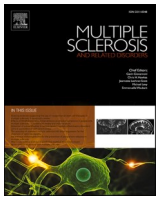
Multiple Sclerosis and Related Disorders 107 (2026) 106984

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Revealing the clinical significance of PASAT rejection in multiple sclerosis: Insights from patient-reported and clinician-assessed outcomes

Jessica Podda [a,*], Federica Di Antonio [a,b], Ludovico Pedullà [a], Erica Grange [a,c], Mario Alberto Battaglia [d], Andrea Tacchino [a], Giampaolo Brichetto [a,e]

[a] NeuroBRITE Research Center, Italian Multiple Sclerosis Foundation, Via Operai 40 16149, Genoa, Italy
[b] Department of Experimental Medicine (DIMES), University of Genoa, Via Leon Battista Alberti 2 16132, Genoa, Italy
[c] Department of Informatics, Bioengineering, Robotics and Systems Engineering (DIBRIS), University of Genoa, Via Opera Pia 13 16145, Genoa, Italy
[d] Department of Life Science, University of Siena, Via Aldo Moro 2 53100, Siena, Italy
[e] AISM Rehabilitation Service, Italian Multiple Sclerosis Society, Via Operai 30 16149, Genoa, Italy

ARTICLE INFO

Keywords:
Multiple Sclerosis
Paced Auditory Serial Addition Test
Patient Reported Outcome
Test Rejection
Assessment

ABSTRACT

Background: The Paced Auditory Serial Addition Test (PASAT) is widely used to assess cognitive functioning and fatigability in people with Multiple Sclerosis (PwMS). However, its poor acceptability and high refusal rates may limit its clinical interpretability, while potentially conveying meaningful information beyond test performance.
Objectives: To determine whether PASAT rejection at the first assessment represents a clinically meaningful marker of overall vulnerability in PwMS, reflected by a tendency toward worsening across demographic, disease-related and clinical domains, using both patient-reported and clinician-assessed outcomes.
Methods: One-way ANOVAs or non-parametric equivalents were run to compare different groups defined by baseline PASAT performance (missing, low, high) in terms of demographic, disease-related and clinical variables.
Results: Retrospective data from 1154 PwMS were analyzed. Participants with missing PASAT (N=224) were significantly older (60.1±13.5 years), had longer disease duration (18.9±12.2 years), higher EDSS (6.1±2.0), lower educational level (9.9±3.9 years), poorer cognitive performances on the Montreal Cognitive Assessment (MoCA) and Symbol Digit Modalities Test (SDMT) (respectively, 17.4±6.5, 22.5±13.6), and higher level of required assistance in daily functioning as measured by the Functional Independence Measure (FIM) (91.1 ±29.3), compared with both low and high PASAT groups (all ps < 0.05).
Conclusions: PASAT rejection at first assessment identifies a subgroup of older PwMS with higher disability, lower education, and more pronounced cognitive and functional impairments, suggesting that test refusal may serve as a clinically relevant marker of overall vulnerability in MS.

1. Introduction

The Paced Auditory Serial Addition Test (PASAT) is a validated measure of sustained attention, working memory, auditory comprehension, and information processing speed (Amato et al., 2006; Benedict et al., 2006; Morrow et al., 2026; Rao, 1696) in Multiple Sclerosis (MS), included in several standard batteries such as the Brief Repeatable Battery of Neuropsychological test (BRB-N) (Rao, 1696) and the Minimal Assessment of Cognitive Function In MS (MACFIMS) (Benedict et al., 2002). PASAT is also part of the Multiple Sclerosis Functional Composite (MSFC) (Benedict et al., 2011), a three-component measure with quantitative evaluations of ambulation, upper extremity function, and cognitive function, developed to be a more sensitive measure of disability than the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Moreover, the test has been widely used to investigate cognitive fatigability (Mackay et al., 2021; Morrow et al., 2026), a phenomenon often observed in people with MS (PwMS) and conceptualized as a progressive decline in performance on continuous cognitive tasks that require information processing speed, sustained attention, and working memory, such as the PASAT (Agyemang et al., 2021).

Despite its effectiveness, PASAT is poorly tolerated. Participants report an overwhelming aversion for the test, describing it as a

* Corresponding author at: NeuroBRITE Research Center, Italian Multiple Sclerosis Foundation, Via Operai 40, 16149, Genoa, Italy.
E-mail addresses: jessica.podda@aism.it (J. Podda), federica.diantonio@fismets.it (F. Di Antonio), ludovico.pedulla@aism.it (L. Pedullà), erica.grange@fismets.it (E. Grange), m.a.battaglia@aism.it (M.A. Battaglia), andrea.tacchino@aism.it (A. Tacchino), giampaolo.brichetto@aism.it (G. Brichetto).

https://doi.org/10.1016/j.msard.2026.106984
Received 30 September 2025; Received in revised form 27 December 2025; Accepted 6 January 2026
Available online 7 January 2026

frustrating, stressful and difficult task (Cortés-Martínez et al., 2019; Tombaugh, 2006). Consequently, there is a tendency to avoid this test in favour of the Symbol Digit Modalities Test (SDMT) when assessing cognitive abilities, as it is more acceptable to PwMS (Sumowski et al., 2018). Refusal to perform the PASAT is not uncommon: previous studies have shown that 5.1% of healthy people refuse the test, mainly due to stress and frustration (Locke et al., 2011), while over 17% of PwMS decline to perform the PASAT (Aupperle et al., 2002). Cortès-Martinez and colleagues (2019) reported an even higher refusal rate, with 35.3% of PwMS declining to undergo the test. Interestingly, rejection of the test was associated to a worse performance in all cognitive tests administered (Cortés-Martínez et al., 2019).

In this context, considering the chronic and progressive nature of MS and the need for ongoing and continuous care, repeated observations of PASAT-related behaviours, such as test rejections, could offer valuable longitudinal clinical indicators (Cortés-Martínez et al., 2019). Based on this premises, the present study set out to explore whether PASAT rejection may represent a clinically meaningful marker of overall vulnerability in PwMS, reflected by a tendency toward worsening across multiple domains. To this end, we examined its associations with demographic, disease-related, and clinical variables in a large cohort of PwMS, using both patient-reported outcomes (PROs) and clinician-assessed outcomes (CAOs).

