Ulm University
Department of Neurology
Heads of Department: Prof. Dr. J. Weishaupt/ Prof. Dr. K. G. Häusler

Non-motor Cerebral Functions and Quality of Life in Multiple Sclerosis

Cumulative Dissertation

submitted to obtain the Doctoral Degree of Human Biology
(Dr. biol. hum.) of the Medical Faculty of Ulm University

Luisa Theresa Balz
Nürtingen, Germany

2025

Acting Dean: Prof. Dr. T. Wirth

1. Reviewer: Prof. Dr. Dr. D. Lulé

2. Reviewer: Prof. Dr. T. Kammer

Date of Graduation: 12.02.2026

“At the end of the day, we can endure much more than we think we can.”

— Frida Kahlo

Table of Contents

List of Abbreviations ..... **V**

1 Introduction **1**

2 Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study [S1] **5**

2.1 Relevance 5

2.2 Materials and Methods 5

2.3 Results 6

2.3.1 Participant Characteristics and Clinical Parameters 6

2.3.2 Intergroup Comparisons at Baseline 7

2.3.3 Intergroup Comparisons at Follow-up 7

2.3.4 Correlation Analyses at Baseline and Follow-up 7

2.3.5 Intragroup Comparisons from Baseline to Follow-up 7

2.4 Conclusion 8

3 Sensitivity and Specificity of a revised version of the TRACK-MS screening battery for early Detection of Cognitive Impairment in Patients with Multiple Sclerosis [S2] **10**

3.1 Relevance 10

3.2 Materials and Methods 10

3.3 Results 11

3.3.1 Cognitive Performance, Affective State, and Fatigue in MS Patients vs. Healthy Controls 11

3.3.2 Diagnostic Performance of TRACK-MS-R 12

3.4 Conclusion 13

4 Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust [S3] **14**

4.1 Relevance 14

4.2 Materials and Methods 14

4.3 Results 15

4.3.1 Participant Characteristics and Clinical Parameters 15

4.3.2 Psychosocial Adjustment in MS 15

4.3.3 Predictors of Psychosocial Adjustment in MS 16

4.3.4 Psychosocial Adjustment in MS vs. ALS 16

4.4 Conclusion 17

5 Synthesis and Outlook **19**

6 Abstract **21**

7 References **23**

8 Appendix **37**

Acknowledgements **79**

Curriculum Vitae **80**

List of Abbreviations

ACSA	Anamnestic Comparative Self-Assessment
ADI-12	ALS Depression Inventory (12 Items)
ALS	Amyotrophic Lateral Sclerosis
ALS-FRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APS	Auditory Processing Speed
BDT	Block Design Test
BICAMS-M	Brief International Cognitive Assessment for Multiple Sclerosis – Modified
BVMT-R	Brief Visuospatial Memory Test – Revised
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Cognitive Impairment
CNS	Central Nervous System
COWAT	Controlled Oral Word Association Test
DMTs	Disease-Modifying Therapies
EDSS	Expanded Disability Status Scale
EF	Executive Functions
EM	Episodic Memory
FN	False Negative
FP	False Positive
FSMC	Fatigue Scale for Motor and Cognitive Functions
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
HADS-D	Hospital Anxiety and Depression Scale – Depression
HC	Healthy Controls
HRQoL	Health-Related Quality of Life
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IPS	Information Processing Speed
MQoL	Mental Quality of Life
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PASAT	Paced Auditory Serial Addition Test
PPMS	Primary Progressive Multiple Sclerosis
PQoL	Physical Quality of Life
PROMs	Patient-Reported Outcome Measures
PSA	Psychosocial Adjustment
QoL	Quality of Life

RMSEA	Root Mean Square Residual
RRMS	Relapsing-Remitting Multiple Sclerosis
RWT	Regensburger Wortflüssigkeitstest
S1	Study 1
S2	Study 2
S3	Study 3
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SF-12	Short-Form Survey 12 Questionnaire
SPMS	Secondary Progressive Multiple Sclerosis
SPSS	Statistical Package for the Social Sciences
SQoL	Subjective Quality of Life
SRMR	Standardized Root Mean Square Residual
TAP	Testbatterie zur Aufmerksamkeitsprüfung
TN	True Negative
TP	True Positive
TRACK-MS	Track Multiple Sclerosis
TRACK-MS-R	Track Multiple Sclerosis - Revised
VF	Verbal Fluency
ViF	Visuospatial Functions
viEM	Visual Episodic Memory
viSM	Visual Short-Term Memory
viWM	Visual Working Memory
VLMT	Verbaler Lern- und Merkfähigkeitstest (Verbal Learning and Memory Test)
veEM	Verbal Episodic Memory
veSM	Verbal Short-Term Memory
veWM	Verbal Working Memory

