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SUSTAINED COGNITIVE DECLINE IN MULTIPLE SCLEROSIS: INVESTIGATING THE ROLE OF WHITE MATTER LESION LOAD USING AN AI-DRIVEN BRAIN IMAGING APPROACH

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SUMMARY

Background: *Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, where cognitive impairment can occur even without physical disability. The underlying mechanisms remain poorly understood. This study investigates the role of white matter lesion load (WMLL) in sustained cognitive decline (SCD) in a real-life MS cohort, using an artificial intelligence(AI)-based brain imaging approach.*

Methods: *Patients from the CHU Helora MS database with ≥3 SDMT assessments and serial brain MRIs were included. SCD was defined as a ≥4-point or ≥10% SDMT drop, confirmed ≥6 months later. Patients were stratified into two groups: those with SCD (COG) and those without (N-COG). WMLL was measured using a AI-based model that provides segmentation masks. Lesion volume was calculated by multiplying segmented voxels by voxel size.*

Results: *Of 109 eligible patients, 43 met inclusion criteria. Seven showed SCD; 36 did not. Imaging data were available for 5 COG and 21 N-COG patients. There was no significant difference in WMLL or its progression between patients with and without SCD. Fewer than half of the patients in the COG group showed an increase in WMLL over time, and those who did were older than the group average. WMLL changes were not a reliable marker of SCD. Consistent with previous findings, the COG group included more males, and disease control appeared more challenging. Vascular pathology may be misclassified by segmentation algorithms, which partially explain why the two patients with WMLL progression were older. Gray matter was not assessed, though it may play a key role in this phenomenon.*

Conclusion: *SCD did not consistently correlate with WMLL progression. Affected patients were predominantly male, consistent with a more aggressive disease course. WMLL may also be influenced by age-related factors. Alternative imaging biomarkers are needed to explain SCD in MS.*

Key words: *multiple sclerosis - white matter lesion load - cognitive impairment - artificial intelligence – neuroimaging*

Abbreviations: *AI: Artificial intelligence; ANTs: Advanced Normalization Tools; BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; CNS: Central Nervous System; COG: Patients exhibiting sustained cognitive decline; DICOM: Digital Imaging and Communication in Medicine; EDSS: Expanded Disability Status Scale; FLAIR: Fluid-Attenuated Inversion Recovery; FLAMeS: FLAIR Lesion Analysis in Multiple Sclerosis; MRI: Magnetic Resonance Imaging; MS: Multiple sclerosis; N-COG: Patients without evidence of sustained cognitive decline; NiFTI: Neuroimaging Informatics Technology Initiative; OCB: Oligoclonal Bands; PMS: Progressive Multiple Sclerosis; pwMS: patients with Multiple Sclerosis; RMS: Relapsing Multiple sclerosis; SCD: Sustained Cognitive Decline; SDMT: Symbol Digit Modalities Test; T: Tesla; WMLL: White Matter Lesion Load*

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS), characterized by a complex interplay of inflammatory demyelination and neuronal damage. The core MS phenotypes defined by clinical course (Lublin et al. 2014) are the relapsing and the progressive forms. Relapsing MS (RMS) is characterized by relapses defined as new or increasing neurologic dysfunction, followed by periods of partial or complete recovery, without apparent progression of the disease during the periods of remission. On imaging, RMS is typically associated with new or enlarging T2 lesions and gadolinium-enhancing lesions on magnetic resonance imaging (MRI), reflecting active inflammation. In contrast, progressive MS (PMS) is characterized by progressive worsening of neurologic function leading to accumulation of

