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Unmasking the invisible: Correlates and impact of cognitive complaints in MS

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ABSTRACT

Background: Patient-reported outcome measures (PROMs) are increasingly used in multiple sclerosis (MS) to capture subjective aspects of disease burden. However, the relationship between perceived cognitive deficits, objective cognitive impairment, psychological symptoms, and functional outcomes remains unclear.
Methods: We conducted a cross-sectional study on 263 people with MS. Objective cognition was assessed using the Brief International Cognitive Assessment for MS (BICAMS). Subjective cognitive complaints were derived from selected items of the Modified Fatigue Impact Scale, while independence was evaluated using items from the Multiple Sclerosis Impact Scale-29. Mood was assessed with the Hospital Anxiety and Depression Scale. Multivariable regression models were applied.
Results: Objective cognitive impairment was detected in 15.2% of patients, whereas 76.8% reported subjective cognitive difficulties. Subjective complaints were not independently associated with objective cognitive performance. Depressive symptoms emerged as the only significant predictor of perceived slowed thinking and concentration difficulties. Physical disability (EDSS) was the sole independent predictor of both dependence on others and limited independence. These findings were consistent across disability subgroups.
Conclusions: Subjective cognitive complaints in MS appear to be more closely related to psychological factors than to objective cognitive impairment, while functional autonomy is primarily driven by physical disability. These results highlight the importance of integrating psychological assessment into routine clinical evaluation to better address patients' perceived cognitive difficulties and overall quality of life.

1. Introduction

Patient-reported outcomes (PROs) are generally defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (FDA, 2009) [1]. They play an increasing role in MS research and clinical practice. These measures are essential for capturing outcomes that are not externally observable, infrequent, or otherwise inaccessible. They often represent the only viable strategy for evaluating treatment effects in conditions such as pain syndromes, fatigue, cognitive symptoms, and other physiological states that are difficult to assess objectively, yet can significantly impact quality of life (QoL)—sometimes as much as physical disability—and may also compromise patients' ability to work [2].

While PROMs are often reported as strongly correlated with physical disability and QoL [3–6], the interplay between psychological outcomes and cognition remains to be fully explored. Indeed, recent studies have reported a significant discrepancy between subjective and objective cognitive performance, with patients showing both overestimation and underestimation of their cognitive deficits, no differences in cognitive fatigue, executive functioning, QoL, and work-related difficulties between cognitively preserved and impaired patients [6–9] and no impact of objective cognitive scores on physical and psychological status as measured by the Multiple Sclerosis Impact Scale-29 (MSIS-29) [10].

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While the discrepancy between subjective complaints and objective neuropsychological performance could be influenced by a complex interplay with disease duration, physical disability, fatigue, and mood state[2,6,8,11,12], methodological reasons might also contribute. Reliance on aggregate PROM scores may reduce sensitivity to domain-specific variability in patients' perceived difficulties. While PROMs such as the MFIS and MSIS-29 are typically analysed at the subscale level, individual items within these instruments often directly reflect clinically meaningful aspects of patients' experience. In this context, focusing on selected items may allow a more fine-grained and clinically interpretable characterization of specific symptom domains, particularly when aiming to align subjective reports with objectively assessed cognitive functions. Accordingly, we adopted an item-level, hypothesis-driven approach to capture domain-specific aspects of perceived cognitive difficulties using items that directly map onto attention and memory domains, as well as to derive clinically meaningful indicators of functional independence.

In this study, we derived information on perceived cognitive deficits and daily independence from well-established PROMs to evaluate (i) the associations between objective cognitive dysfunction and perceived cognitive deficits across domains commonly affected in MS, such as information processing speed, attention/concentration, and memory, while accounting for clinic-demographic confounders; and (ii) the influence of perceived and objective cognitive deficits, disability, and psychological factors on daily functioning.