1 Introduction

Multiple Sclerosis (MS) is the most common immune-mediated disease of the central nervous system (CNS) in young adults [1, 2, 3]. It involves chronic inflammation, demyelination, and axonal degeneration, which leads to a variety of neurological symptoms, including visual and gait problems as well as limb weakness, causing permanent disability [2]. Focal and diffuse lesions in T1 MRI images in both white and grey matter closely correlate with these clinical symptoms and may thus underlie the MS pathology of demyelination and axonal loss [4], which finally disrupt neural pathways and functional brain networks. These lesions are progressively found, particularly in the periventricular, juxtacortical, and infratentorial areas of the brain and the spinal cord [5, 6, 7, 8, 9, 10]. The clinical classification of MS distinguishes between different phenotypes of disease progression, with the most frequent being the relapsing-remitting MS (RRMS), which comprises about 85% of initial diagnoses [11]. Over time, approximately 25–40% of RRMS cases transition into secondary progressive MS (SPMS), where patients experience an enduring decline in neurological function [11, 12]. Primary progressive MS (PPMS) is a subtype of MS with continuous progression from the onset, affecting about 10–15% of patients, characterized by no relapses or remissions [13]. While this traditional classification into distinct phenotypes remains widely used, recent evidence has increasingly challenged the idea of sharply separated disease courses. The concept of a continuum, sometimes referred to as smouldering MS, emphasizes that both inflammatory and neurodegenerative processes are present from the earliest stages and contribute to disability across all phenotypes [14].

Overall, all phenotypes not only differ in their clinical course but also in underlying pathology and, most importantly, in non-motor cerebral functions [11].

Traditionally, MS is viewed as a pure motor disease, with a clinical focus on the progression of physical disability [15, 16]. Vast evidence from recent years [16, 17, 18, 19, 20, 21, 22] has led to a significant shift in this perspective, showing that MS not only affects motor functions but also leads to a wide range of non-motor symptoms, including cognitive impairment (CI), fatigue, and depression. These symptoms may be even more disruptive to patients' daily lives, mental well-being, and quality of life (QoL) than physical impairment alone [21, 23, 24]. Importantly, non-motor symptoms may vary in severity and presentation depending on disease stage and phenotype [11, 12, 25, 26, 27]. CI, fatigue, and depression have been documented across all MS phenotypes and can even occur before motor symptoms, highlighting their role as early and persistent features of MS [20, 28, 29, 30]. However, the understanding of non-motor symptoms in MS subtypes within clinical cohorts and their pattern of progression is limited, and numbers may vary substantially according to the literature.

What is known is that among the non-motor symptoms, CI is one of the most common and impactful, affecting about 40–70% of patients with MS [31, 32, 33]. CI has been shown to significantly affect employment, social participation, and overall

well-being in patients with MS [26, 34]. In the most common MS subtype, RRMS, CI is observed in approximately 21–45% of patients, usually affecting information processing speed (IPS), verbal fluency (VF), and visual episodic memory (viEM) [12, 26, 32]. In SPMS, cognitive deficits are much more common, affecting up to 80% of patients [32, 35]. These impairments tend to be broader and more severe, often involving IPS, VF, episodic (EM), and working memory (WM), visuospatial functions, and executive functions (EF) [25, 35, 36]. In the rarest MS phenotype, PPMS, it was initially believed that patients were relatively spared from CI [36]. However, recent studies using extensive neuropsychological assessments on cognition have shown that between 56% and 91% of individuals with PPMS also experience cognitive deficits, particularly in domains such as attention, WM, EF, and EM [26, 37]. Among the affected cognitive domains in MS, slowed IPS is often regarded as the most prominent impairment and is frequently seen as a "red flag" in the cognitive profile of MS [32, 38].

Notably, CI often develops before and thus independently of physical symptoms [39]. The high patient burden in combination with the low predictive value of CI highlights the importance of early detection and longitudinal monitoring of cognitive deficits in routine clinical settings [17, 28, 32, 40, 41, 42, 43]. Despite its clinical relevance, screening for cognitive deficits is still rare in MS in clinical and non-clinical settings [44, 45, 46]. Various obstacles prevent its incorporation into clinical workflows. Among these are limited time resources, a lack of trained neuropsychologists/neurologists, and the absence of time-efficient cognitive screening tools that can be used by clinicians in both clinical and outpatient settings [44, 45, 46]. Consequently, CI often stays unnoticed, despite growing consensus that regular monitoring of cognitive functions is crucial, not only for early detection but also for tracking disease progression and guiding treatment decisions [40, 45, 46, 47]. This may cause delay in proper therapeutic interventions and appropriate, patient-centred support [45, 46]. Standardized screening tools such as the Brief International Cognitive Assessment for MS (BICAMS) and its country-specific versions are a first milestone [48], considered the gold standard in MS cognitive screening [48, 49, 50]. However, the BICAMS administration time of 15–20 minutes may still be difficult to fit into fast-paced inpatient and outpatient settings. This highlights the need for even shorter, but still psychometrically reliable screening tools that may be used in different healthcare settings [48].