disability over time independent of relapses (Lorscheider et al. 2016). Imaging in PMS typically shows no new lesion formation, but is characterized by greater brain and spinal cord atrophy, along with the presence of slowly expanding lesions, reflecting chronic and ongoing neurodegeneration. Epidemiological data from both community-based and clinical cohorts suggest that cognitive impairment affects up to 65% of patients with MS (pwMS) (R. H. B. Benedict et al. 2020). These symptoms adversely affect work productivity (Kobelt et al. 2017) and exert a significant impact on the quality of life (Bergmann et al. 2023). Cognitive decline can also be observed in individuals with radiologically isolated syndrome - a condition defined by incidental brain MRI findings suggestive of MS - even in the absence of overt neurological deficits (Amato et al. 2012). As with other symptoms of MS, cognitive impairment exhibits substantial interindividual variability and may be influenced by comorbid mood disorders (Margoni et al. 2023) and medication side effects (Zheng et al. 2021; Atiyeh et al. 2025). While comprehensive neuropsychological assessment remains the gold standard for cognitive profiling, brief screening tools such as the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) are increasingly used in clinical practice to monitor cognitive decline in pwMS (R. H. Benedict et al. 2012). Among the most commonly reported cognitive symptoms, impaired information processing speed stands out as the most sensitive indicator of of MS-related cognitive impairment (R. H. B. Benedict et al. 2017). The Symbol Digit Modalities Test (SDMT), a key component of the BICAMS battery, has proven particularly effective in detecting deficits in this domain and it is well-suited for use in longitudinal assessments (R. H. Benedict et al. 2017; R. Benedict et al. 2008). The performance of this test is consistently associated with global cognitive decline and disease relapses across multiple cohorts outperforming other BICAMS components such as the California Verbal Learning Test–Second Edition (CVLT-II) and the Brief Visuospatial Memory Test–Revised (BVMT-R) (Amato et al. 2010; Costers et al. 2017; Filser et al. 2018; Hämäläinen et al. 2021; Walker et al. 2016; Farghaly et al. 2021). Although several hypotheses exist, the mechanisms underlying cognitive decline in pwMS are still not fully understood. Artificial intelligence (AI) holds significant potential to advance the understanding of this phenomenon. For example, manual segmentation of MS lesions is time-consuming and subject to interrater variability, particularly in patients with a high lesion burden. In contrast, automated approaches provide a more efficient and reproducible alternative, enhancing the reliability of MS imaging studies. Through the analysis of large-scale clinical and neuroimaging datasets, AI can uncover latent patterns and identify predictive biomarkers associated with cognitive decline and disease progression (Nabizadeh et al. 2023; Amin et al. 2024).

SUBJECTS AND METHODS

This retrospective study included a cohort of pwMS from the MS Database of the University Hospital HELORA Site Kennedy in Mons (Belgium).

Inclusion Criteria:

- Age ≥18 years;
- Diagnosis of MS based on the 2017 McDonald criteria;
- Availability of at least three oral SDMT scores recorded in the MS Database;
- Availability of follow-up brain MRI data during the observational period.

Exclusion Criteria:

- Relapse during observational period.

Baseline Functional Assessment:

- Expanded Disability Status Scale (EDSS): ranging from 1 to 10;
- Symbol Digit Modalities Test (SDMT): oral version, scored from 0 to 110.

Definition of Sustained Cognitive Decline (SCD):

- A decrease of ≥4 points or ≥10% on the SDMT compared to baseline (Bsteh et al. 2019);
- Confirmation of deterioration at a subsequent evaluation conducted at least six months later.

Patient Stratification

Eligible patients were stratified into two groups:

- COG group: patients exhibiting SCD confirmed at follow-up assessment;
- N-COG group: patients without confirmed cognitive decline at follow-up, including those with stable or fluctuating cognitive performance over time.

Imaging Analysis

Brain MRI scans acquired during the observational period were used for this analysis, including those performed up to one year before the initial SDMT assessment and up to one year after the final SDMT evaluation. The automated pipeline used to quantify white matter lesion load (WMLL) first converts raw, pseudonymized DICOM (Digital Imaging and Communications in Medicine) format into the 3D NIfTI (Neuroimaging Informatics Technology Initiative) format without loss of information. Each image is then pre-processed using the Advanced Normalization Tools (ANTs) suite for spatial normalization to the MNI-152 standard space and for intensity non-uniformity correction (N4 bias correction), which locally adjusts image intensity to mitigate inhomogeneities caused by magnetic field variations or receiver coil sensitivity. Brain extraction (skull stripping) was conducted using SynthStrip, a deep learning-based tool optimized for isolating brain tissue across diverse MRI modalities. White matter lesion

