



Longitudinal MRI Correlates of Cognitive Trajectories in Multiple Sclerosis: a multicenter study

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Background and Aims

Cognitive decline in Multiple Sclerosis (MS) can occur over time, with some individuals transitioning from a cognitively preserved (CP) to a cognitively impaired (CI) status. Identifying MRI-derived structural markers associated with cognitive decline may be crucial for early intervention. Our aim was to identify MRI-derived structural correlates of CI at follow-up in people with MS (pwMS).

Materials and Methods

388 pwMS from four Italian MS Centers participating to the Italian Neuroimaging Network Initiative (INNI) consortium underwent neuropsychological assessment with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) at baseline and follow-up (≥4 years later). CI was defined by adjusted Z scores ≤-1.5 SD below normative values in ≥2 cognitive domains (verbal memory, visual memory, attention, verbal fluency). An additional classification was performed by combining BRB-N domains into two cognitive macrodomains—memory and executive functions. Baseline 3T MRI-derived measures - including subcortical volumes and cortical thickness (CTH) extracted with FreeSurfer - were used to predict follow-up cognitive scores via multiple linear regression, adjusting for age, sex, education, disease duration, phenotype, site, and, for CTH measures, global CTH. The results were Bonferroni corrected ($p < .05$).

Results

- ✓ The mean follow-up of neuropsychological evaluation was 7.3 (2.7) years. At baseline, 104 pwMS (26.8%) were classified as CI, while 111 CP (28.6%) showed impairment in a single domain. 28 CP converted to CI at follow-up, while among pwMS with impairment in a single domain, those with executive dysfunction were being more likely to transition to CI than those with memory impairment ($\chi^2 = 3.88, p = .0486$).
- ✓ Among different subcortical volumes associated with follow-up cognitive performance, the thalamus emerged as a strong predictor of Symbol Digit Modalities Test (SDMT; $B = 0.25, p = .006$) and Word List Generation (WLG; $B = 0.27, p = .001$) scores. Additional significant associations were found with the putamen (SPART), accumbens (WLG), hippocampus (SDMT), and pallidum (SRT; all $p < .05$).
- ✓ SDMT scores were inversely associated with the CTH of the rostral anterior cingulate cortex (rACC; $B = -0.22, p = .041$).

	N (%)	Mean (SD)	Range
Age (years)	F	39.3 (11.2)	18-64
	M	146 (37.6%)	-
Education (years)		13.2 (3.4)	5-23
Phenotype	CIS	23 (5.9%)	-
	RRMS	305 (78.6%)	-
	PPMS	12 (3.1%)	-
	SPMS	48 (12.4%)	-
EDSS		2.4 (1.7)	0-8
Disease duration (years)		10.2 (8.9)	0-42.6

Table 1. Sample characteristics at baseline (N = 388)

Region	score	beta_fu	p_fu	p_fu_adj
Putamen	SPART_Z	0.317	<0.001	<0.001
Thalamus	WLG_Z	0.266	<0.001	0.001
Thalamus	SDMT_Z	0.252	<0.001	0.006
Accumbens	WLG_Z	0.220	<0.001	0.025
Hippocampus	SDMT_Z	0.208	<0.001	0.030
Pallidum	SRT_Its_Z	0.199	<0.001	0.030

Table 2. Model with subcortical volumes as predictors: significant predictors of BRB-N tests at follow-up.

Region	Score	Beta_fu	p_fu	p_fu_adj
Rostral anterior cingulate (rACC)	SDMT_Z	-0.224	<0.001	0.041

Table 3. Model with CTH regions as predictors: significant predictors of BRB-N tests at follow-up.

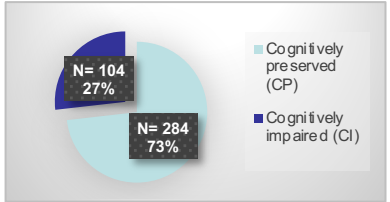


Figure 1. Cognitive status of pwMS (N=388) at baseline evaluation.

Conclusions

PwMS with subtle executive deficits are at higher risk of cognitive decline. Patterns suggest domain-specific contributions of subcortical volumes and highlight/confirm role of thalamus and striatum in processing speed and fluency, and hippocampal involvement in memory/processing. Thicker rACC was inversely related to processing speed, possibly reflecting maladaptive or inefficient compensatory mechanisms. Baseline MRI-based measures may support early interventions to preserve cognitive functioning in MS.

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