In addition to CI, fatigue is one of the most frequently reported and debilitating symptoms in MS, impacting between 18.2% and up to 97% of patients at various stages of the disease [20]. It is often viewed as more burdensome than motor impairments due to its unpredictable and fluctuating nature [23, 30, 51, 52]. Unlike regular tiredness, MS-related fatigue usually does not get better with rest or sleep. It may significantly affect social and mental functions, regardless of physical disability or disease stage [51]. Clinically, it presents as an intense feeling of exhaustion and low energy, often interfering with even simple daily tasks [51]. Research indicates that fatigue in MS is multifactorial, likely caused by a combination of immune-mediated neuroinflammatory processes, structural and functional brain changes (such as disruption in thalamocortical and frontostriatal

circuits), and neuroendocrine dysregulation [53, 54, 55, 56]. Furthermore, fatigue interferes with psychological factors in MS like depression and sleep disturbances [52, 56, 57, 58]. Fatigue can appear early in the course of the disease and is known to persist over time [20]. Fatigue may affect either cognitive or physical abilities. Cognitive fatigue shows as a decline in mental efficiency during sustained cognitive tasks and is especially important because it contributes to attentional deficits and worsens existing cognitive deficits [32, 59, 60]. Motor fatigue is defined as a progressive decline in muscle strength or motor performance during sustained activity [57]. Research has consistently shown that fatigue is associated with greater disability in patients with MS, but also patients' psychopathology, including lower health-related quality of life (HRQoL) and higher emotional distress [19, 21, 61]. Despite its clinical importance, fatigue remains difficult to measure objectively. Thus, subjective reports are the gold standard to determine patients' level of cognitive and motor fatigue. Further, effective treatment options are still limited [53, 59]. This highlights the urgent need for both standardized patient-reported outcome measures (PROMs) and personalized fatigue management strategies [59].

Finally, MS is associated with MS typical psychopathology of significant non-motor symptoms, including depression and anxiety, leading to reduced QoL. Depression, characterized by the cardinal symptoms of an altered affective state of low mood and a lack of drive for activity, along with anxiety symptoms such as feeling nervous, restless, or tense, are quite frequently reported in MS. The lifetime prevalence rates are believed to be two to three times higher than those in the general population, with up to 50% of MS patients experiencing at least one clinically relevant depressive episode during the course of the disease [62, 63]. Notably, the risk of developing clinically significant depressive symptoms is especially high in the early years following the diagnosis in the sense of adjustment disorder (F43.2 according to ICD-10 [64]), when patients often encounter substantial emotional distress and uncertainty [65, 66, 67]. Importantly, depression in MS may not be regarded as a pure psychological response to disease-related disability or stress caused by the diagnosis. Instead, MS is a complex and multifactorial condition shaped by neuroinflammatory processes, neurotransmitter dysregulation, and structural and functional changes in fronto-limbic brain regions [68, 69, 70], leading to a vast syndrome of motor and non-motor symptoms in MS. Among these non-motor symptoms, depression and CI often occur together and interact interchangeably both on the physical and psychological level. In this sense, the latter studies have shown that depression exacerbates cognitive deficits, particularly in attention, memory, and EF [71, 72, 73]. This, in turn, diminishes patients' capacity to manage the disease, stay independent, and finally, maintain mental well-being [19, 72]. This self-reinforcing cycle may finally attenuate QoL [19, 21, 74].

Overall, non-motor symptoms highlight the importance of cognitive and emotional abilities in adjusting to the changed circumstances. Coping with and integrating a chronic disease into daily life may be referred to as psychosocial adjustment (PSA) [75, 76, 77]. QoL and depression have been discussed in the literature as possible indicators and outcome measures of PSA along the disease trajectory [74, 75, 78, 79]. Whereas there is a strong consensus on the definition of depression, there is a

lack of a universal definition of QoL, with different suggested approaches. Traditionally, in the medical context, physical markers were seen as the most reliable indicators of QoL (HRQoL), but research increasingly differentiates between HRQoL, which may encompass physical and mental aspects, and subjective QoL (SQoL), which refers to personal life satisfaction and emotional well-being [80]. This distinction is important because vast evidence shows that the level of physical disability does not primarily determine subjective markers of QoL in MS, which are more closely connected to cognitive function, affective state, and fatigue [21, 76, 77]. Failing to evaluate and address these subjective dimensions of coping abilities by addressing HRQoL only may lead to underestimating the disease burden and hinder the ability to deliver patient-centred care [81, 82].

Considering these findings, there is an urgent need to systematically address the non-motor impact of MS in both research and clinical practice. Implementing brief cognitive screening tools and PROMs in clinical workflows, along with better access to neuropsychological assessments, is one important step. This may all facilitate early detection and monitoring of CI in the MS disease trajectory. In addition, describing facilitators and predictors of PSA in MS will also help promote patient-centred disease management in the future, most probably leading to more favorable PSA and higher QoL in MS patients.
This dissertation aims to contribute to this effort by exploring the impact of MS on non-motor cerebral functions and QoL.
To achieve this goal, the following three original studies, which have been published in international, peer-reviewed journals, are included. Each study relates to different aspects of the non-motor impact of MS:

[S1] Taranu D., **Balz L.T.**, Holbrook J., Tumani V., Schreiber H., Tumani H. & Uttner I. Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study. *Journal of Neurol*ogy 2025;272(6):398. doi:10.1007/s00415-025-13115-y

[S2] **Balz, L. T.**, Uttner, I., Taranu, D., Erhart, D. K., Fangerau, T., Jung, S., Schreiber, H., Senel, M., Vardakas, I., Lule, D. E. & Tumani, H. Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis. *Biomedicines* 2025;13(8):1902. doi: 10.3390/biomedicines13081902

[S3] **Balz, L.T.**, Uttner, I., Weishaupt, J., Ludolph, A.C., Taranu, D., Vardakas, I., Jung, S., Fangerau, T., Erhart, D.K., Senel, M., Tumani, H. & Lulé, D. Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust. *Brain Sciences* 2025;15(7):745. doi:10.3390/brainsci15070745

2 Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study [S1]

2.1 Relevance

This publication [S1] aimed to investigate how MS phenotypes (RRMS, SPMS, PPMS) differ with regard to cognitive profile, psychopathology (symptoms of depression and anxiety), and fatigue across the disease trajectory of a one-year period.