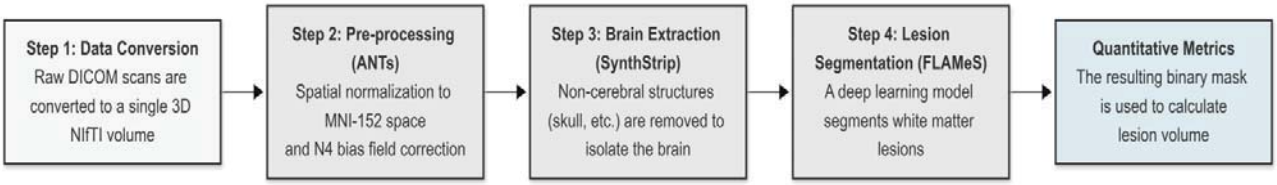
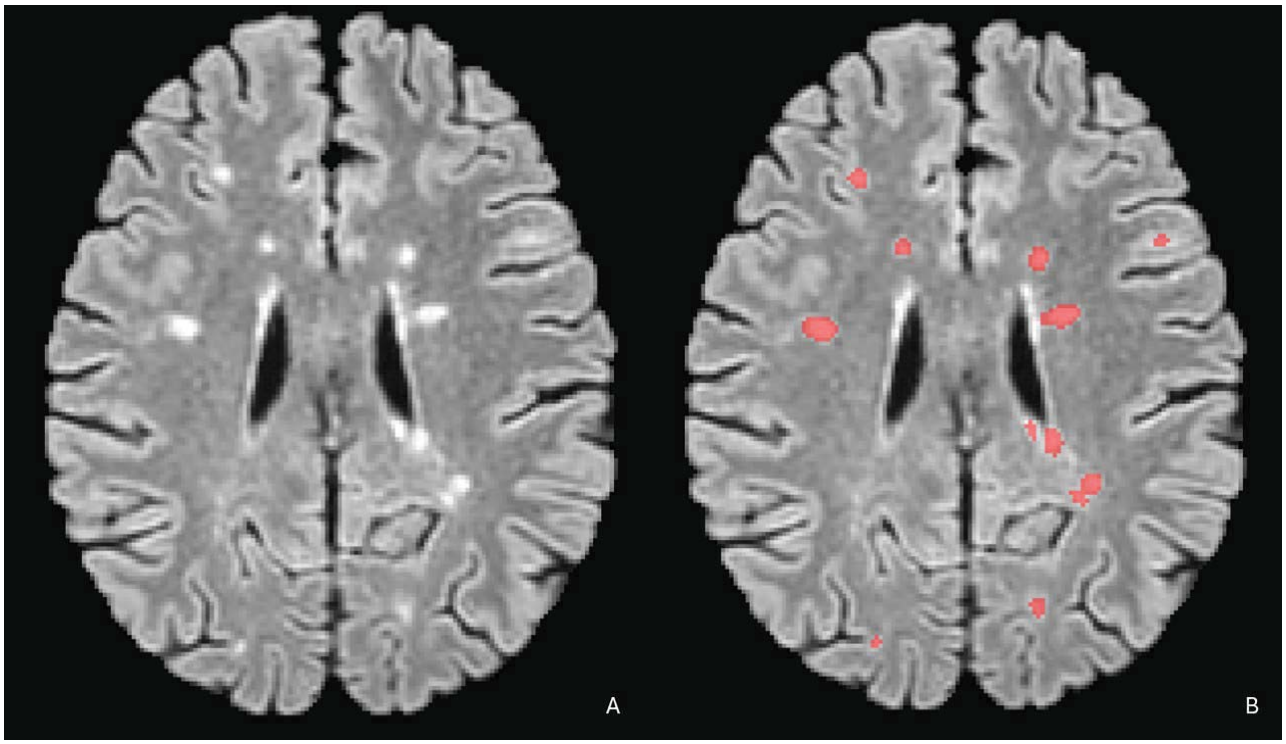


