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Identifying the Distinct Cognitive Phenotypes in Multiple Sclerosis

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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.

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Supplemental content

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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 clinically[1] 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] cortical[7] and deep[8] 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.

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.

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 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 Battery[15] 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 SCWT[16] 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 values[17] 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 disability)[20] 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-filled[23] 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-filled[23] 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 models[25] 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 Nylund et al[29] 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 individuals; (2) mild-verbal memory/semantic fluency com-

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.

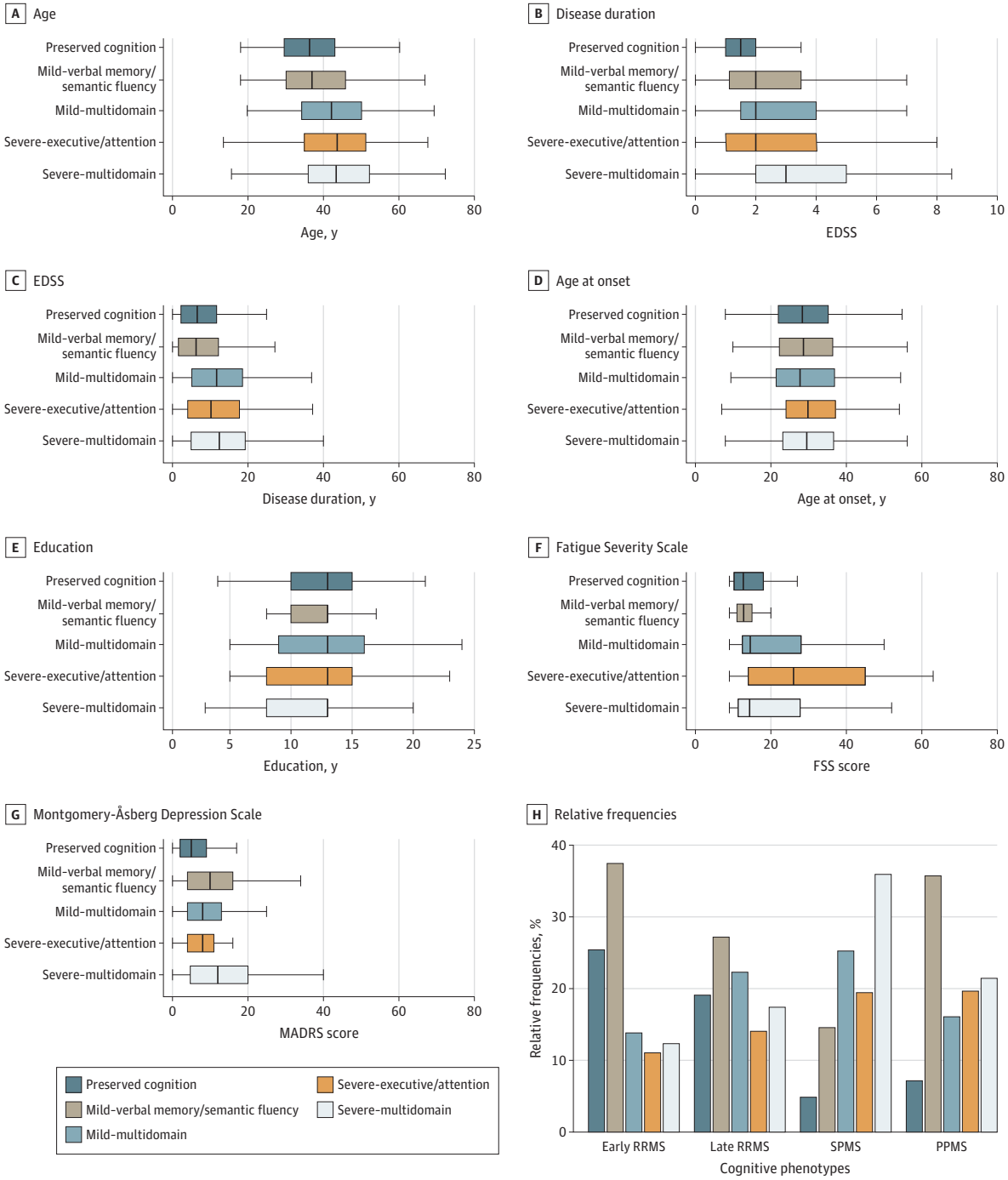
prised 362 patients (29.9%) who showed only mildly decreased performance in SRT (mean [SD] *z* score, −0.59 [0.85]; Cohen *d* = −0.69; 95% CI, −0.89 to −0.50; *P* < .001) and WLG (mean [SD] *z* score, −1.29 [0.71]; Cohen *d* = −1.41; 95% CI, −1.89 to −1.39; *P* < .001) compared with healthy control individuals; (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 phenotypes (median [range] EDSS score, 3.0 [0.0-8.0]; *P* ≤ .001).