2.2 Materials and Methods

In this one-year prospective longitudinal study, sixty-six MS patients (N=22 each with RRMS, SPMS, and PPMS) were included and recruited from the Department of Neurology at Ulm University, and twenty-two healthy controls (HC), who were matched for age, sex, and education. The inclusion criteria for MS patients were a confirmed diagnosis of MS according to the revised McDonald criteria [83], sufficient language proficiency at the level of native fluency to ensure valid neuropsychological assessments, and an age range of at least 18 to 85 years. The exclusion criteria were any other neurological comorbidities besides MS, severe mental disorders, and impairments in speech or language that would affect test validity. Exclusion criteria also included recent corticosteroid treatment, as well as unstable clinical status or relapses within the past 30 days prior to the assessment. Another criterion was no changes to symptomatic (e.g., antidepressants) or disease-modifying therapies (DMTs) during the follow-up period. The study was approved by the ethics committee of Ulm University (No. 157/16).
Neurological examinations and neuropsychological assessments were performed at baseline (T0) and after one year (T1). During neuropsychological assessments, the following cognitive domains were assessed: IPS with the Symbol Digit Modalities Test (SDMT) [38], auditory processing speed (APS) and WM with the Paced Auditory Serial Addition Test (PASAT) [84], verbal episodic memory (veEM) with the Verbal Learning and Memory Test (VLMT) [85], viEM with the Brief Visuospatial Memory Test – revised (BVMT-R) [86], VF with the Controlled Oral Word Association Test (COWAT) [87], and visuospatial functions (ViF) with the Block Design Test (BDT) [88]. To minimize practice effects, alternative versions of the VLMT and BVMT-R were used during follow-up. Psychopathology (depression and anxiety) was assessed using the Hospital Anxiety and Depression Scale (HADS) [89]. Fatigue was recorded using the Fatigue Scale for Motor and Cognitive Functions (FSMC) [59]. The Expanded Disability Status Scale (EDSS, ranging from 0 = normal function to 10 = death) [90] was used to rate physical disability in patients with MS. Statistical analyses were conducted using the software packages SPSS version 29 and R. Further, an a priori power analysis indicated that a total sample size of N=88 ensures sufficient power (Cohen's d= 0.70, α= 0.05). Intergroup

differences were analyzed using ANCOVA (accounting for age and education) and ANOVA (with post-hoc tests), while intragroup differences were assessed with paired t-tests. Correlation analyses (Pearson) were used to examine the relationship between cognition, psychopathology, and fatigue. Data were z-standardized based on the 22 HCs at baseline. Then, composite scores for global cognition, psychopathology, and fatigue were built by averaging the respective z-standardized subscores, with higher scores indicating better functioning (scores for fatigue and psychopathology were inverted). The global cognition score combined all z-standardized cognitive subtests into a single measure.

2.3 Results

2.3.1 Participant Characteristics and Clinical Parameters

While the groups were comparable in terms of gender and education, significant differences were found in age, with patients with PPMS being the oldest. SPMS patients had the longest disease duration and presented with the highest level of physical disability (mean EDSS = 5.96, indicating moderate to severe physical disability), indicating also more advanced disease progression (see Table 1).

Table 1. Demographics and clinical data of MS patients and HC

	RRMS (*N*=22)	**SPMS (*N*=22)**	**PPMS (*N*=22)**	**HC (*N*=22)**	**Statistics**
Characteristics	Mean (SD) / N (%)	Mean (SD) / N (%)	Mean (SD) / N (%)	Mean (SD) / N (%)	
Age (years)	40.23 (10)	51.41 (8.78)	53.27 (6.64)	49.82 (14.81)	***F*(3, 84)=6.75, *p*< .001**
Female	15 (68.2)	12 (54.5)	14 (63.6)	11 (50)	$\chi^2(3)=1.88$, *p*= .598
Education (years)	10.32 (2.53)	10.09 (2.71)	11.18 (1.89)	11.82 (2.22)	*F*(3, 84)=2.51, *p*= .064
EDSS	2.61 (1.47)	5.96 (1.07)	4.61 (1.72)		
Time since onset (years)	11.82 (8.75)	18.23 (8.30)	10.82 (7.25)		***F*(2, 63)=5.39, *p*= .007**
Time since diagnosis (years)	8.18 (6.22)	14.64 (8.09)	6.14 (4.49)		***F*(2, 63)=10.4, *p*< .001**

RRMS = Relapsing Remitting Multiple Sclerosis. SPMS = Secondary Progressive Multiple Sclerosis. PPMS = Primary Progressive Mulitple Sclerosis. HC = Healthy Controls. EDSS = Expanded Disability Status Scale. Significant results are highlighted in bold.
Table recreated/modified from Taranu et al. (2025) [S1], page 3, licensed under CC BY 4.0.