2. Methods

2.1. Subjects

Data from 263 consecutive patients with MS were prospectively collected. Inclusion criteria for MS patients were: (I) age 18–65 years; (II) MS diagnosis according to 2017 McDonald's criteria [13]. Exclusion criteria were: (I) neurological disorders other than MS that might influence cognitive functioning (e.g., dementia or brain injury); (II) concomitant psychiatric or personality disorders diagnosis that could influence cognitive performance (e.g. dissociative disorders, schizophrenia, or psychotic symptoms).

2.1.1. Patient consent statement

The study was approved by the local Ethics Committee (approval no. 74/2020; DB ID 10346; approved on 27 April 2020). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants for participation and for the use of their clinical data for research and publication purposes.

2.2. Measures

Demographic and disease-related variables included age, sex, years of education, disease duration, MS phenotype (relapsing-remitting MS [RRMS], primary progressive MS [PPMS], and secondary progressive MS [SPMS]), treatment category (no treatment, autologous hematopoietic stem cell transplantation [aHSCT], low- to moderate-efficacy treatments, including teriflunomide, dimethyl fumarate, and glatiramer acetate, and high-efficacy treatments [HET], including cladribine, fingolimod, ofatumumab, natalizumab, ponesimod, siponimod, ocrelizumab, and alemtuzumab), and neurological disability, assessed using the Expanded Disability Status Scale (EDSS).

A trained neuropsychologist assessed patients using the Italian version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) [14]. Patients also completed questionnaires evaluating mood, fatigue, and quality of life. The BICAMS battery was administered to assess the presence of objective cognitive impairment, while the presence of perceived cognitive deficit was determined according to the patients' responses to specific items of the Modified Fatigue Impact Scale (MFIS) [15]. Information on daily independence was derived from the Multiple Sclerosis Impact Scale-29 (MSIS-29) [10]. Finally, mood disturbances were assessed using the Hospital Anxiety and Depression Scale (HADS).

2.2.1. Objective cognitive impairment

2.2.1.1. Symbol digit modalities test (SDMT). The SDMT presents a series of nine symbols, each paired with a number in a legend at the top of a standard sheet of paper. Subjects are asked to verbally respond with the paired digits as quickly as possible when presented with a pseudo-random sequence of symbols. The outcome measure of the SDMT is the number of correct responses in 90 s. The impairment on each BICAMS subtest was defined based on Italian normative data [14] (T-score $\leq$ 35).

2.2.2. The California verbal learning test 2nd ed. (CVLT-II)

In the CVLT-II, the examiner reads a list of 16 words. Subjects must recall the word list in the order they wish. This is repeated 5 times. The measured outcome is the total number of words recalled over the five trials.

2.2.3. The brief visuospatial memory test (BVMT-R)

The BVMT-R measures the visuospatial learning and memory. Subjects are given 10s to memorize six abstract figures in a 2 $\times$ 3 grid; after this time, they are asked to remember and reproduce the stimuli on a sheet of paper. This is repeated 3 times. Each drawing is assigned a score of 0,1 or 2 based on criteria of accuracy and positioning of the six figures. The measured outcome is total recall score across the three trials.

2.2.4. Perceived cognitive deficit

2.2.4.1. Modified fatigue impact scale (MFIS). The MFIS is a sensitive instrument for assessing and discriminating the effects of fatigue in people with MS, evaluating its impact on physical, cognitive, and psychosocial functioning. We selected four items assessing difficulty maintaining attention for extended periods, forgetfulness, slowed thinking, and trouble concentrating. These items were chosen because they reflect deficits in attention, concentration, memory, and processing speed, which are domains frequently involved in MS and objectively assessed by the BICAMS. Each domain was considered impaired when patients reported experiencing the symptom at least “sometimes”.

