Identifying distinct cognitive phenotypes in multiple sclerosis

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INTRODUCTION and PURPOSE

Cognitive impairment affects 40% to 70% of multiple sclerosis (MS) patients, depending on study population, tests, and cut-off values.[1] It can alter the behavior and quality of life of MS patients, leading to social and personal difficulties, sometimes in spite of minimal concurrent physical disability.[2] Information processing speed and episodic memory are the cognitive functions more frequently affected in MS however additional difficulties in executive function, verbal fluency, and visuospatial abilities have been reported.[2]

MRI has proven to represent a powerful tool in investigating the neuroanatomical substrates of cognitive impairment in MS patients, however leading to heterogeneous results. Early MRI studies linked cognitive deficits to greater brain lesion load,[3] while 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 and abnormal pattern of cerebral activation.[9] The lacking of such a specific characterization of cognitive deficit at patient-level may hamper an accurate definition of the neuroanatomical basis of cognitive features as well as the development of efficient rehabilitative strategies, which need be targeted to specific profiles/severity of cognitive deficits. A promising approach to achieve the personalization required, is to individuate cognitively homogeneous subgroups of patients, which may be defined as "*cognitive phenotypes*".

The aims of the present study are:

- To identify **cognitive phenotypes** of MS patients embracing the whole spectrum of the disease by using a data driven approach;
- To characterize **clinical features** of each cognitive phenotype;
- To identify the underlying **MRI substrates**.

METHODS

Subjects

- 1212 MS patients referring to eight different italian MS centers
- 196 age-, sex- and education-matched healthy controls (HC)

Clinical evaluation

- EDSS

Neuropsychological assessment

- RAO's brief repeatable battery
- Stroop test
- Fatigue Severity Scale and Montgomery Asberg Depression Rating Scale

→ Calculation of z-scores of each test performed

MRI acquisition (3.0 Tesla scanner) (172 MS patients and 50 HC from Milan and Siena)

- 3DT1-weighted turbo field echo;
- Dual-echo turbo spin echo yielding proton density (PD) and T2-weighted images

MRI analysis

- Measurements of T2 hyperintense and T1 hypointense lesion volumes (LV);
- Quantification of normalized brain (NBV), WM (WMV) and GM (GMV) volumes (SIENAx).
- Deep gray matter segmentation (FIRST software)

Statistical analysis

- To identify latent cognitive profiles defined as cognitive phenotypes, we performed latent-profile analysis on cognitive tests' z-scores
- Models including from one to six classes were run
- For choosing the optimal number of classes the Bootstrapped Likelihood Ratio Test, the Bayesian Information Criterion and the Integrated Completed Likelihood were inspected
- Between-group comparisons of demographic, clinical and MRI parameters were performed by using age- and sex-adjusted linear models, non-parametric tests or linear mixed effect models, as appropriate

RESULTS

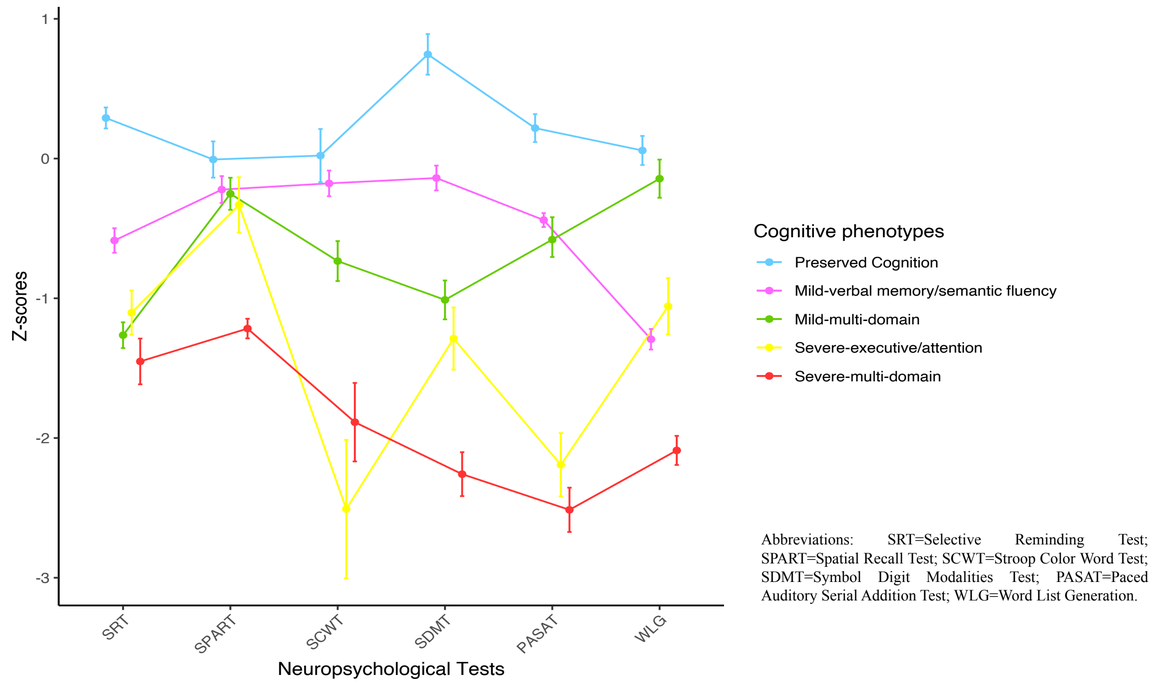
Table 1 summarizes the main demographic and clinical features of the study subjects.

