

Identifying distinct cognitive phenotypes in multiple sclerosis

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

Objectives. We sought to define homogeneous cognitive phenotypes in a large cohort of MS patients by using a data-driven approach, and to assess their distinctive clinical and MRI features. Our aim was to go beyond traditional preserved/impaired classification dichotomy, setting the stage for future research and tailored management approaches.

Methods. 1212 clinically stable MS patients and 196 HC not using psychoactive drugs, without any history of other neurological/medical disorders, learning disability, severe head trauma, alcohol/drug abuse were enrolled in this **multicenter cross-sectional study**.

All subjects underwent neurological examination and cognitive evaluation with Rao's Brief Repeatable Battery and Stroop Color Word Test. MRI protocol included brain 3DT1-weighted and dual-echo sequences for atrophy and lesion assessment. Latent-profile analysis was used on cognitive test z-scores for identifying cognitive phenotypes. Linear regression and mixed effects models were used to define clinical and MRI features of each phenotype.

Results. Mean (standard deviation) age was 41.1 (11.1) years for MS patients (784 [65%] females), and 40.4 (8.6) for HC (130 [66%] females). Five cognitive phenotypes were identified: "preserved-cognition" (19%), "mild verbal memory/semantic fluency" (30%), "mild-multi-domain" (19%), "severe-attention/executive" (14%), and "severe-multi-domain" (18%) involvement. "Preserved

cognition” and “mild-verbal memory/semantic fluency” patients were younger and had shorter disease duration compared to the other phenotypes. Physical disability was lowest in “preserved cognition” and highest in “severe-multi-domain” patients. Severe cognitive phenotypes prevailed in progressive patients. At MRI evaluation, compared to “preserved-cognition”, “mild verbal memory/semantic fluency” patients exhibited reduced hippocampal volume, “mild-multi-domain” reduced cortical gray matter volume, “severe-attention/executive” higher T2-hyperintense lesion volume and severe-multi-domain” extensive brain damage.

Conclusions. By defining homogenous and clinically-meaningful phenotypes, this study can pave the way to future research on neuroanatomical substrates of MS-related cognitive impairment and help define tailored management strategies.