Figure 1. Flowchart of the automated pipeline used for white matter lesion segmentation



(A) Unsegmented brain image; (B) automated segmentation and labeling performed by the algorithm

Figure 2. Example of segmentation performed by FLAMeS

segmentation was performed using the FLAIR Lesion Analysis in Multiple Sclerosis (FLAMeS) tool (Dereskewicz et al. 2025; Isensee et al. 2021), which is based on the No New U-Net (nnU-Net) architecture. This deep learning model is specifically trained on MS brain imaging data to automatically segment white matter lesions and generate binary masks used for quantitative analysis. WMLL was computed by multiplying the number of voxels within the lesion mask by the volume of a single voxel, derived from the spatial resolution of the image. Lesion burden was subsequently expressed as a percentage of the total brain volume (Figure 1, 2).

Statistical Analysis

Clinical and paraclinical data from the database were analyzed using inferential statistical methods. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Based on the distribution, between-group comparisons were performed using either two-sided t-tests for normally distributed data or Mann–Whitney U tests for non-normally distributed data. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Correlations between variables were evaluated using Pearson's correlation coefficient or Spearman's rank correlation test. P-values < 0.05 were considered statistically significant.

RESULTS

Of the 109 eligible patients, 43 met the inclusion criteria and were included in the study. Among these, 7 patients exhibited SCD over the study period, while the remaining 36 showed either stable or fluctuating cognitive performance. The results are summarized in Table 1.

Baseline Characteristics

The mean age was 54.0 years (±16.2) in the COG group and 47.5 years (±11.4) in the N-COG group, with no statistically significant difference between groups ($p = 0.34$).

Sex distribution differed significantly: women accounted for 42.9% of the COG group and 86.1% of the N-COG group ($p = 0.02$). The median EDSS score was 2.25 in the COG group and 2.00 in the N-COG group.

Table 1. Baseline characteristics of patients with and without cognitive decline (COG vs. N-COG)

	COG (N=7)	N-COG (N=36)	P-value
Age (years) means ± SD	54 ± 16.19	47.53 ± 11.36	0.34[1]
Sexe, women (%)	3 (42.86%)	31 (86.11%)	*0.02*[*2]
Tabaco, n (%)	4/7 (57.14%)	10/32 (31.25%)	0.23[2]
Years between first symptom and diagnosis, median (n)	0.75 (7)	0.13 (35)	0.46[3]
First Symptoms, n (%)			0.13[4]
Hemi-hypoesthesia	0/6 (0.0%)	6/28 (21.4%)	
Hemiparesis	3/6 (50%)	3/28 (10.7%)	
Optic neuritis	1/6 (16.67%)	10/28 (35.7%)	
Vestibular symptom	0/6 (0.0%)	3/28 (10.7%)	
Other	2/6 (33.33%)	6/28 (21.4%)	
First Treatment, n (%)			0.28[4]
Interferon	4/7 (57.14%)	11/35 (31.4%)	
Natalizumab	0/7 (0.0%)	5/35 (14.29%)	
Glatiramer acetate	2/7 (28.57%)	3/35 (8.57%)	
Teriflunomide	0/7 (0.0%)	9/35 (25.71%)	
Dimethyl fumarate	0/7 (0.0%)	4/35 (11.43%)	
Ocrelizumab	1/7 (14.29%)	2/35 (5.71%)	
Cladribine	0/7 (0.0%)	1/35 (2.86%)	
Current/Last treatment, n (%)			0.16[4]
Interferon	0/7 (0.0%)	0/36 (0.0%)	
Natalizumab	2/7 (28.57%)	22/36 (61.11%)	
Rituximab	1/7 (14.29%)	0/36 (0.0%)	
Teriflunomide	1/7 (14.29%)	1/36 (2.78%)	
Dimethyl fumarate	0/7 (0.0%)	3/36 (8.33%)	
Ocrelizumab	2/7 (28.57%)	5/36 (13.89%)	
Cladribine	0/7 (0.0%)	1/36 (2.78%)	
Ofatumumab	0/7 (0.0%)	2/36 (5.56%)	
Siponimod	0/7 (0.0%)	1/36 (2.78%)	
Fingolimod	1/7 (14.29%)	1/36 (2.78%)	
Number of prior treatments, median (n)	3 (7)	1 (35)	0.26[3]
Presence of spinal cord lesions, yes (%)	5/5 (100%)	16/22 (72.73%)	0.56[2]
Presence of OCB, yes (%)	3/4 (75%)	13/15 (86.67%)	0.53[2]
Number of relapses, n (%)			0.17[4]
0–1	0/6 (0.0%)	10/29 (34.48%)	
2–4	5/6 (83.33%)	13/29 (44.83%)	
≥5	1/6 (16.67%)	6/29 (20.69%)	
Number of relapses under last treatment, n (%)			0.08[2]
0	3/6 (50.0%)	30/35 (85.71%)	
1	3/6 (50.0%)	5/35 (14.28%)	
SDMT, means ± standard deviation	45.29 ± 15.91	48.72 ± 16.68	0.62[1]
EDSS, median (n)	2.25 (6)	2 (25)	0.38[3]