	Healthy controls	Multiple sclerosis patients	*p* values
No.	196	1212	-
Mean age (SD) [range] [years]	40.4 (8.6) [20.2 – 60.9]	41.1 (11.1) [18.0 – 77.2]	0.38
Female/Male	130/66	784/428	0.87
Median EDSS (range)	-	2.0 (0.0 – 8.5)	-
Mean disease duration (SD) [range] [years]	-	10.5 (9.0) [0.20 - 55.2]	-
Mean age of onset (SD) [range] [years]	-	29.8 (9.9) [7.0 – 58.0]	-
Education (SD) [range] [years]	12.5 (3.4) [5.0-19.0]	12.2 (3.8) [5.0-24.0]	0.38
Mean FSS score (SD) [range]	-	14.9 (17.4) [1.0 – 63.0]	-
Mean MADRS score (SD) [range]	-	10.1 (9.3) [0.0 – 59.0]	-

Abbreviations: EDSS=Expanded Disability Status Scale; SD=standard deviation; FSS=Fatigue Severity Scale; MADRS=Montgomery-Asberg Depression Rating Scale.

- According to Bootstrapped Likelihood Ratio Test, the Bayesian Information Criterion and the Integrated Completed Likelihood the model including **5 classes** was the best fitting one.

Figure 1 provides a graphical representation of cognitive phenotypes obtained from latent profile analysis.



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

Cognitive performance of each phenotype is represented: points indicate mean z-scores obtained at each neuropsychological test and error bars reflect the 95% confidence interval. "Preserved cognition" phenotype is represented in cyan blue, "mild-verbal memory/semantic fluency" in purple, "mild-multi-domain" in green, "severe-attention/executive" in yellow and "severe-multi-domain" in red.

Figure 2 summarizes between-phenotypes comparisons of demographic and clinical features