2.2.5. Independence

2.2.5.1. The multiple sclerosis impact scale (MSIS-29). The MSIS-29 measures the physical (20 items) and psychological (9 items) impact of MS. The MSIS-29 asks how much each item has bothered the patient in the previous two weeks. Among all available items, we selected seven items from the physical subscale, related to the dependence on caregiver and limitation in daily activities, to derive information useful for the assessment of “independence” domains. Specifically, we selected the following items: difficulties moving indoors, dependence on others for daily activities, limitations in social and leisure activities at home, reduced time spent on work or other daily activities, problems using transportation, difficulty acting spontaneously, and urgency in going to the toilet. A symptom was considered present when patients reported experiencing it at least “quite a bit.” Independence was operationalized using two criteria: (1) *dependence on others*, defined as reporting at least “quite a bit” on the item assessing dependence on others for daily activities; and (2) *limited independence*, defined as reporting at least “quite a bit” on at least two of the remaining items.

2.2.6. Mood

2.2.6.1. The hospital anxiety and depression scale (HADS). HADS is a self-administered questionnaire consisting of 14 multiple-choice (0–3 Likert scale) items probing symptoms of anxiety (7 items) and depression (7 items). HADS anxiety (HADS-A) and depression (HADS-D) scores range from 0 (no symptoms) to 21 (most severe symptoms). The presence of depression or anxiety was defined as a cut-off ≥11 which indicates the probable presence of a mood disorder [16,17].

2.3. Statistical analysis

Statistical analyses were performed using Jamovi (version 2.6.44). Descriptive statistics were used to characterize the study sample. Pearson correlation analyses were performed to explore associations among demographic (age, sex, education) and clinical variables (EDSS, disease duration), objective cognitive performance (BICAMS subtests), and subjective cognitive complaints. Variables showing significant associations in this preliminary analysis were subsequently included in multivariable models.

Binary logistic regression models were fitted to examine the association between subjective cognitive domains and objective cognitive performance, adjusting for demographic and clinical covariates identified in the preliminary analysis. In these models, subjective cognitive complaints (slowed thinking and concentration difficulties) were treated as dependent variables, while objective cognitive measures (SDMT, BVMT-R) and mood variables (HADS-A, HADS-D) were considered as predictors, while accounting for demographic and clinical variables showing association with the outcome of interest in the preliminary analyses.

Similarly, binary logistic regression models were used to assess the relationship between subjective cognitive complaints and independence outcomes (dependence on others and limited independence), which were treated as dependent variables. In these models, predictors included objective cognitive measures (SDMT, CVLT-II, BVMT-R), subjective cognitive complaints, while demographic and clinical variables showing association with the outcome of interest in the preliminary analyses were entered as variables of no interest. Anxiety and depression were not entered into the independence models, as they were conceptualized as upstream determinants.

Post-hoc analyses were conducted to examine in detail the role of mood disorders (by excluding patients affected by clinical depression and anxiety) and physical disability (by running analyses on subgroups of patients with EDSS <3.5 and < 5.5.). To explore the impact of significant predictors emerging from the logistic analysis across the spectrum of the severity of subjective outcomes, multinomial logistic regression models were tested.

Finally, sensitivity analyses were conducted to evaluate the robustness of the findings to alternative operationalizations of the dependent variables. Specifically, the primary regression model examining subjective cognitive complaints was repeated using the MFIS cognitive subscale score as the dependent variable instead of the selected MFIS item. Similarly, the regression model examining perceived dependence on others was repeated using the MSIS-29 physical subscale score as the dependent variable instead of the selected item assessing dependence on others.

All tests were two-tailed, and statistical significance was set at $p < 0.05$. To control for type I error, Bonferroni corrections were applied, accounting for both the number of models tested and the number of predictors within each model, with analysis-specific significance thresholds defined accordingly.

3. Results

3.1. Sample characteristics

The demographic and clinical characteristics of the study sample are summarized in Table 1. Based on the HADS cut-off score (≥11), 31.17% of patients were classified as having clinically relevant anxiety and 15.97% as having clinically relevant depression. Cognitive impairment in at least one BICAMS subtest was observed in 15.2% of patients, whereas a substantially larger proportion (76.80%) reported subjective cognitive difficulties in at least one domain. Fatigue (MFIS ≥38) was reported by 41.06% of the sample.