2. Materials and methods

2.1. Participants

The dataset was acquired retrospectively from PROMOPRO-MS initiative (Brichetto et al., 2020) that consists of a large, multicenter and longitudinal study that involves the Italian MS Society Rehabilitation Services of Genoa, Padua and Vicenza (Italy). In PROMOPRO-MS, all the PwMS, followed as outpatients or at-home, have been assessed every four to five months using clinical evaluations and self-administered questionnaires related to a variety of domains, including fatigue, cognitive and physical impairment and psychological well-being. For the purposes of this study, we considered only the first assessment in the longitudinal series. The current cohort included in this study was composed by PwMS that met PROMOPRO-MS inclusion criteria, as a definite diagnosis of MS, all MS courses and an age above 18 years. The study was approved by the Ethics Committee of the Liguria Region (approval number: 023REG20l4). Each participant gave their written consent before starting the study. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

2.2. Outcome measure

The PASAT, the primary outcome of the study, was administered according to standard procedures (Fischer et al., 2001). Participants listened to a series of single-digit numbers presented every 3 seconds through an audio recording. They were instructed to add each new number to the one immediately preceding it and provide the sum aloud. Importantly, they were not asked to give a running total, but to sum only the last two numbers heard. Performance was scored as the total number of correct sums, with a maximum possible score of 60. In addition, for each participant, demographic (i.e., age, gender, years of education) and disease-related (i.e., disease duration, MS course, and disability level as measured by the EDSS) information were collected. The clinical features chosen from PROMOPRO-MS database to be used in the analysis were those that pertain to cognitive, fatigue, psychological and functional status domains. Cognitive functioning was evaluated using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and Symbol Digit Modalities Test (SDMT) (Amato et al., 2006). Specifically, subjective cognitive fatigue was tested using the Modified Fatigue Impact Scale (MFIS) (Flachenecker et al., 2002). Psychological aspects as mood disorders and quality of life were assessed through the Hospitalized Anxiety and Depression Scale (HADS) (Honarmand and Feinstein, 2009) and the Life Satisfaction Index (LSI) (Franchignoni et al., 1999), respectively. In addition, the Functional Independence Measure (FIM) was administered to quantify the functional status based on the level of assistance required across different domains (self-care, sphincter control, transfers, locomotion, communication, and social cognition) (Granger et al., 1990). PASAT was administered in the middle of the assessment, prior to the MoCA and SDMT, and this placement was kept consistent across all participants. By positioning the PASAT early in the session, we aimed to minimize potential effects of test fatigue on performance.

2.3. Statistical analysis

A descriptive statistical analysis was conducted to characterize the sample at baseline. Continuous variables were summarized using mean (M) and standard deviation (SD), while median and interquartile range (IQR) were reported for questionnaire scores and non-normally distributed data. Normality was assessed using the Kolmogorov-Smirnov test. The pattern of missing values across all scales and questionnaires was explored through visual inspection using histograms of percentages. Missing values in variables other than PASAT were replaced with the median. Particular attention was given to the first assessment to characterise the sub-sample of PwMS who were prone to omit the PASAT assessment. For the purposes of the present study, PASAT refusal was operationally defined as either failure to complete the practice sequences according to manual criteria or explicit refusal to attempt the practice phase after receiving standardized oral instructions from the therapist. To retain these cases in the analyses without excluding relevant data, missing PASAT scores were imputed with the value -1 as a placeholder. The sample was subsequently stratified into three groups based on PASAT performance at baseline: participants with PASAT score $\geq$ 35 (high PASAT), those with a low PASAT score $<$ 35 (low PASAT) (López-Góngora et al., 2015), and those who refused to complete PASAT (missing PASAT). Group comparisons across demographic (age, gender, education), disease-related (EDSS, disease duration, MS course), and clinical (FIM, MoCA, MFIS, HADS, LSI, and SDMT) variables at baseline were performed using one-way ANOVAs for normally distributed continuous variables, Kruskal–Wallis tests for non-normally distributed variables, and chi-square tests for categorical variables. To account for multiple testing across the large number of outcome variables, a Bonferroni correction was applied across all group-level comparisons, adjusting the significance threshold according to the total number of variables examined. For variables showing significant group differences after this initial correction, post hoc pairwise comparisons were conducted to further characterize between-group effects. Specifically, independent-samples t-tests, Mann–Whitney U tests, or pairwise chi-square tests were used when appropriate. Bonferroni correction was additionally applied to each set of post hoc comparisons to control the family-wise error rate within each variable. Effect sizes were calculated using eta squared for ANOVA and Kruskal–Wallis tests (Tomczak and Tomczak, 2014), and Cramer's V for chi-square tests. Eta squared were interpreted as small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), and large ($\eta^2 = 0.14$), whereas Cramer's V values were reported without conventional interpretation due to their dependence on the dimensions of the contingency tables (Cohen, 2013). Cut-offs of the MoCA seven dimensions were used to isolate specific impaired cognitive domains (Liew Tau et al., 2018; Podda et al., 2024): Visuospatial-Executive ($<$ 4), Attention ($<$ 6), Abstraction ($<$ 1), Delayed Recall Memory ($<$ 4), Language ($<$ 3), Naming ($<$ 3), and Orientation ($<$ 6). In addition, given the association between cognitive fatigability and subjective cognitive fatigue remains still unclear in MS (Harrison et al., 2017), Pearson correlation coefficients (r) were calculated between PASAT and MFIS total and subscale scores at baseline. Correlation coefficients ranging from 0.20 to 0.39 were considered as moderate, from 0.40 to 0.59 as

relatively strong, from 0.60 to 0.79 as strong, and higher as very strong correlation (Rea and Parker, 2014).

3. Results

1154 PwMS have been included in the analysis (See Table 1 for a detailed demographic and clinical characterization of the sample).

