.1186/s12984-016-0193-y
80. Hubacher M, Kappos L, Weier K, Stöcklin M, Opwis K, Penner IK. Case-based fMRI analysis after cognitive rehabilitation in MS: a novel approach. *Front Neurol.* 2015;6:78. doi:10.3389/fneur.2015.00078
81. Fink F, Rischkau E, Butt M, Klein J, Eling P, Hildebrandt H. Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial. *Mult Scler.* 2010;16(9):1148-1151. doi:10.1177/1352458510375440
82. Hanssen KT, Saltyté Benth J, Beiske AG, Landrø NI, Hessen E. Goal attainment in cognitive rehabilitation in MS patients. *Neuropsychol Rehabil.* 2015;25(1):137-154. doi:10.1080/09602011.2014.971818
83. Chiaravalloti ND, Moore NB, DeLuca J. The efficacy of the modified Story Memory Technique in progressive MS. *Mult Scler.* 2020;26(3):354-362. doi:10.1177/1352458519826463
84. Enzinger C, Pinter D, Rocca MA, et al. Longitudinal fMRI studies: exploring brain plasticity and repair in MS. *Mult Scler.* 2016;22(3):269-278. doi:10.1177/1352458515619781
85. Filippi M, Rocca MA. Present and future of fMRI in multiple sclerosis. *Expert Rev Neurother.* 2013;13(12 suppl):27-31. doi:10.1586/14737175.2013.865871
86. Forn C, Barros-Loscertales A, Escudero J, et al. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. *Neuroimage.* 2006;31(2):686-691. doi:10.1016/j.neuroimage.2005.12.030
87. Forn C, Barros-Loscertales A, Escudero J, et al. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. *Hum Brain Mapp.* 2007;28(5):424-430. doi:10.1002/hbm.20284
88. Amato MP, Krupp LB. Disease-modifying therapy aids cognition in multiple sclerosis. *Nat Rev Neurol.* 2020;16(10):525-526. doi:10.1038/s41582-020-0383-x
89. Landmeyer NC, Bürkner PC, Wiendl H, et al. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: a meta-analysis. *Neurology.* 2020;94(22):e2373-e2383. doi:10.1212/WNL.0000000000009522
90. Mollison D, Sellar R, Bastin M, et al. The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: a systematic review and meta-analysis. *PLoS One.* 2017;12(5):e0177727. doi:10.1371/journal.pone.0177727
91. Weinstock-Guttman B, Eckert S, Benedict RH. A decline in cognitive function should lead to a change in disease-modifying therapy—yes. *Mult Scler.* 2018;24(13):1681-1682. doi:10.1177/1352458518783364
92. Amato MP. A decline in cognitive function should lead to a change in disease-modifying therapy—commentary. *Mult Scler.* 2018;24(13):1685-1686. doi:10.1177/1352458518787721