2.3.2 Intergroup Comparisons at Baseline

At baseline, HC consistently outperformed all three MS subtypes in nearly all cognitive domains. Both progressive subtypes (SPMS and PPMS) showed significantly reduced global cognition performance compared to HC (SPMS: Δ= –1.32, p< .001; PPMS: Δ= –1.29, p< .001), while only PPMS patients scored significantly lower than RRMS (Δ= –0.77, p= .040). In progressive subtypes, cognitive deficits were most pronounced in viEM and veEM (SPMS: Δ= –1.45, p= .002; PPMS: Δ= –1.39, p= .003), and attention (SPMS: Δ= –1.54, p= .009; PPMS: Δ= –1.67, p= .002), with PPMS showing significantly lower scores than RRMS in both domains (e.g., attention: Δ= –1.33, p= .027). SPMS patients also reported higher levels of psychopathology (Δ= 0.77, p= .030). Fatigue scores were elevated across all MS subtypes (SPMS: Δ= 2.37, p< .001; PPMS: Δ= 1.76, p< .001; RRMS: Δ= 1.13, p= .010), with SPMS patients showing significantly higher fatigue levels than RRMS (Δ= –1.24, p= .004). Executive dysfunction was evident in all MS subtypes, while deficits in ViF were more pronounced in progressive MS (SPMS: Δ= –1.11, p= .002; PPMS: Δ= –1.31, p< .001).

2.3.3 Intergroup Comparisons at Follow-up

At follow-up, 87 out of the initial 88 participants continued to participate in the study. Cognitive deficits persisted in progressive subtypes, particularly in veEM, attention, EF, and ViF. Compared to RRMS, progressive subtypes presented with significantly lower global cognition performance (SPMS: Δ= –1.03, p= .007; PPMS: Δ= –0.85, p= .010). Further cognitive deficits compared to RRMS were found in veEM (SPMS: Δ= –1.08, p= .009), attention (SPMS: Δ= –1.47, p= .022; PPMS: Δ= –1.35, p= .009), and ViF (SPMS: Δ= –0.99, p= .010). SPMS patients also reported a higher burden of psychopathology (Δ= 0.82, p= .030) and fatigue (Δ= 1.21, p= .005) compared to RRMS.

2.3.4 Correlation Analyses at Baseline and Follow-up

At baseline, significant correlations were found between fatigue and psychopathology in RRMS (r= .57, p= .005) and PPMS (r= .66, p< .001), as well as between fatigue and global cognition in RRMS (r= .45, p= .035). No significant correlations were found in SPMS (all p> .05). At follow-up, the association between fatigue and psychopathology remained significant across all MS subtypes (RRMS: r= .46, p= .030; SPMS: r= .51, p= .015; PPMS: r= .86, p< .001), while correlations with global cognition were not significant in all groups (all p> .05).

2.3.5 Intragroup Comparisons from Baseline to Follow-up

Over the one-year period, RRMS patients showed significant improvements in the global cognition composite score (t(21) = –5.09, p< .001, d= –1.09), with particularly

strong gains in composite scores of veEM (VLMT total: $t(21)= -3.75$, $p= .001$, $d= -0.799$; recall: $t(21)= -3.05$, $p= .006$, $d= -0.651$) and attention (PASAT: $t(21)= -3.52$, $p= .002$, $d= -0.751$). PPMS patients showed significant improvements in ViF (BDT: $t(20)= -3.72$, $p= .001$, $d= -0.812$) and gains in global cognition ($t(20)= -2.13$, $p= .045$, $d= -0.466$). No significant cognitive changes were observed in the SPMS group over one year ($p> .05$) (Figure 1).