3.1.1. Attention domain

3.1.1.1. Objective processing speed (SDMT) and self-reported slowed thinking. Thirty patients exhibited impaired performance on the SDMT. Among these, all reported experiencing slowed thinking, either "rarely" or "sometimes" ($n = 23$) or "often" or "almost always" ($n = 7$). However, 28 patients (10.64%) reported experiencing slowed thinking "often" or "almost always" over the previous four weeks despite preserved objective processing speed (SDMT).

3.2. Bivariate associations with subjective attention complaints

In bivariate correlation analyses, self-reported sustained attention difficulties were not associated with objective cognitive performance (SDMT, CVLT-II or BVMT-R), but showed significant positive correlations with anxiety ($r = 0.351$, $p < 0.001$) and depression ($r = 0.500$, p <

Table 1
Demographic and clinical data.

N.	263
Female, n(%)	180 (68.40%)
Age, mean (SD)	44.38 (±11.82)
Education, mean (SD)	14.22 (±3.36)
EDSS, median (range)	2.00 (0–6.5)
Phenotype	
RRMS, n(%)	211 (80.20%)
PPMS, n(%)	25 (9.50%)
SPMS, n(%)	27 (10.30%)
Disease duration, mean (SD)	11.82 (±9.92)
Treatment	
No treatment, n(%)	27 (10.26%)
aHSCT	16 (6.0%)
LMET, n(%)	20 (7.60%)
HET, n(%)	200 (75.80%)
SDMT, mean (SD)	50.89 (±13.14)
Impaired at SDMT, n(%)	30 (11.40%)
CVLT-II, mean (SD)	62.19 (±11.44)
Impaired at CVLT-II, n(%)	14 (5.30%)
BVMT-R, mean (SD)	29.55 (±6.46)
Impaired at BVMT-R, n(%)	10 (3.8%)
Impaired in ≥1 domain, n(%)	40 (15.20%)
HADS-A, mean (SD)	7.28 (±4.29)
n. of anxious (%)	82 (31.17%)
HADS-D, mean (SD)	5.44 (±3.64)
n. of depressed (%)	42 (15.97%)
MFIS	
Physical, mean (SD)	15.54 (±9.61)
Cognitive, mean (SD)	12.73 (±8.80)
n. of patients with clinical fatigue, n(%)	108 (41.06%)
Subjective cognitive difficulties	202 (76.80%)

Abbreviations: SD = Standard deviation; LMET = low–moderate efficacy treatments: teriflunomide, dimethyl fumarate, and glatiramer acetate; HET = high-efficacy treatments: cladribine, fingolimod, ofatumumab, natalizumab, ponesimod, siponimod, ocrelizumab, and alemtuzumab; SDMT = Symbol digit modalities test; CVLT-II = California Verbal Learning Test, 2nd edition; BVMT-R = Brief Visuospatial Memory Test–Revised; HADS = Hospital Anxiety and Depression Scale; MFIS = Modified Fatigue Impact Scale

0.001).

Self-reported slowed thinking was negatively correlated with SDMT ($r = -0.239$, $p = 0.011$) and BVMT-R ($r = -0.139$, $p = 0.025$), as well as with female sex ($r = -0.179$, $p = 0.004$) and years of education ($r = -0.161$, $p = 0.009$). Positive correlations were observed with anxiety ($r = 0.333$, $p < 0.001$) and depression ($r = 0.509$, $p < 0.001$). Similarly, self-reported concentration difficulties were weakly negatively correlated with SDMT performance ($r = -0.156$, $p = 0.011$) and female sex ($r = -0.240$, $p < 0.001$), and positively correlated with anxiety ($r = 0.434$, $p < 0.001$) and depression ($r = 0.533$, $p < 0.001$).

3.3. Predictors of subjective attention complaints

To further explore the association between subjective and objective cognitive disability binary logistic regression models were fitted with self-reported slowed thinking and concentration difficulties as dependent variables. As shown in Table 2, depressive symptoms (HADS-D) emerged as the only significant predictor of both outcomes. In the multinomial logistic regression, depression emerged as the only significant predictor, across severity of slowed thinking across categories, specifically in the comparison between the lowest and highest levels of slowed thinking (*Never* vs *almost always*; $\beta = -0.430$, $p < 0.001$; See Supplementary Table 1).