Note: SD: Standard Deviation; OCB: Oligoclonal Bands; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale; [1] Student's t-test; [2]Fisher's exact test; [3]Mann-Whitney U test; [4]Chi-squared test of independence

The mean SDMT score was 45.3±15.91 in the COG group and 48.7±16.7 in the N-COG group. Neither SDMT nor EDSS scores differed significantly between groups (p = 0.62; p = 0.38). Smoking was more prevalent in the COG group (57.1%) compared to the N-COG group (31.3%), although the difference did not reach statistical significance (p = 0.23). The median interval from first symptom to diagnosis was longer in patients with SCD (9 months) than in those without (1.5 months), but this difference was not statistically significant (p = 0.46). While the initial clinical presentation varied between groups, it also did not differ significantly (p = 0.13). The overall distribution of first-line therapies did not differ significantly between groups (p = 0.28). When evaluating the most recent treatment regimen, similar trends were observed, with the same therapies predominating in both groups. The COG group had more prior treatments (median = 3 vs. 1), though not statistically significant (p = 0.26). The total number of relapses did not differ significantly between groups (p = 0.17). However, under disease modifying treatment, 50% of patients in the COG group experienced at least one relapse, compared to 14.3% in the N-COG group. Although not statistically significant, this difference approached significance (p = 0.08).

Table 2. Change in white matter lesion load (WMLL) between first and last follow-up of patients with and without cognitive decline (COG vs. N-COG)

	COG (N=5)	N-COG (N=21)	P-value
WMLL T0, median % [IQR1–IQR3]	1.2 [0.7-1.8]	0.3 [0.2-0.4]	0.20[1]
WMLL Tf, median % [IQR1–IQR3]	2.4 [0.7-2.4]	0.3 [0.2-0.5]	0.21[1]
ΔWMLL, median % [IQR1–IQR3]	0 [0.0-0.6]	0 [0.0-0.1]	0.49[1]

Note: WMLL: White Matter Lesion Load; IQR: Interquartile Range; T0: WMLL at baseline; Tf: WMLL at last follow-up; ΔWMLL: Change in WMLL between baseline and last follow-up; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale; [1]Mann-Whitney U test

Table 3. Brain White Matter Lesion Load (WMLL) from first to last follow-up in the sustained cognitive decline group (COG)

	Time point	Lb	VpW
Patient 1	T0	0.7	0
Male, 36 years	T1	0.7	
Patient 2	T0	1.8	+33%
Woman, 73 years	T1	1.9	
	T2	2.0	
	T3	2.4	
Patient 3	T0	0.1	0
Male, 49 years	T1	0.1	
	T2	0.1	
	T3	0.1	
Patient 4	T0	4.6	-7%
Male, 47 years	T1	4.6	
	T2	4.4	
	T3	4.2	
	T4	4.3	
Patient 5	T0	1.2	+100%
Male, 68 years	T1	1.4	
	T2	1.6	
	T3	2.0	
	T4	2.4	