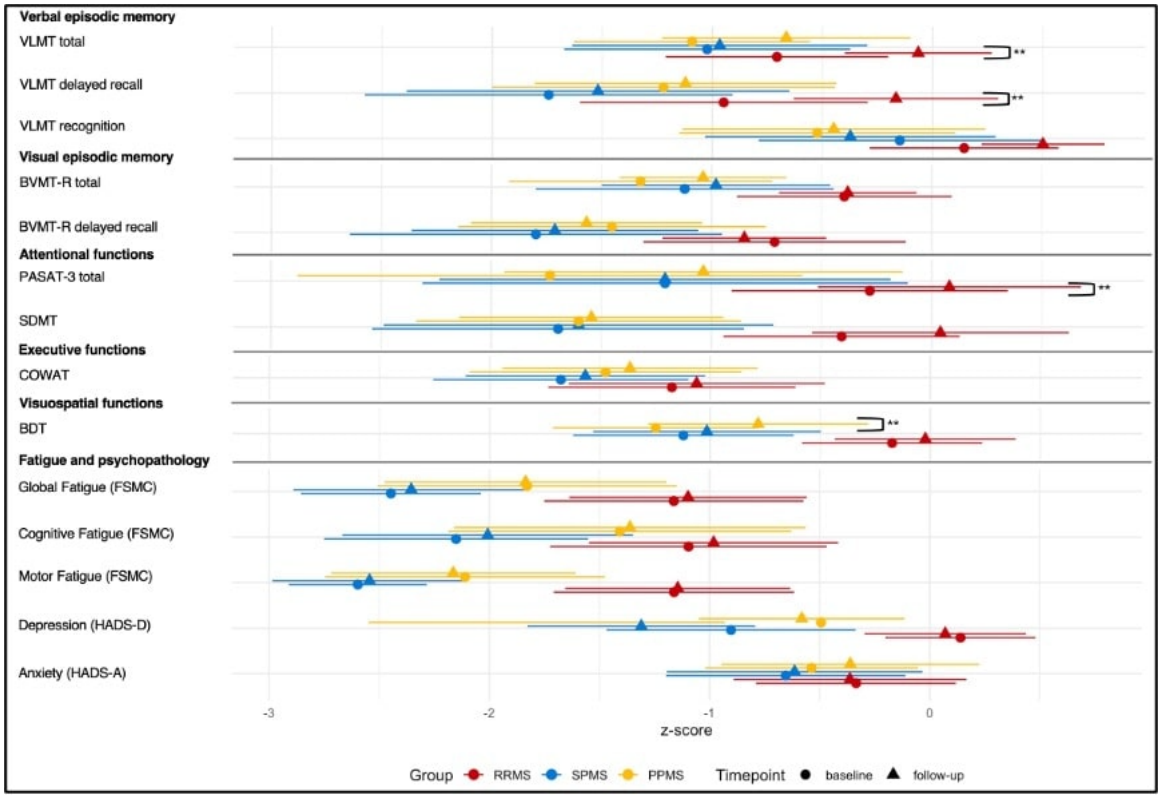


Figure 1. Between-group comparison from baseline to follow-up.
The error bar chart illustrates the intragroup comparison of MS subtypes (RRMS, SPMS, PPMS) in cognitive domain subtests from baseline to follow-up. Performance changes over time are shown, with significant improvements denoted by square brackets: * indicates $p<.05$, and ** indicates $p<.01$. Error bars represent confidence intervals, while data points for each timepoint indicate mean values. Reprinted from Taranu et al. (2025) [S1], page 10, licensed under CC BY 4.0.

2.4 Conclusion

Within this study [S1], evidence was provided that non-motor symptoms in MS, particularly CI, fatigue, and psychopathology, are not only clinically relevant but also differ among MS subtypes with dynamics over the disease course of one year. The longitudinal study design allowed for a detailed comparison of disease trajectories in RRMS, SPMS, and PPMS, revealing more severe cognitive deficits in progressive subtypes, particularly in SPMS, with prominent deficits in EF and EM, consistent with previous research [27, 37, 91, 92]. In contrast, RRMS patients showed, although minor, significant cognitive improvements, which might be linked to higher cognitive reserve, periods of disease stability, or the impact of DMTs. Improvements in this subgroup may have been facilitated by slightly reduced cognitive fatigue over time, the ability to benefit from repetition effects, and stabilizing treatment effects.

This lack of learning effect in the other subgroups (PPMS and SPMS) may suggest cognitive decline, potentially reflecting how ongoing disease progression impacts cognitive reserve and diminishes the ability to benefit from repetition effects.

Throughout the various MS subtypes, fatigue, depression, and anxiety were common and remained largely stable during the study timeframe, in line with recent studies [71, 93]. Notably, while strong associations were consistently found between fatigue and psychopathology, there were no significant correlations between cognitive performance and psychopathology, suggesting that these symptoms may involve different neurobiological mechanisms, particularly in progressive MS [22, 52].

In conclusion, these results highlight the importance of routinely assessing both cognitive and psychopathological symptoms in clinical and non-clinical settings, emphasizing the importance of personalized and subtype-specific care strategies.

Collectively, this study [S1] enhances current understanding by integrating cognitive and psychopathological aspects into the clinical perspective on MS. It therefore supports a holistic, symptom-driven management of non-motor symptoms in MS.

3 Sensitivity and Specificity of a revised version of the TRACK-MS screening battery for early Detection of Cognitive Impairment in Patients with Multiple Sclerosis [S2]