At baseline, 224 PwMS (19 % of the total sample) refused to complete the PASAT (missing PASAT group). As the database included longitudinal assessments, visual inspection indicated that the proportion of refusals remained consistent across visits. Histograms of the percentage of missing data of the selected tests (i.e., total score) across sessions are presented in Fig. 1. The PASAT refusal rate was substantially higher than for other measures: 0.3% for FIM, 1.3% for HADS and LSI, 1.0% for MFIS, 5.1% for SDMT and 1.2% for MoCA.

Results from the ANOVA (or equivalent tests) comparing missing PASAT, low PASAT (20.99 ± 9.09), and high PASAT (46.83 ± 7.42) groups indicated that many variables considered significantly differed across groups (see Table 2). Participants with missing PASAT data displayed the most impaired profile across all measures. They were older (60.05 ± 13.53 years, all ps <.001), with a higher EDSS scores indicating a moderate disability level (6.14 ± 1.97, all ps < 0.001), a longer disease duration (18.93 ± 12.21 years, all ps < 0.01) and a lower educational level (9.93 ± 3.91 years, all ps < 0.05). The majority had a SP course (62.7%), while only 23.1% had a RR course. Gender distribution (71.1% female) did not differ between groups (all ps > 0.05).

Cognitively, they showed significantly lower MoCA total scores (17.43 ± 6.51, all ps < 0.001) and each subdomains score (all ps < 0.01): Visuospatial–Executive (1.69 ± 1.67), Naming (2.48 ± 0.89), Attention (3.56 ± 1.79), Language (1.64 ± 0.85), Abstraction (1.08 ± 0.75), Delayed Recall Memory (1.36 ± 1.45), and Orientation (4.95 ± 1.56). In addition, performance at SDMT (22.50 ± 13.58; p < 0.001) was significantly lower compared to both low and high PASAT groups, below the clinical cut-off of 34.2 (Kappos et al., 2018). They showed significantly lower FIM scores across all subdomains, including social cognition, communication, sphincter control, self-care, locomotion, and transfers, with a lower FIM total score (91.05 ± 29.26) compared with both the low PASAT group (109.37 ± 20.45) and the high PASAT group (118.67 ± 11.17; all ps < 0.001), indicating a greater need for assistance across multiple functional domains.

From a psychological perspective, the missing PASAT and low PASAT groups did not differ substantially. Both groups showed comparable levels of depressive symptoms as measured by the HADS-D (missing PASAT: 5.94 ± 3.88; low PASAT: 5.56 ± 3.64; p > 0.05). In contrast, high PASAT reported significantly lower depressive symptoms (4.77 ± 3.57; p < 0.001), compared with both groups. Anxiety levels, as assessed by the HADS-A, did not statistically differ across groups (p < 0.05). Similarly, quality of life, as measured by LSI, was significantly higher in the high PASAT group (12.97 ± 4.31) compared with both participants in the missing PASAT (11.34 ± 4.72; p < 0.001) and those in the low PASAT (11.89 ± 4.46; p < 0.01).

Regarding fatigue, the missing PASAT group showed an increasing trend across all MFIS dimensions, although not statistically significant, except for psychosocial subscale. Here, the high PASAT group reported lower perceived psychosocial fatigue compared with the low PASAT (p < 0.05) and the missing PASAT group (p < 0.01). Fig. 2 showed boxplots comparing a selection of features at baseline across groups based on PASAT performance.

In line with group-level results, Pearson correlations revealed weak, but statistically significant associations between the PASAT and the MFIS (see Table 3). The low coefficients obtained for MFIS cognitive and psychosocial subscales, and total score suggest that the statistical significance is primarily driven by the large sample size.

Table 1
PwMS' demographic, disease-related and clinical information.

Variable	M ± SD	Median (IQR)	Total
Demographic data			
N	—	—	1154
Age (years)	54.3 ± 12.9	—	—
Gender (F) - GEND	—	—	750
Education (years) - EDU	11.6 ± 4.0	13 (5)	—
Disease-related data			
EDSS (0-10)	5.2 ± 2.0	6 (2.5)	—
Disease duration (years)	14.8 ± 10.6	13.5 (15)	—
MS course			RR 486
	—	—	SP 513
			PP 155
Clinically assessed outcomes (CAOs)			
FIM_TOT (18-126)	109.2 ±22.2	119 (18)	—
MoCA_TOT (0-30)	22.8 ± 5.1	24 (6)	—
Patient-reported outcomes (PROs)			
MFIS_TOT (0-84)	37.5 ± 17.9	37 (25)	—
HADS_TOT (0-42)	12.1 ± 7.2	11 (10)	—
HADS_D (0-21)	*5.3 ± 3.7*	*5.3 (5)*	—
HADS_A (0-21)	*6.8 ± 4.4*	*6.8 (6)*	—
LSI (0-22)	12.2 ± 4.5	12 (7)	—
Performance Test			
SDMT (0-110)	35.5 ± 15.6	36 (21)	—
PASAT (0-60)	32.5 ± 15.3	32 (23)	—

M (Mean); SD (Standard Deviation); IQR (Interquartile Range); EDSS (Expanded Disability Status Scale); MS course = RR (Relapsing-Remitting); MS course = SP (Secondary Progressive); MS course = PP (Primary Progressive); FIM_TOT (Functional Independence Measure – Total Score); MoCA_TOT (Montreal Cognitive Assessment – Total Score); MFIS_TOT (Modified Fatigue Impact Scale – Total Score); HADS_TOT (Hospital Anxiety and Depression – Total Score); HADS_D (Hospital Anxiety and Depression – Depression subscale); HADS_A (Hospital Anxiety and Depression – Anxiety subscale); LSI (Life Satisfaction Index); SDMT (Symbol Digit Modalities Test); PASAT (Paced Auditory Serial Addition Test). PASAT scores reported here refer to participants who completed the test at baseline, categorized into high and low PASAT groups.

4. Discussion

The present study aimed to explore whether PASAT rejection could represent a clinically meaningful marker of vulnerability in PwMS, examining demographic, disease-related and clinical variables in a large cohort of 1154 PwMS, using both PROs and CAOs. Taken together, findings indicate that missing PASAT participants represented a distinct subgroup with a more compromised clinical profile.