3.3.1. Memory domain

3.3.1.1. Objective memory performance and self-reported forgetfulness. Thirteen patients showed impairment on the CVLT-II, and eight on the BVMT-R. Sixty-five patients (24.7%) reported experiencing forgetfulness "often" or "almost always" over the previous four weeks despite demonstrating preserved processing speed on the CVLT-II (66 patients according to the BVMT-R). Among patients with CVLT-II impairment, 9 reported experiencing forgetfulness "rarely" or "sometimes," three "often," and one did not consider themself forgetful.

3.4. Bivariate associations with subjective memory complaints

In bivariate correlation analyses, self-reported forgetfulness was not correlated with BICAMS subtests, nor with EDSS, age, education, or disease duration, but was significantly associated only with anxiety ($r = 0.350$, $p < 0.001$) and depression ($r = 0.400$, $p < 0.001$).

3.5. Predictors of subjective memory complaints

Given the lack of significant associations between self-reported forgetfulness and objective cognitive measures in the preliminary analyses, no further multivariable logistic regression models were performed for this domain.

Repeating the analyses after excluding patients affected by clinical depression and anxiety, the results remained substantially unaltered for both attention and memory domains (see Supplementary Table 2).

3.5.1. Dependence on others and limited independence

3.5.1.1. Bivariate associations with independence outcomes. Dependence on others for daily activities was negatively correlated with SDMT performance ($r = -0.124$, $p = 0.044$) and positively correlated with age ($r = 0.178$, $p = 0.004$) and baseline disability (EDSS) ($r = 0.416$, $p < 0.001$). Significant positive correlations were also observed with anxiety ($r = 0.224$, $p < 0.001$) and depression ($r = 0.322$, $p < 0.001$). Among subjective cognitive complaints, dependence on others was positively correlated with slowed thinking ($r = 0.241$, $p < 0.001$), concentration difficulties ($r = 0.247$, $p < 0.001$), sustained attention complaints ($r = 0.157$, $p = 0.011$) and forgetfulness ($r = 0.145$, $p = 0.019$).

Similarly, limited independence showed negative correlations with objective cognitive performance, including SDMT ($r = -0.190$, $p = 0.002$), CVLT ($r = -0.160$, $p = 0.009$), and BVMT ($r = -0.138$, $p = 0.025$). Positive correlations were observed with age ($r = 0.140$, $p = 0.023$), baseline disability (EDSS) ($r = 0.347$, $p < 0.001$), anxiety ($r = 0.356$, $p < 0.001$), and depression ($r = 0.444$, $p < 0.001$). All subjective cognitive complaints were significantly associated with limited independence, including slowed thinking ($r = 0.312$, $p < 0.001$), concentration difficulties ($r = 0.333$, $p < 0.001$), sustained attention complaints ($r = 0.285$, $p < 0.001$), and memory complaints ($r = 0.237$, $p < 0.001$).

3.6. Predictors of independence outcomes

To further investigate these associations, two binary logistic regression models were fitted with dependence on others and limited independence as dependent variables. As shown in Table 3, EDSS emerged as the only significant predictor in both models.

Repeating the analyses considering both subgroups of patients with EDSS <3.5 and < 5.5, the results remained substantially unaltered for both *dependence on others and limited independence domains* (see Supplementary Table 3a and 3b).

Table 2
Binary logistic regression models predicting subjective cognitive difficulties.