Note: VpW: Variation in percentage of WMLL from first to last timepoint; Lb: Lesion burden (% of total brain volume)

Imaging

Brain imaging suitable for AI-based processing during the observational period was available for 5 of 7 patients in the cognitive decline group (COG) and 21 of 36 in the non-cognitive decline group (N-COG). Exclusions were mainly due to the unavailability of DICOM files from the acquired imaging, with an additional two cases in the N-COG group excluded due to poor image quality. Participants without usable imaging data were excluded from imaging-related statistical analyses. The results are summarized in Table 2. No statistically significant differences were observed in WMLL between patients with SCD and those without at any timepoint. At baseline (T0), the COG group had a higher median WMLL percentage compared to the N-COG group (1.2% vs. 0.3%), but this difference did not reach significance (p = 0.201). Similarly, at the last follow-up (Tf), the median WMLL remained higher in the COG group (2.4% vs. 0.3%, p = 0.211). The median change in WMLL (ΔWMLL) over time was minimal in both groups and not significantly different (p = 0.491). Individual patient results from the COG group are summarized in Table 3. In the group of patients with SCD, white matter lesion load (WMLL) trajectories varied across individuals. Two patients (Patients 2 and 5) showed a marked increase in WMLL over time, with relative increases of +33% and +100%, respectively. Two patients (Patients 1 and 3) exhibited no change in lesion burden across follow-ups, while one patient (Patient 4) showed a slight reduction in WMLL (−7%).

DISCUSSION

Despite the limited sample size, this study serves as a pilot investigation highlighting the potential role of WMLL in SCD, as well as the utility of AI-based analysis for assessing white matter lesions in a real-world cohort of pwMS. Although baseline SDMT and EDSS scores were similar between groups, patients who experienced SCD were predominantly male and slightly older. This observation is consistent with previous research indicating sex-related differences in MS progression. Despite the higher overall prevalence of MS in women, men are more likely to reach disability milestones earlier, show a greater lesion burden on MRI, and exhibit more severe cognitive impairment (R. H. B. Benedict & Zivadinov, 2011; Schoonheim et al. 2012; Rotstein & Montalban, 2019). A trend toward a longer interval between symptom onset and diagnosis was observed in patients who later developed SCD, although it did not reach statistical significance. This may suggest that delayed intervention could contribute to the emergence of cognitive symptoms. Disease control also appeared more challenging in the COG group, as evidenced by a higher median number of prior treatments and a greater frequency of relapses during ongoing therapy. These findings may reflect a more aggressive disease phenotype. In the COG group, longitudinal imaging revealed that WMLL remained stable over time in two of the five cases. Interestingly, one patient even demonstrated a reduction in lesion load - a phenomenon well known to MS specialists but not considered to have prognostic value (Pongratz et al. 2019). This decrease likely reflects the natural waning of acute inflammation rather than true