Specifically, PwMS who declined to perform the PASAT at the first assessment showed a higher frequency of cognitive impairment compared with the low PASAT and high PASAT groups. Specifically, PASAT rejection was associated with lower scores across various cognitive domains, including attention, executive functioning, delayed recall memory, orientation and visuospatial abilities, as measured by the MoCA subdomain and total scores. Additionally, SDMT scores were significantly lower in this group compared to those who completed the PASAT. These findings are consistent with previous research indicating that PASAT performance is closely related to multiple cognitive functions, such as sustained attention, working memory, information processing speed, and executive functioning (Cortés-Martínez et al., 2019; Eizaguirre et al., 2020). Moreover, since rejections included both failures to complete the practice sequences or explicit refusal to attempt the practice phase after receiving standardized oral instructions from the therapist, results suggest that PASAT-based groups may reflect not only cognitive efficiency, but also the ability and willingness to engage with a cognitively demanding and often poorly tolerated task.

Notably, PASAT rejections provide additional valuable insights into the clinical profile of PwMS, extending beyond established associations with cognitive abilities (Locke et al., 2011). PwMS in the missing PASAT group were older, with higher EDSS, a progressive MS course, a longer disease duration, in comparison to individuals with high PASAT and those with low PASAT. They also had lower educational levels, supporting previous evidence that years of formal education strongly

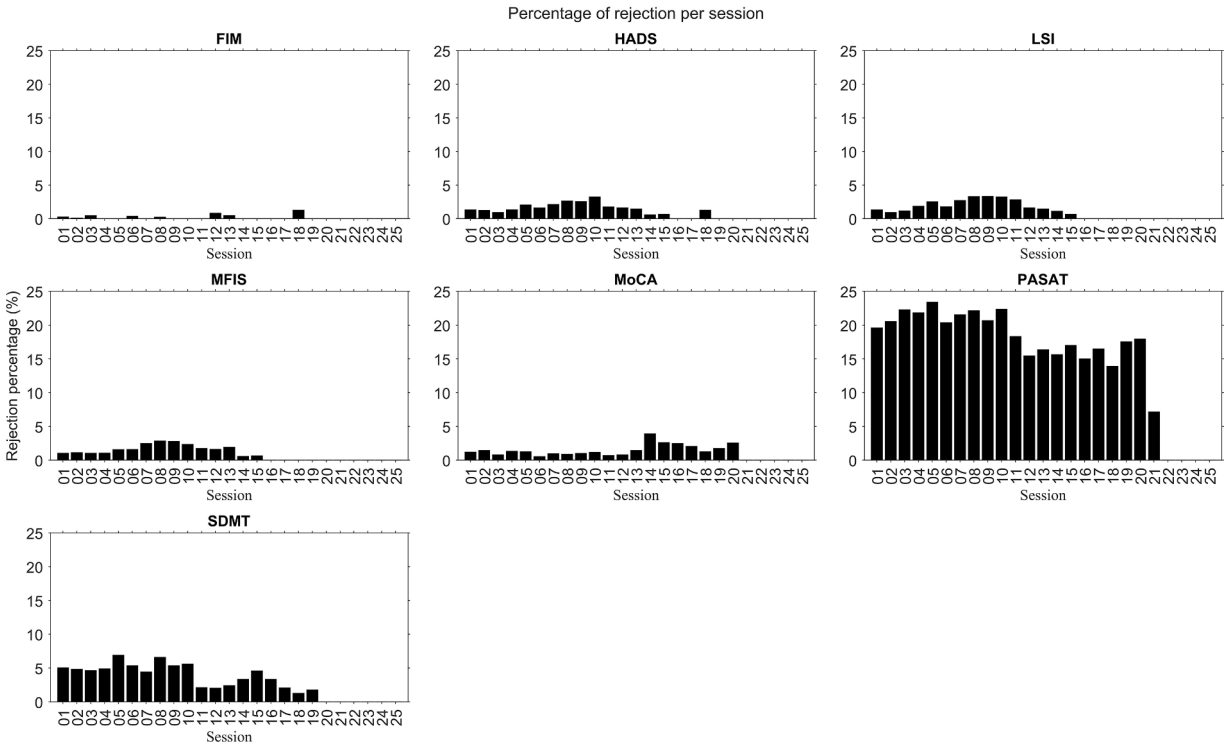


Fig. 1. Graphical representation of the percentage of rejections in the selected tests across sessions. For clarity of visualization, only total scores from FIM, HADS, LSI, MFIS, MOCA, SDMT and PASAT are included. Y axis presents rejection percentage, while x axis session number.

influence the likelihood of completing or refusing the test (Cortés-Martínez et al., 2019).

Focusing on psychological domains, the missing PASAT group appeared more vulnerable, showing an overall tendency toward higher anxiety and depressive symptoms, in line with previous evidence linking lower PASAT performance to mood disturbances (Berard et al., 2018). Although differences in anxiety were not statistically significant in line with previous evidence (Bosnes et al., 2015), depressive symptoms were clearly elevated compared to those with high PASAT performance. Conversely, participants with high PASAT scores reported better quality of life than both missing and low PASAT groups, suggesting that preserved cognitive performance may be associated with greater psychological well-being.

Interestingly, missing PASAT had significantly lower scores in FIM subscales, indicating that PwMS who rejected PASAT had an overall lower grade of the functional status. This result supported the ecological validity of current measures as PASAT reflecting that those who rejected PASAT at first assessment require more assistance in everyday demands and activities as social cognition, communication, sphincter control, self-care, locomotion and transfers (Harrison et al., 2017).

Taken together, these findings support the interpretation of PASAT refusal as a behavioral marker of overall vulnerability in MS, integrating disease-related factors, functional limitations, cognitive difficulties, and reduced tolerance to cognitive effort.