	Slowed thinking			Concentration		
χ^2 (df)	75.24 (7)			78.15 (4)		
p	<0.001			<0.001		
Predictor	β	OR (95% CI)	p	β	OR (95% CI)	p
Sex[a]	−0.623	0.54 (−1.28–0.03)	0.063	−0.802	0.45 (−1.43–(−0.18)	0.012
Education	−0.108	0.90 (−0.20–(−0.02)	0.023		–	–
EDSS (baseline)	0.011	1.01 (−0.16–0.18)	0.900		–	–
SDMT	−0.031	0.97 (−0.06–0.00)	0.055	−0.015	0.99 (−0.04–0.01)	0.252
BVMT-R	0.004	1.00 (−0.02–0.03)	0.774		–	–
HADS-A	−0.019	0.98 (0.07–0.04)	0.672	0.015	1.02 (−0.07–0.10)	0.727
HADS-D	0.302	1.35 (0.19–0.06)	<0.001	0.333	1.40 (0.22–0.45)	<0.001

Table 2 reports binary logistic regression models examining the association between demographic, clinical, and cognitive variables and subjective cognitive difficulties, including slowed thinking and trouble concentrating. Variables included in each model were those identified as significant in the preliminary bivariate correlation analyses.

Bonferroni-adjusted significance thresholds were set at $p < 0.007$ for the slowed thinking model and $p < 0.012$ for the concentration model.

Abbreviations: β = regression coefficient; OR = odds ratio; CI = confidence interval; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; BVMT-R = Brief Visuospatial Memory Test; HADS-A = Hospital Anxiety and Depression Scale–Anxiety; HADS-D = Hospital Anxiety and Depression Scale–Depression.

[a] Sex was dichotomized as 0 = female and 1 = male.

Table 3
Binary logistic regression models predicting independence domains.

	Dependence on others			Limited Independence		
χ^2 (df)	59.83 (7)			72.74 (10)		
p	<0.001			<0.001		
Predictors	β	OR (95% CI)	p	β	OR (95% CI)	p
Age	1.027	1.03 (−0.01–0.06)	0.163	0.018	1.02 (−0.001–0.05)	0.195
Education		–	–	−0.013	0.99 (−0.11–0.08)	0.782
EDSS (baseline)	**0.589**	**1.80 (0.36–0.82)**	**<0.001**	**0.397**	**1.49 (0.22–0.58)**	**<0.001**
SDMT	−0.016	0.98 (−0.05–0.02)	0.357	−0.014	0.99 (−0.05–0.02)	0.365
CVLT-II		–	–	−0.018	0.98 (−0.05–0.001)	0.185
BVMT-R		–	–	−0.014	0.99 (−0.04–0.02)	0.374
Perceived deficits in sustained attention	0.183	1.20 (−0.30–0.66)	0.454	0.337	1.40 (−0.04–0.71)	0.078
Perceived deficits in slowed thinking	−0.012	0.99 (−0.52–0.49)	0.962	0.018	1.02 (−0.39–0.43)	0.931
Perceived deficits in concentration	0.549	1.73(−0.06–1.17)	0.082	0.302	0.35(−0.16–0.77)	0.205
Perceived deficits in memory	0.029	1.03(−0.41–0.47)	0.899	0.137	1.15 (−0.21–0.48)	0.440

Table 3 reports binary logistic regression models examining the association between demographic, clinical, and cognitive variables and independence domains, including dependence on others and limited independence. Variables included in each model were those identified as significant in the preliminary bivariate correlation analyses. Bonferroni-adjusted significance thresholds were set at $p < 0.007$ for the dependence on others model and $p < 0.005$ for the limited independence model.
Abbreviations: β = regression coefficient; OR = odds ratio; CI = confidence interval; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; CVLT-II = California Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test;

3.6.1. Sensitivity analysis

Sensitivity analyses were conducted to assess whether the main findings were robust to the use of full validated subscales in place of the selected questionnaire items used in the primary analyses.

When the primary regression model was repeated using the MFIS cognitive subscale as the dependent variable, results were largely consistent with the main analyses. Anxiety ($\beta = 0.425$, $p < 0.001$) and depressive symptoms ($\beta = 1.140$, $p < 0.001$) remained significant predictors of subjective cognitive difficulties, whereas objective cognitive measures were not independently associated with self-reported cognition (all $p > 0.05$). In addition, sex emerged as a significant predictor ($\beta = -1.844$, $p = 0.046$).