structural recovery. The two patients who showed a more pronounced increase were among the oldest in the group, suggesting that age-related factors - such as vascular pathology (e.g., leukoaraiosis) - may have contributed to this progression. Vascular comorbidities - more common in older individuals and independently associated with both lesion accumulation and cognitive decline - may have influenced the cognitive outcomes observed in this study. Since the segmentation algorithm cannot reliably differentiate between white matter lesions caused by MS and those related to vascular pathology, some of the detected lesion burden may reflect age-related cerebrovascular changes rather than MS-specific activity. Additionally, the higher prevalence of smokers in the COG group, although not statistically significant, warrants consideration. Prior research has linked smoking before MS onset with an increased risk of disease development (Hedström et al. 2011; Oturai et al. 2021) and progression (Tanasescu et al. 2018). Although white matter lesions can disrupt key tracts connecting cortical and subcortical regions - thereby impairing functional connectivity essential for cognitive processing (Guimarães & Sá 2012) – cognitive decline in MS is likely influenced by additional factors beyond lesion load (Wybrecht et al. 2017). Current literature increasingly points toward the role of cortical lesions, rather than purely white matter involvement, in the development of cognitive impairment in MS. Advanced imaging techniques have demonstrated that cortical demyelination, grey matter atrophy, and whole-brain atrophy are more strongly associated with cognitive decline than conventional measures of white matter lesion volume (Granberg et al. 2017; Calabrese et al. 2012; Harrison et al. 2015; Azevedo et al. 2018). Just as motor and sensory symptoms can progress in the absence of new lesions, cognitive decline may reflect underlying neurodegenerative processes that are not detectable with standard lesion-focused imaging techniques. Disability progression independent of relapse activity in MS remains incompletely understood, with chronic active lesions among the few white matter imaging biomarkers currently recognized (Absinta et al. 2020; Husseini et al. 2024). These lesions may expand very slowly, often requiring years to show a measurable increase in volume, and may therefore go undetected by conventional WMLL quantification techniques, especially when imaging is performed over a relatively short time lapse. This highlights the need for more sensitive imaging techniques, advanced biomarkers, and the potential integration of specialized tools. AI-driven algorithms enable rapid, reproducible, and precise detection of white matter alterations that often escape conventional visual assessment. By automating complex tasks, these tools greatly reduce the burden of manual processing while improving sensitivity to early or specific pathological changes. Lesion segmentation is one of the most common and clinically relevant tasks in the interpretation of brain MRI scans in pwMS. Deep learning models, particularly those utilizing convolutional neural networks, have emerged as the leading approach for lesion segmentation, consistently surpassing tradetional machine learning methods in accuracy (La Rosa et al. 2020; Wiltgen et al. 2024). These models typically require both T2-weighted FLAIR and T1-weighted MRI sequences as input (Brugnara et al. 2020); however, the latter is not consistently acquired in routine clinical practice (Wattjes et al. 2021), thus limiting the real-world applicability of such approaches. FLAMeS, the algorithm employed in this study, is a deep learning-based segmentation tool trained on a heterogeneous dataset. Notably, it relies solely on the FLAIR sequence for lesion segmentation and was developed using acquisitions from both 1.5 T and 3T MRI scanners, enhancing its suitability for real-world clinical applications. Although not yet fully optimized for longitudinal analysis, FLAMeS provides robust and consistent automated lesion segmentation, representing a significant improvement over traditional subjective qualitative assessments.

Study Limitations and Future perspectives

The small sample size limits statistical power and generalizability, while the retrospective design precludes causal inference. Cognitive decline was assessed using a single tool, which may not fully capture its complexity in MS. Additionally, the MRI segmentation did not specifically focus on brain regions typically implicated in cognitive dysfunction, including gray matter structures and critical white matter tracts, potentially overlooking important anatomical correlates. Future studies with larger cohorts are needed to refine biomarkers of SCD, incorporating detailed lesion characterization, regional localization (e.g., intracortical and specific white matter tract involvement), and measures of both focal and global brain atrophy.

CONCLUSION

Despite the limited sample size, this study identified few factors potentially associated with cognitive decline in MS. Male sex was associated with SCD, supporting previous evidence of potential sex-related differences in the neurodegenerative processes underlying MS progression. While WMLL alone may be insufficient as a standalone biomarker for cognitive dysfunction, AI-driven neuroimaging tools offers promising opportunities to quantify pathological changes and deepen our understanding of the mechanisms underlying clinical symptoms in MS.

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Contribution of individual authors:

Vito Tota: design of the study, literature searches and analyses, statistical analyses, interpretation of data, manuscript writing.

Astrid Mehuys: collecting data, analysis of the data, literature searches and analyses, statistical analyses, manuscript writing.

Tanguy Vansnick: collecting data, analysis of the data, review of the manuscript.

Otmane Amel, Fatma Chahbar & Lamia Mahmoudi: collecting data, analysis of the data.

Sidi Ahmed Mahmoudi, Giovanni Briganti & Laurence Ris: securing funding for the research, review of the manuscript.

Said Mahmoudi: literature searches and analyses, providing critical feedback on the research or manuscript, ensuring the accuracy and integrity of the research.

All authors approved the final manuscript.

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