Regarding perceived fatigue, the missing PASAT group showed an increasing trend across all MFIS dimensions, although not statistically significant, except for psychosocial dimensions. Interestingly, correlation analyses revealed only weak but statistically significant associations between PASAT performance and MFIS scores (total score and psychosocial subscale). This suggests that the observed statistical significance may be largely influenced by the large sample size rather than reflecting a strong linear association. Indeed, evidence on relationship between cognitive fatigability and subjective fatigue in MS remains mixed and inconclusive, partly due to differences in scoring methods, sample heterogeneity and the choice of assessment tools (Harrison et al., 2017). Some studies report significant correlations between subjective ratings of cognitive fatigue and cognitive fatigability (Locke et al., 2011; Walker et al., 2012), while others found no or weak relationships in line with our study (Bakirtzis et al., 2020; Mackay et al., 2021). This aligns with a general observation that some PwMS may perform well on objective cognitive tasks yet report high levels of fatigue, while others may show measurable cognitive decline but report little or no subjective sense of exhaustion, as in this case (Agyemang et al., 2021). However, caution is warranted when interpreting such discrepancies, which often arise from the assumption that objective and subjective measures are inherently opposed. We argue that objective assessments should not be considered superior to PROs since self-report instruments remain a valid and essential tool for capturing individuals' perceptions of fatigue and other symptoms, as well as their impact on daily life. From a clinical perspective, recognizing PASAT refusal as a marker of vulnerability has practical implications. Given the demanding nature and limited tolerability of the task, PASAT administration may benefit from a flexible approach that considers individual characteristics and the likelihood of refusal. When refusal is anticipated, the test may be omitted to prioritize patient comfort, while acknowledging that the occurrence of refusal itself can still provide clinically meaningful information, particularly when interpreted alongside other cognitive, psychological, and functional indicators.

Some limitations should be acknowledged. Other variables not considered in this study may have affected PASAT performance. For example, sleep disturbances are known to negatively impact attention and processing speed (Amato et al., 2019), potentially confounding the interpretation of results. Moreover, PwMS frequently experience central auditory processing deficits, including reduced temporal resolution, auditory pattern recognition, and speech discrimination in noise, which can adversely affect performance in cognitively demanding auditory tasks (Valadbeigi et al., 2014) such as the PASAT. While MS-specific batteries such as BRB-N or MACFIMS may provide a more comprehensive assessment of cognitive functions, the use of MoCA can be seen as a limitation, as it does not capture MS domain-specific deficits in detail.

Table 2
Results of statistical analyses comparing groups based on baseline PASAT performance.

Variables	High PASAT (M ±SD) N= 413 (36%)	Low PASAT (M ±SD) N= 517 (45%)	Missing PASAT (M±SD) N=224 (19%)	p values	Effect size
AGE (years)	49.27 ± 11.12	55.99 ± 12.50	60.05 ± 13.53	all ps <0.001	0.1
GEND (F)	62.5% (258)	64.2% (332)	71.1% (160)	p > 0.05	0.048
GEND (M)	37.5% (155)	35.8% (185)	28.9% (64)		
EDU (years)	12.99 ± 3.55	11.13 ± 3.96	9.93 ± 3.91	a-b, a-c <0.001 b – c <0.05	0.08
EDSS	4.41 ± 1.91	5.38 ± 1.79	6.14 ± 1.97	all ps <0.001	0.11
Disease Duration (years)	11.67 ± 8.27	15.57 ± 10.81	18.93 ± 12.21	a – b, a – c <0.001 b – c <0.01	0.05
MS course (RR)	56.9% (235)	38.7% (200)	23.1% (51)	all ps <0.001	0.13
MS course (SP)	32.0% (132)	46.4% (240)	62.7% (141)		
MS course (PP)	11.1% (46)	14.9% (77)	14.2% (32)		
FIM_TOT	118.67 ± 11.17	109.37 ± 20.45	91.05 ± 29.26	all ps <0.001	0.18
FIM_SUB_ social cognition	20.54 ± 0.83	19.78 ± 1.99	17.56 ± 4.28	all ps <0.001	0.129
FIM_SUB_communication	13.91 ± 0.47	13.53 ± 1.23	12.46 ± 2.46	all ps <0.001	0.126
FIM_SUB_sphincter control	12.74 ± 1.92	11.78 ± 3.15	9.96 ± 4.18	all ps <0.001	0.07
FIM_SUB_self care	39.88 ± 4.81	36.36 ± 8.93	29.65 ± 12.07	all ps <0.001	0.133
FIM_SUB_locomotion	12.20 ± 2.70	10.74 ± 3.63	8.03 ± 4.24	all ps <0.001	0.135
FIM_SUB_transfers	19.46 ± 3.16	17.22 ± 5.31	13.40 ± 6.76	all ps <0.001	0.139
MoCA_TOT	25.91 ± 2.52	22.57 ± 3.99	17.43 ± 6.51	all ps <0.001	0.31
MoCA_Visuospatial-Executive domain	4.19 ± 0.99	3.09 ± 1.58	1.69 ± 1.67	all ps <0.001	0.24
MoCA_Naming domain	2.92 ± 0.33	2.84 ± 0.42	2.48 ± 0.89	a-b <0.01 b-c, a-c <0.001	0.06
MoCA_Attention domain	5.60 ± 0.75	4.91 ± 1.21	3.56 ± 1.79	all ps <0.001	0.23
MoCA_Language domain	2.58 ± 0.60	2.09 ± 0.79	1.64 ± 0.85	all ps <0.001	0.17
MoCA_Abstraction domain	1.66 ± 0.54	1.39 ± 0.71	1.08 ± 0.75	all ps <0.001	0.07
MoCA_Delayed Memory domain	2.71 ± 1.56	2.03 ± 1.57	1.36 ± 1.45	all ps <0.001	0.09
MoCA_Orientation domain	5.92 ± 0.29	5.66 ± 0.82	4.95 ± 1.56	all ps <0.001	0.106
MFIS_TOT	35.07 ± 17.03	38.56 ± 18.53	39.54 ± 17.82	p > 0.05	0.010
MFIS_SUB_cognitive	11.80 ± 9.10	13.63 ± 10.40	14.15 ± 9.95	p > 0.05	0.007
MFIS_SUB_physical	19.98 ± 8.98	21.21 ± 8.66	21.31 ± 8.56	p >0.05	0.003
MFIS_SUB_psychosocial	3.30 ± 2.19	3.73 ± 2.46	4.08 ± 2.63	a-b <.05, a-c <.01	0.011
HADS	11.3 ± 6.7	12.4 ± 7.2	12.8 ± 7.6	p > 0.05	0.005
HADS_D	4.77 ± 3.57	5.56 ± 3.64	5.94 ± 3.88	a-b, a-c <0.001	0.015
HADS_A	6.52 ± 3.99	6.87 ± 4.55	7.05 ± 4.68	p >0.05	0
LSI	12.97 ± 4.31	11.89 ± 4.46	11.34 ± 4.72	a-b < 0.01, a-c <.001	0.016
SDMT	47.06 ±12.07	30.75 ± 12.42	22.50 ± 13.58	all ps <0.001	0.35