When the regression model was repeated using the MSIS-29 physical subscale score as the dependent variable, disability severity, as measured by the Expanded Disability Status Scale (EDSS), remained the strongest predictor (standardized $\beta = 0.562$, $p < 0.001$), confirming the robustness of the primary findings obtained using the selected item assessing dependence on others.

4. Discussion

This study aimed to characterize the relationship between objective cognitive impairment, perceived cognitive deficits, physical disability, and psychological symptoms in people with multiple sclerosis (PwMS), using targeted patient-reported outcome measures (PROMs). By focusing on individual questionnaire items rather than aggregated subscale scores, we sought to capture subjective experiences that may be obscured by broader categorizations, while preserving clinical applicability using well-validated instruments.

Our findings corroborate previous evidence of a discrepancy between subjective and objective measures of cognitive function [18,19]. Specifically, although impairment in at least one BICAMS subtest was identified in a relatively small proportion of patients (15.2%), nearly 80% reported subjective difficulties in at least one cognitive domain. Notably, approximately 11% of patients reported clinically relevant slowed thinking over the preceding four weeks despite preserved performance on the SDMT, while about 25% described significant forgetfulness despite intact scores on the CVLT-II and BVMT-R. The relatively low prevalence of objectively measured cognitive impairment in our sample is likely attributable to the cohort's low level of disability. In addition, more than 75% of participants were receiving high-efficacy disease-modifying therapies, which may have contributed to the reduced rate of cognitive impairment compared with other similar cohorts [17]. While this limits the generalizability of our findings to more cognitively impaired or more disabled populations, it represents a specific and clinically relevant context. In particular, our sample provides an opportunity to investigate the dissociation between subjective cognitive complaints and objective cognitive performance in individuals with relatively preserved cognition. Notably, recent evidence suggests that the relationship between subjective cognitive complaints and objective performance in multiple sclerosis may be more complex than what is captured by global summary measures [17]. In this context, our domain-specific, item-level approach provides a more fine-grained characterization of subjective cognitive experience, allowing a closer alignment with specific cognitive domains and potentially offering additional insight into the observed dissociation between subjective and objective cognition.

In regression analyses, self-reported difficulties in attention domains and memory complaints were not independently associated with their respective objective cognitive measures. These findings highlight the importance of assessing subjective cognitive decline even in individuals classified as cognitively preserved, in order to identify early at-risk profiles and potentially mitigate future objective cognitive deterioration, as well as to improve quality of life.

Despite the relatively young age of the sample, the dissociation between perceived and objectively measured cognitive deficits was pronounced. Additionally, age was not significantly associated with increased perceived deficits in any cognitive domain, whereas self-reported symptoms of depression and anxiety appeared to largely mediate the experience of cognitive difficulties in everyday functioning. This finding is consistent with previous studies reporting that subjective cognitive complaints in multiple sclerosis are not uniformly associated with age, but may be more closely linked to psychological and neuropsychiatric factors [20]. In this context, age-related changes in objective cognition may not directly translate into increased perceived cognitive difficulties.

Moreover, depressive symptoms emerged as the only significant predictor of both slowed thinking and concentration difficulties in models accounting for possible confounders. This association was further supported by multinomial analyses across levels of symptom severity, in which depressive symptoms were the only variable distinguishing patients reporting subjective cognitive complaints from

those who did not.

These findings suggest that perceived cognitive difficulties are more closely related to psychological factors than to objective cognitive impairment. Indeed, depression emerged as a strong predictor of cognitive fatigue also considering overall cognitive MS-related fatigue rather than individual domains [21]. This interpretation is consistent with a growing body of literature indicating that self-reported cognitive difficulties in multiple sclerosis are more strongly associated with depressive symptoms, anxiety, and broader neuropsychiatric factors than with objective cognitive performance [6,11,17]. Mood disturbances may influence patients' perception of their cognitive functioning through mechanisms such as negative bias, reduced cognitive confidence, and altered metacognitive appraisal [12,20,21]. Importantly, post-hoc analyses excluding patients with clinically significant anxiety and depression yielded comparable results, indicating that the observed dissociation is not solely driven by overt mood disturbances but may also reflect more subtle psychological or metacognitive processes influencing patients' self-perception of cognitive functioning [11,12,21].