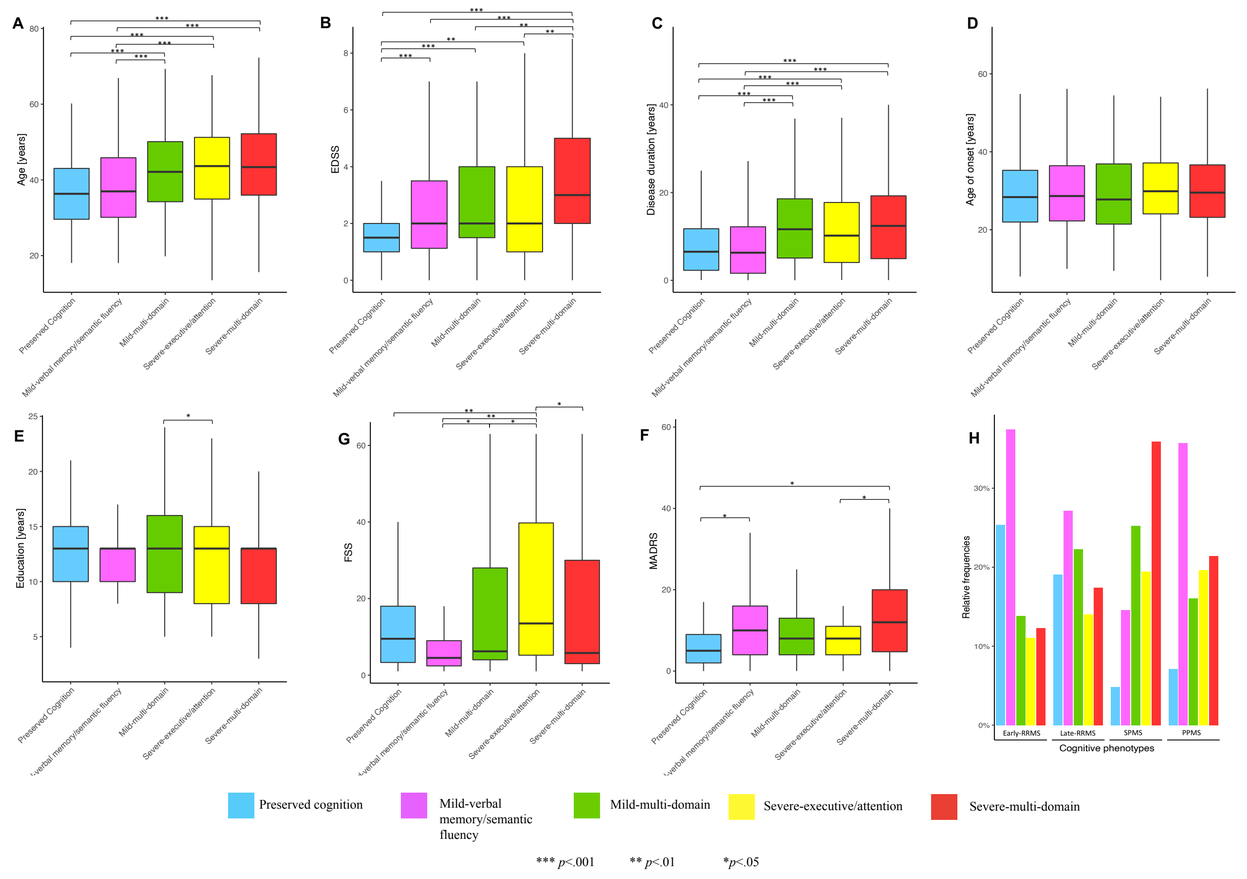
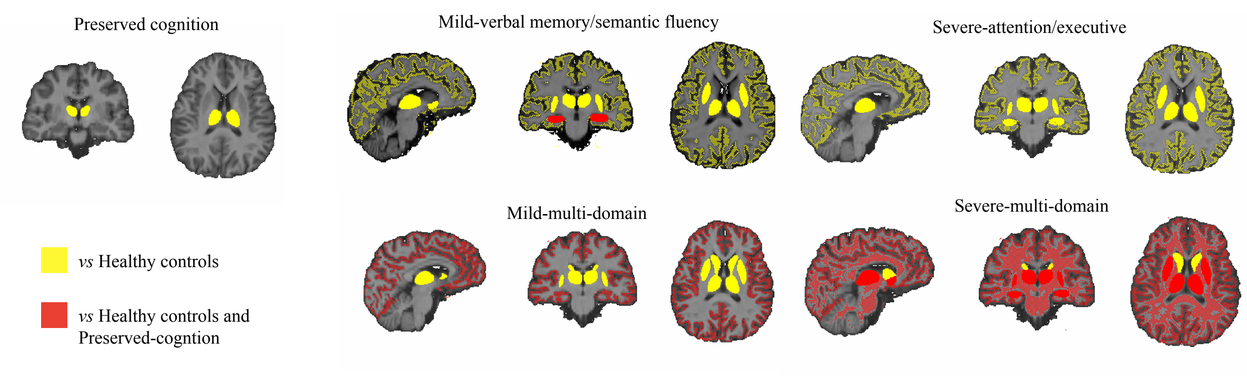


Figure 3 showes brain compartment with reduced volume in each phenotype compared to HC (yellow) and "preserved-cognition" patients (red).



CONCLUSIONS

- By using a complete neuropsychological evaluation in a large and heterogeneous cohort of MS patients and a data-driven approach, we were able to identify five homogeneous cognitive phenotypes
- We confirmed that cognitive impairment occurs since from the earliest stages of disease, although more severe phenotypes are more frequent in progressive patients, as well as later in the disease course
- Furthermore, we were described separate underlying neuroanatomical substrates, supporting data-driven findings with a biological basis
- By defining cognitively homogenous groups, this classification can be useful for future research on cognitive impairment in MS, and for defining personalized management approaches and rehabilitative strategies in clinical practice

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