Mean and standard deviation of demographic, disease-related and clinical variables across groups: high PASAT score (≥35), low PASAT score (<35), and those with a PASAT rejection. *p* values indicate results of pairwise post hoc comparisons between groups, adjusted using Bonferroni correction for multiple comparison. When the overall group comparison was not significant, a single *p*-value is reported. Effect sizes are reported as eta squared for continuous variables and Cramer's V for categorical ones.
GEND = F (Gender: Female); GEND = M (Gender: Male); EDU (Years of Education); EDSS (Expanded Disability Status Scale); MS course = RR (Relapsing-Remitting); MS course = SP (Secondary Progressive); MS course = PP (Primary Progressive); MOCA_TOT (Montreal Cognitive Assessment – Total Score); MOCA_Visuospatial-Executive domain (MOCA – Visuospatial/Executive domain); MOCA_Naming domain (MOCA – Naming domain); MOCA_Attention domain (MOCA – Attention domain); MOCA_Language domain (MOCA – Language domain); MOCA_Abstraction domain (MOCA – Abstraction domain); MOCA_Delayed Memory domain (MOCA – Delayed Memory domain); MOCA_Orientation domain (MOCA – Orientation domain); HADS_D (Hospital Anxiety and Depression Scale – Depression subscale); HADS_A (Hospital Anxiety and Depression Scale – Anxiety subscale); FIM_TOT (Functional Independence Measure – Total Score); FIM_SUB_social cognition (FIM – Social Cognition subscale); FIM_SUB_communication (FIM – Communication subscale); FIM_SUB_sphincter control (FIM – Sphincter Control subscale); FIM_SUB_self care (FIM – Self-Care subscale); FIM_SUB_locomotion (FIM – Locomotion subscale); FIM_SUB_transfers (FIM – Transfers subscale); LSI (Life Satisfaction Index); SDMT (Symbol Digit Modalities Test); MFIS_TOT (Modified Fatigue Impact Scale – Total Score); MFIS_SUB_cognitive (MFIS – Cognitive subscale); MFIS_SUB_physical (MFIS – Physical subscale); MFIS_SUB_psychosocial (MFIS – Psychosocial subscale). All ps indicate pairwise comparisons between groups: a-b, b-c, c-a.

However, the primary aim of the PROMOPRO-MS database, from which MoCA was selected, is not to measure cognitive deficits in isolation, but to collect large-scale, multidimensional data spanning cognitive, motor, and psychological domains to detect rapid changes due to disease progression and to plan timely interventions. Additionally, evidence supports the value of MoCA as a screening tool for cognitive dysfunction in MS, even in individuals with mild disability as indicated by EDSS (Dagenais et al., 2013). Future studies could complement MoCA with other MS-specific cognitive batteries to provide more detailed cognitive profiling when needed. Participants' emotional state before the test, such as elevated state anxiety, which could be measured with the State-Trait Anxiety Inventory (STAI) (Santangelo et al., 2016), may have contributed to reduced performance, independently of cognitive resources. Finally, in PROMOPRO-MS only corrected responses from PASAT were collected. Although in line with test manual, this decision prevented the use of additional validated methods for assessing cognitive abilities, such as analyzing omission errors or comparing performance between the first and last thirds of the test (Bosnes et al., 2015).

A key strength of this study is the use of data from PROs from the large PROMOPRO-MS dataset. PROs are increasingly recognized in MS clinical trials and routine care, providing essential insights into how treatments and the disease itself affect patients' lives (Brichetto and Zaratin, 2020). Incorporating PROs in MS routine care has the potential