Physical disability, as measured by EDSS, showed a strong and consistent association with functional outcomes. In multivariable models, EDSS emerged as the only independent predictor of both dependence on others and limited independence, whereas subjective cognitive complaints and objective cognitive performance were not independently associated with these outcomes. These findings underscore the predominant role of physical disability in determining functional autonomy in PwMS. Although subjective cognitive complaints were associated with independence outcomes in univariate analyses, these associations did not persist when accounting for other relevant predictors, suggesting that their relationship with functional outcomes may be mediated by overall disability level.

Importantly, repeating the analyses in subgroups of patients with lower disability (EDSS <3.5 and < 5.5) yielded substantially similar results across both dependence and limited independence domains. This consistency indicates that the lack of association between cognitive measures and functional outcomes is not merely driven by higher disability levels but may reflect a more general pattern across the disability spectrum.

Overall, these findings highlight a complex relationship between objective cognitive performance, subjective cognitive experience, and functional outcomes in PwMS. While physical disability remains the primary determinant of functional autonomy, patients' perceptions of their cognitive functioning appear to be more closely linked to psychological and affective processes than to measurable neuropsychological impairment.

It is possible to assume that subjective cognitive complaints in PwMS may reflect alterations in self-monitoring, metacognitive appraisal, and emotional processing rather than early markers of objective decline alone. Even in the absence of clinically significant mood disorders, subtle affective vulnerability may shape how patients interpret and report their cognitive efficiency in everyday life. This may promote heightened attention to discrepancies between perceived and expected cognitive performance, leading to negative bias in self-evaluation, reduced confidence, and a consequent decline in perceived quality of life [19,22].

Our study is not free from limitations. First, the cross-sectional design precludes causal interpretations, and longitudinal studies are needed to clarify temporal relationships between psychological symptoms and perceived or objective cognitive changes. Additionally, although the use of selected items from validated PROMs allowed a focused and clinically oriented assessment, this approach may have excluded other relevant dimensions of patient experience. Importantly, perceived cognitive difficulties were derived from selected MFIS items, which may capture both subjective cognitive complaints and aspects of cognitive fatigue. Given the known overlap between these constructs in MS, this measure likely reflects a broader patient-reported cognitive experience, encompassing fatigue-related and metacognitive processes that may contribute to the observed dissociation with objective performance. Accordingly, future studies should adopt methodological approaches specifically designed to disentangle these constructs, including the use of dedicated instruments for subjective cognitive complaints and analytical strategies capable of capturing potential non-linear dynamics between subjective experience and objective performance.

Conclusions

Despite these limitations, our findings underscore the importance of integrating psychological assessment into routine clinical evaluation of PwMS. Addressing mood symptoms, illness perception, and metacognitive processes may not only improve subjective cognitive well-being but also enhance patients' overall quality of life and engagement in daily activities. Future longitudinal studies should further explore whether subjective cognitive complaints represent an early psychological marker of vulnerability, a target for intervention, or a dynamic interaction between emotional and cognitive domains over the disease course.

CRediT authorship contribution statement

Elisa Leveraro: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review and editing. Maria Petracca: Conceptualization; Formal analysis; Methodology; Writing – review and editing; Funding acquisition. Lorenza Nasone: Data curation; Investigation. Gabriele Guerrieri: Investigation. Caterina Lapucci: Investigation; Resources. Nicola Cavalli: Investigation; Resources. Sabrina Al Qudsi: Investigation; Resources. Francesco Baldisseri: Investigation; Resources. Giacomo Boffa: Investigation; Resources; Supervision. Matilde Inglese: Conceptualization; Funding acquisition; Project administration; Supervision; Writing – review and editing.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2026.126022.

Data availability

The data presented in this study are available on request from the corresponding author.

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