3.1 Relevance

This study [S2] investigated the validity of a revised version of TRACK-MS, a brief, resource-efficient cognitive screening tool to reliably detect CI in MS patients. In clinical settings, comprehensive neuropsychological assessments are often not feasible due to time constraints and a limited workforce. TRACK-MS was originally developed within the workgroup of Prof. Tumani at Ulm University as a cognitive screening tool for MS, which can be administered in a relatively short period of time (less than 5 minutes) [94]. Former studies provided evidence for TRACK-MS to be a reliable tool to diversify CI on the group level between MS subtypes and HC [94]. However, TRACK-MS lacked language-specific norms for German-speaking cohorts. Accordingly, the initial version of TRACK-MS included the SDMT and the COWAT [87]. The goal of the current study was to develop a revised version of TRACK-MS (TRACK-MS-R). For TRACK-MS-R, we replaced the COWAT with the RWT as the German equivalent of verbal fluency measures. Accordingly, TRACK-MS-R combines the SDMT [38] and the Regensburger Wortflüssigkeitstest (RWT; letter “S”) [95]. Thus, TRACK-MS-R unites the advantages of TRACK-MS to be a brief cognitive screening tool with the development of validated norms for German-speaking populations. TRACK-MS-R was validated with reference to the German version of the well-established gold standard BICAMS (BICAMS-M) [48], which includes the SDMT, VLMT [85], and BVMT-R [86]. BICAMS-M mainly assesses memory functions and takes approximately 20 minutes to administer. Both TRACK-MS-R and BICAMS-M, in addition to an extensive neuropsychological protocol, were used in both HC and MS patients to prove the constructive validity of TRACK-MS-R compared to BICAMS-M. HC data were used to determine normative data. Finally, TRACK-MS-R was used to stratify clinical samples of MS patients according to cognitive phenotypes in relation to HC. With this, the study assessed whether TRACK-MS-R can serve as a brief and practical alternative screening tool to BICAMS-M for early detection of CI in daily clinical practice.

3.2 Materials and Methods

In this prospective cross-sectional study, one hundred and two MS patients were included and recruited from the Department of Neurology at Ulm University, and ninety-four HC, who were matched for age, sex, and education. The inclusion criteria for MS patients were a confirmed diagnosis of MS according to the revised McDonald criteria [83], and sufficient language proficiency at the level of native fluency to ensure a valid neuropsychological assessment. Those with any other neurological comorbidities besides MS, severe mental disorders, and impairments

in speech or language that would affect test validity, or recent corticosteroid use (within the past 30 days prior to the assessment), or unstable clinical states were excluded. Ethical approval was obtained from the ethics committee of Ulm University (No. 335/23).

MS patients underwent a standardized neurological examination, and both MS patients and HC completed an extensive neuropsychological assessment, including TRACK-MS-R, which covers VF using the RWT with the letter “S” [95], and IPS with the SDMT [38], and BICAMS-M, also covering IPS with the SDMT, as well as veEM with the VLMT [85] and viEM with the BVMT-R [86]. Additionally, the following cognitive domains were included: verbal (veSM; veWM) and visual (viSM; viWM) short-term and working memory were assessed using the Digit Span [96] and Block-Tapping Test [96], attention with the Testbatterie zur Aufmerksamkeitsprüfung (TAP) [97], VF using the COWAT [87], and EF with the Matrices test [98]. Affective state (depression and anxiety) and fatigue were assessed using the HADS [89] and FSMC [59], respectively, while physical disability was measured with the EDSS [90].

Statistical analyses included ANOVA and ANCOVA (accounting for gender) for group comparisons, with cognitive scores standardized as z-scores using 94 HC to create composite scores of TRACK-MS-R and BICAMS-M. Sensitivity and specificity of TRACK-MS-R were evaluated relative to both BICAMS-M and HC, using 2×2 contingency tables to determine diagnostic accuracy (TN = true negative, TP = true positive, FP = false positive, FN = false negative), with the following formulas: specificity = TN/(TN+FP) and sensitivity = TP/(TP+FN).

3.3 Results

3.3.1 Cognitive Performance, Affective State, and Fatigue in MS Patients vs. Healthy Controls

MS patients and HC were comparable in terms of age and education, although HC had a significantly higher percentage of females (69% HC vs. 61% MS patients). In the extensive neuropsychological assessment, MS patients showed significantly lower performance in most cognitive domains compared to HC, particularly in veEM and viEM (e.g., VLMT total: $F(196)= 30.16$, $p< .001$, $\eta^2= .238$), attention and IPS (e.g., SDMT: $F(196)= 17.05$, $p< .001$, $\eta^2= .150$), EF and VF (e.g., RWT: $F(196)= 14.95$, $p< .001$, $\eta^2= .135$). No significant differences were observed between groups for viWM or specific subtests of visual recognition (BVMT-R) and auditory attention (TAP; see Table 2).

Additionally, MS patients reported significantly higher levels of depression (HADS-D: $F(196)= 16.26$, $p< .001$, $\eta^2= .144$), anxiety (HADS-A: $F(196)= 15.06$, $p< .001$, $\eta^2= .135$), as well as cognitive and motor fatigue (FSMC cognitive: $F(196)= 32.46$, $p< .001$, $\eta^2= .253$; motor: $F(196)= 46.19$, $p< .001$, $\eta^2= .325$).