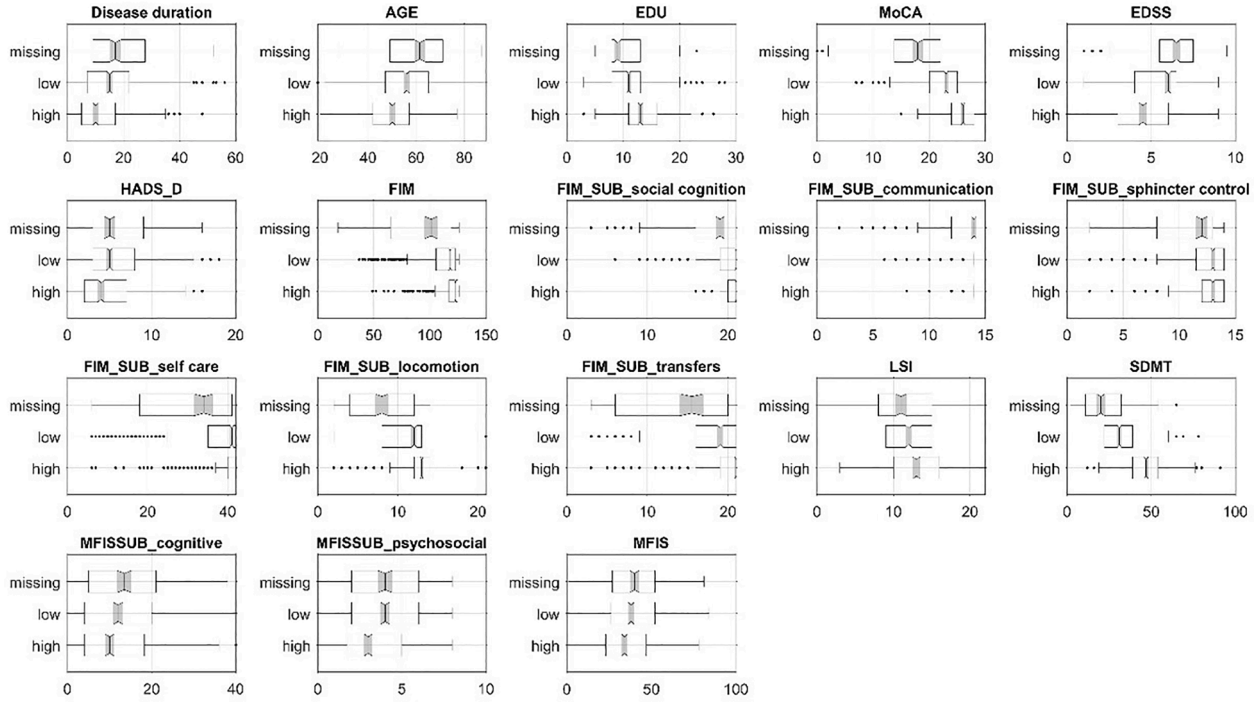


Fig. 2. Boxplots comparing a selection of demographic, disease-related and clinical features at baseline across the three groups based on PASAT performance. Y axis represents missing PASAT, low PASAT (<35), and high PASAT (≥35).

Table 3
Pearson correlation between MFIS subscale and total scores and PASAT.

MFIS_item	Coefficient	p values
MFIS_SUB_cognitive	-0,1351	0.0005
MFIS_SUB_physical	-0,0424	0.2766
MFIS_SUB_psychosocial	-0,0992	0.0107
MFIS_TOT	-0,1081	0.0054

MFIS_SUB_cognitive (MFIS – Cognitive subscale); MFIS_SUB_physical (MFIS – Physical subscale); MFIS_SUB_psychosocial (MFIS – Psychosocial subscale); MFIS_TOT (Modified Fatigue Impact Scale – Total Score).

to improve quality of care, promote patient-centred care, and improve treatment adherence. Future research should focus on integrating objective outcome measures alongside PROs, aiming to complement rather than replace or devalue them.

5. Conclusion

Our study demonstrates that PASAT rejection is associated with a more compromised demographic, disease-related and clinical characteristics in PwMS. Specifically, missing PASAT participants showed higher EDSS scores, longer disease duration, and a higher proportion of progressive disease. They also exhibited stronger impairments in functional and cognitive outcomes, as well as in some psychological variables, compared with the other PASAT-based groups (low and high PASAT). These findings suggest that test refusal may serve as a clinical marker of broader vulnerability in PwMS, providing valuable insights for both research and routine clinical practice. To our knowledge, this is the first study highlighting the importance of looking beyond cognitive performance and basic demographic or disease-related characteristics when examining patients' clinical profiles using PROs. Such an approach may help clinicians better anticipate PwMS' behaviors during assessments. Given the demanding nature and limited tolerability of the task, PASAT administration may benefit from a flexible approach that considers individual characteristics and the likelihood of refusal. Clinically, recognizing individuals at risk of PASAT rejections can streamline the assessment process, reduce frustration, and support more personalized care planning.

Ethical Considerations

The study was approved by the Ethics Committee of the Liguria Region (approval number: 023REG2014). This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Consent to participate

Each participant gave their written consent before starting the study.

Funding statement

The study was funded by Fondazione Italiana Sclerosi Multipla (project name: PROMOPRO-MS; grant number: FISM 2013/S3) and by the European Union - NextGenerationEU - and the Ministry of University and Research (MUR) National Recovery and Resilience Plan (NRRP), Mission 4, Component 2, Investment 1.5 (project name: RAISE - Robotics and AI for Socio-economic Empowerment; grant number: ECS00000035).

Data availability

The dataset is available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare the use of ChatGPT OpenAI to ensure linguistic accuracy and readability of the manuscript.

CRediT authorship contribution statement

Jessica Podda: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Federica Di Antonio:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Data curation. **Ludovico Pedullà:** Writing – review & editing, Investigation, Conceptualization. **Erica Grange:** Writing – review & editing, Resources, Investigation. **Mario Alberto Battaglia:** Writing – review & editing, Project administration. **Andrea Tacchino:** Writing – review & editing, Conceptualization. **Giampaolo Brichetto:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

Giampaolo Brichetto reports that financial support was provided by Fondazione Italiana Sclerosi Multipla, the European Union - NextGenerationEU - and the Ministry of University and Research (MUR) National Recovery and Resilience Plan (NRRP). Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank the Italian Multiple Sclerosis Foundation (Fondazione Italiana Sclerosi Multipla, FISM ETS), the European Union - NextGenerationEU - and the Ministry of University and Research (MUR) within the RAISE ecosystem for their support of this study. We are especially grateful to all people with Multiple Sclerosis followed as outpatients at the Rehabilitation Services of Genoa, Padua and Vicenza of the Italian Multiple Sclerosis Society (AISM) for their participation in this research. We also thank the FISM Secretariat for their assistance with the enrolment of people with Multiple Sclerosis.

