Cognitive age in multiple sclerosis: the role of brain and cognitive reserve

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INTRODUCTION

Cognitive impairment is increasingly recognized as a common clinical feature in multiple sclerosis (MS), affecting 30–70% of patients. These deficits may involve multiple domains, including processing speed, memory, and executive functions [1]. Ageing represents a key contributor to cognitive decline[1], but individual protective factors such as *cognitive reserve* (e.g., education, premorbid IQ) and *brain reserve* may help mitigate its impact[2]. More recently, *brain age*— an MRI-derived estimate of biological brain aging— has emerged as a promising global marker of brain health[3]. However, its relationship with cognitive functioning in MS has not been proven.

AIMS

- **Cognitive Age Gap Estimate** (CogAGE, meaning MS patients' predicted cognitive age and chronological age gap, based on a cognitive-age model) assessment;
- Neuroanatomical correlates identification;
- Brain and cognitive reserve role evaluation.

METHODS

113 MS patients

Neuropsychological evaluation

- SDMT, Symbol Digit Modalities Test (information processing speed)
- BVMT, Brief Visuospatial Memory Test (visuospatial memory)
- CVLT California Verbal Learning Test (verbal memory)

MRI acquisition (3T scanner)

MRI derived biomarkers

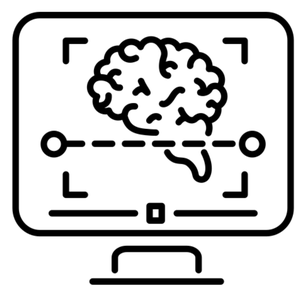
- Normalized Brain Volume
- Normalized Cortical Gray Matter Volume
- Normalized Thalamic Volume
- Normalized White Matter Volume
- Lesion Volume

Application of a **COGNITIVE-AGE MODEL** trained on cognitive test scores from 990 healthy individuals using Gaussian processes

CogAGE
Predicted cognitive age- Chronological age difference

Exploration of the association between CogAGE and MRI-derived metrics

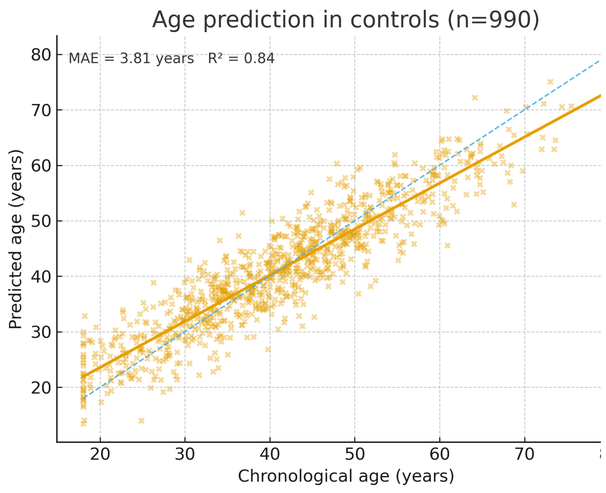
Linear regression models to assess the impact of **Cognitive reserve (**Education, premorbid IQ) **Brain reserve (**Intracranial volume)

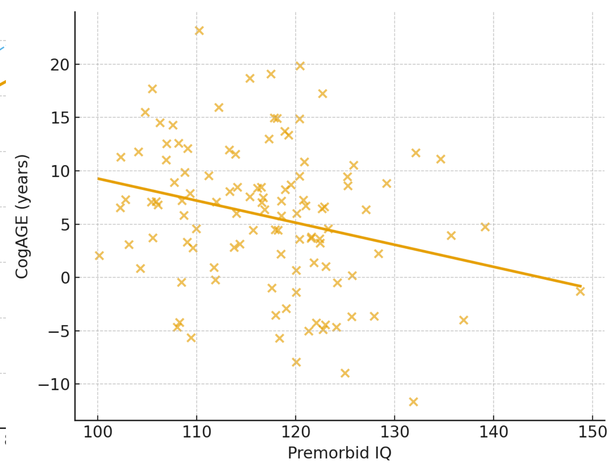


RESULTS

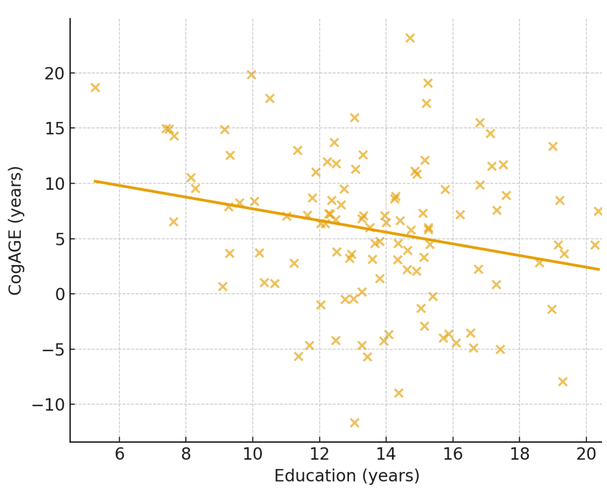
Table 1. Study cohort clinical features

	Healthy individuals (n=990)	MS patients (n= 113)	MS vs HC p values
Men/Women	350/640	30 / 83	0.52
Mean age (SD) [years]	42.7 (12.8)	43.7 (11.5)	0.15
Mean education (SD) [years]	14 (3)	14.05 (3.35)	0.88
BVMT z-score (SD)	0.02 (1.01)	-0.37 (1.04)	<0.001
SDMT z-score (SD)	-0.01 (1.01)	-0.63 (1.34)	<0.001
CVLT z-score (SD)	-0.04 (0.98)	-0.49 (-0.26)	<0.001

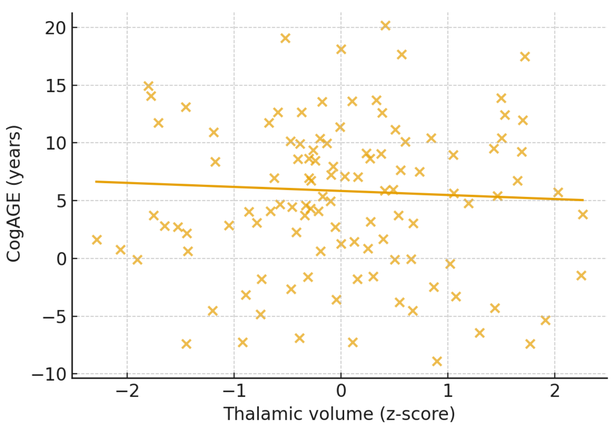




β = –0.32, SE = 0.09, p < 0.001



β = –0.17, SE = 0.07, p = 0.03



β = –0.35,SE = 0.10, p < 0.001

MS patients mean CogAGE: 5.84 ± 7.04 years

Higher premorbid IQ and education protect against cognitive aging

Higher thalamic volume associated with lower CogAge

No effect observed for brain reserve

CONCLUSIONS

Cognitive reserve might buffer against "cognitive age" in MS patients
Patients with higher cognitive reserve show lower CogAGE, consistent with the idea that enriched neural networks and flexible recruitment of alternative circuits help sustain performance against neurodegeneration.

Thalamic atrophy emerged as a structural hallmark of accelerated cognitive ageing in MS.
Protecting deep grey-matter hubs (e.g., via early disease control and neuroprotective strategies) and strengthening reserve may be complementary routes to slow cognitive ageing in MS.

THANK YOU FOR YOUR ATTENTION!

REFERENCES

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