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.

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.

To improve the readability of the study and the interpretation of results, we named cognitive phenotypes according

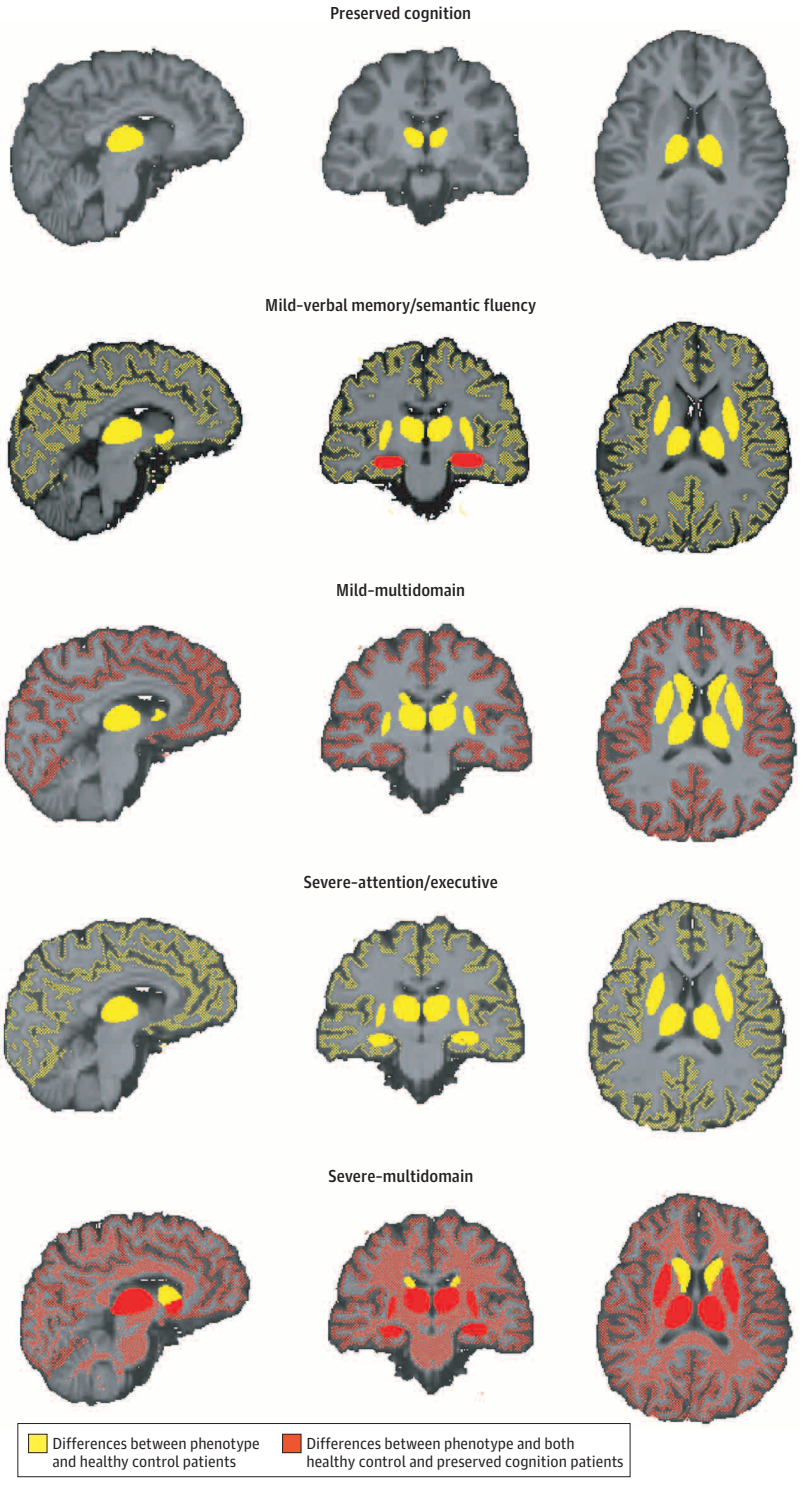
Table 3. Estimated Marginal Means of Magnetic Resonance Imaging Features of Cognitive Phenotypes

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		22	NA	NA	24	NA	NA
T2 LV	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 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 fluency[40] 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 subfields[51] 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 findings[54] 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 level[58] and on cerebral activation[35] to assess 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 attentive[60] 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 cognition[62] 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 strategies[77-83] 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 stud-

ies 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.

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