References

Agyemang, C., Berard, J.A., Walker, LAS., 2021. Cognitive fatigability in multiple sclerosis: how does performance decline over time on the paced auditory serial addition test? Mult. Scler. Relat. Disord. 54, 103130.
Amato, M.P., Portaccio, E., Goretti, B., et al., 2006. The Rao's brief repeatable battery and stroop test: normative values with age, education and gender corrections in an italian population. Mult. Scler. 12, 787–793.
Amato, M.P., Prestipino, E., Bellinvia, A., 2019. Identifying risk factors for cognitive issues in multiple sclerosis. Expert. Rev. NeurOther 19, 333–347.
Aupperle, R.L., Beatty, W.W., NAP, Shelton F de, et al., 2002. Three screening batteries to detect cognitive impairment in multiple sclerosis. Mult. Scler. 8, 382–389.
Bakirtzis, C., Nikolaidis, I., Boziki, M-K, et al., 2020. Cognitive fatigability is independent of subjective cognitive fatigue and mood in multiple sclerosis. Cogn. Behav. Neurol. 33, 113–121.
Benedict, R.H.B., Cookfair, D., Gavett, R., et al., 2006. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J. Int. Neuropsychol. Soc. 12, 549–558.
Benedict, R.H.B., Fischer, J.S., Archibald, C.J., et al., 2002. Minimal neuropsychological assessment of ms patients: a consensus approach. Clin. Neuropsychol. 16, 381–397.
Benedict, R.H.B., Holtzer, R., Motl, R.W., et al., 2011. Upper and lower extremity motor function and cognitive impairment in multiple sclerosis. J. Int. Neuropsychol. Soc. 17, 643–653.
Berard, J.A., Smith, A.M., Walker, LAS., 2018. A longitudinal evaluation of cognitive fatigue on a task of sustained attention in early relapsing-remitting multiple sclerosis. Int. J. MS. Care 20, 55–61.
Bosnes, O., Dahl, O.P., Almkvist, O., 2015. Including a subject-paced trial may make the PASAT more acceptable for MS patients. Acta Neurol. Scand. 132, 219–225.
Brichetto, G., Monti Bragadin, M., Fiorini, S., et al., 2020. The hidden information in patient-reported outcomes and clinician-assessed outcomes: multiple sclerosis as a proof of concept of a machine learning approach. Neurol. Sci. 41, 459–462.
Brichetto, G., Zaratin, P., 2020. Measuring outcomes that matter most to people with multiple sclerosis: the role of patient-reported outcomes. Curr. Opin. Neurol. 33, 295–299.
Cohen, J., 2013. Statistical Power Analysis For The Behavioral Sciences. Academic press.
Cortés-Martínez, A., Matias-Guiu, J.A., Pytel, V., et al., 2019. What is the meaning of PASAT rejection in multiple sclerosis? Acta Neurol. Scand. 139, 559–562.
Dagenais, E., Rouleau, I., Demers, M., et al., 2013. Value of the MoCA test as a screening instrument in multiple sclerosis. Can. J. Neurol. Sci. 40, 410–415.
Eizaguirre, M.B., Ciufia, N., Roman, M.S., et al., 2020. Perceived fatigue in multiple sclerosis: the importance of highlighting its impact on quality of life, social network and cognition. Clin. Neurol. Neurosurg. 199. https://doi.org/10.1016/j.clineuro.2020.106265. Epub ahead of print.
Fischer, J.S., Ph, D., Jak, A.J., et al., 2001. Multiple sclerosis functional composite (MSFC). Adm. Scoring Man.
Flachenecker, P., Kümpfel, T., Kallmann, B., et al., 2002. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult. Scler. 8, 523–526.
Franchignoni, F., Tesio, L., Ottonello, M., et al., 1999. Life satisfaction index: italian version and validation of a short form. Am. J. Phys. Med. Rehabil. 78, 509–515.
Granger, C V, Cotter, A.C., Hamilton, B.B., et al., 1990. Functional assessment scales: a study of persons with multiple sclerosis. Arch. Phys. Med. Rehabil. 71, 870–875.
Harrison, A.M., das Nair, R., Moss-Morris, R., 2017. Operationalising cognitive fatigability in multiple sclerosis: a gordian knot that can be cut? Mult. Scler. 23, 1682–1696.
Honarmand, K., Feinstein, A., 2009. Validation of the hospital anxiety and depression scale for use with multiple sclerosis patients. Mult. Scler. 15, 1518–1524.
Kappos, L., Bar-Or, A., Cree, B.A.C., et al., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391, 1263–1273.
Kurtzke, JF., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.
Liew Tau, Ming, Junhong, Yu, Rathi, Mahendran, et al., 2018. Neuropsychiatric and cognitive subtypes among community-dwelling older persons and the association with DSM-5 mild neurocognitive disorder: latent class analysis. J. Alzheimer's Dis. 62, 675–686.
Locke, Dona E.C., Stonnington, C., Thomas, Michael L., Casellii, R.J., 2011. Correlates of quitting the paced auditory serial addition test in cognitively normal older adults participating in a study of normal cognitive aging. J. Clin. Exp. Neuropsychol. 33, 937–943.
López-Góngora, M., Querol, L., Escartín, A., 2015. A one-year follow-up study of the symbol digit modalities test (SDMT) and the paced auditory serial addition test (PASAT) in relapsing-remitting multiple sclerosis: an appraisal of comparative longitudinal sensitivity. BMC. Neurol. 15, 40.
Mackay, L., Johnson, A.M., Moodie, S.T., et al., 2021. Predictors of cognitive fatigue and fatigability in multiple sclerosis. Mult. Scler. Relat. Disord. 56, 103316.
Morrow, S.A., Rosehart, H., Johnson, AM., 2026. Diagnosis and quantification of cognitive fatigue in multiple sclerosis. Cogn. Behav. Neurol. 28.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., et al., 2005. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699.
Podda, J., Di Antonio, F., Tacchino, A., et al., 2024. A taxonomy of cognitive phenotypes in multiple sclerosis: a 1-year longitudinal study. Sci. Rep. 14, 1–10.
Rao, SM., 1696. A manual For The Brief Repeatable Battery Of Neuropsychological Tests In Multiple Sclerosis. Medical College of Wisconsin, Milwaukee.
Rea, L.M., Parker, RA., 2014. Designing And Conducting Survey Research: A Comprehensive Guide. John Wiley & Sons.
Santangelo, G., Sacco, R., Siciliano, M., et al., 2016. Anxiety in multiple sclerosis: psychometric properties of the state-trait anxiety inventory. Acta Neurol. Scand. 134, 458–466.
Sumowski, J.F., Benedict, R., Enzinger, C., et al., 2018. Cognition in multiple sclerosis: state of the field and priorities for the future. Neurology. 90, 278–288.
Tombaugh, TN., 2006. A comprehensive review of the paced auditory serial addition test (PASAT). Arch. Clin. Neuropsychol. 21, 53–76.
Tomczak M, Tomczak E. The need to report effect size estimates revisited. an overview of some recommended measures of effect size. 2014.
Valadbeigi, A., Weisi, F., Rohbakhsh, N., et al., 2014. Central auditory processing and word discrimination in patients with multiple sclerosis. Eur. Arch. Otorhinolaryngol. 271, 2891–2896.
Walker, L.A.S., Berard, J.A., Berrigan, L.I., et al., 2012. Detecting cognitive fatigue in multiple sclerosis: method matters. J. Neurol. Sci. 316, 86–92.