Table 2. Cognitive profile, affective state, and fatigue of MS patients and HC

Neuropsychological Tests/PROMs	**MS Patients (N=102)**	**HC (N=94)**
	Mean (SD)	Mean (SD)
Digit span forward	7.00 (1.85)	8.11 (1.65)
Block-tapping test forward	8.17 (1.83)	9.39 (1.77)
Digit span backwards	5.75 (1.97)	6.81 (1.86)
Block-tspping test backwards	8.45 (6.70)	10.59 (10.89)
VLMT total	50.55 (11.45)	59.31 (8.05)
VLMT delayed recall	10.14 (3.94)	12.78 (2.64)
VLMT recognition	13.37 (2.60)	14.48 (0.86)
BVMT-R total	24.55 (8.04)	28.20 (5.49)
BVMT-R delayed recall	9.73 (2.88)	10.85 (1.73)
BVMT-R recognition	5.65 (0.94)	5.87 (0.42)
TAP divided attention (auditory)	657.82 (159.65)	613.09 (111.74)
TAP divided attention (visual)	871.54 (214.88)	757.03 (95.60)
TAP incompatibility	573.99 (180.83)	501.68 (109.98)
SDMT	50.13 (13.31)	59.77 (9.33)
RWT – S	18.99 (7.16)	24.47 (7.01)
COWAT	34.25 (9.95)	43.77 (12.11)
Matrices	17.16 (4.81)	19.51 (3.13)
Cognitive fatigue	30.12 (12.05)	18.46 (7.50)
Motor fatigue	31.83 (11.60)	18.34 (7.31)
Depression	5.81 (4.20)	2.96 (2.64)
Anxiety	7.19 (4.48)	4.29 (2.55)

PROMs = Patient-Reported Outcome Measures; HC = Healthy Controls; VLMT = Verbal Learning Memory Test; BVMT-R = Brief Visuospatial Memory Test—Revised; TAP = Testbatterie zur Aufmerksamkeitsprüfung; SDMT = Symbol Digit Modalities Test; RWT = Regensburger Wortflüssigkeitstest; COWAT = Controlled Oral Word Association Test; FSMC = Fatigue Scale for Motor and Cognitive Functions; HADS = Hospital Anxiety and Depression Scale. Table recreated/modified from Balz et al. (2025a) [S2], page 6-7, licensed under CC BY 4.0.

3.3.2 Diagnostic Performance of TRACK-MS-R

Compared to the gold standard BICAMS-M, TRACK-MS-R showed a high sensitivity of 97.44%, providing evidence for the validity of a screening tool, and a moderate specificity of 62.90% (Figure 2A). When compared to HC, TRACK-MS-R in MS patients achieved a high specificity of 82.98%, indicating the validity as a cognitive marker, and a low sensitivity of 59.80% (Figure 2B).

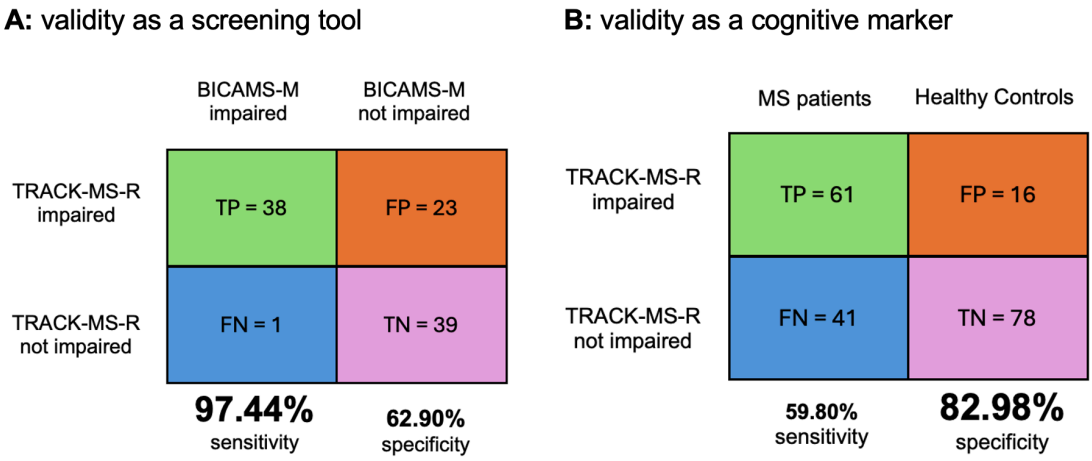


Figure 2. Validity of TRACK-MS-R. Standard 2x2 contingency tables demonstrating the psychometric performance of TRACK-MS-R as a screening tool (A) and as a cognitive marker (B). The matrices show true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) to assess sensitivity and specificity. (A): categorization of MS patients using TRACK-MS-R in comparison to the gold standard BICAMS-M. (B): performance of TRACK-MS-R in distinguishing MS patients from healthy controls. Reprinted from Balz et al. (2025a) [S2], page 7, licensed under CC BY 4.0.

3.4 Conclusion

This study [S2] introduced TRACK-MS-R as a culturally adapted, reliable, and time-efficient (less than 5 minutes) screening tool that reliably addresses cognitive profile in daily MS care. TRACK-MS-R demonstrated a high sensitivity (97.44%) and a moderate specificity (82.98%) in detecting CI in MS. This new approach thus may have high potential to improve early diagnosis of MS and reduce underdiagnosis in clinical settings [41, 99]. Compared to the gold standard BICAMS-M, TRACK-MS-R offers practical advantages due to its brief administration time and ease of use. It thus allows for improved detection of non-motor symptoms in various clinical settings, including outpatient clinics and general practice. Using the German version of VF measures (RWT), its cultural adaptation improves linguistic validity and supports broader use also in international (research) settings, as normative data for VF are available in many different languages [100]. While the TRACK-MS-R screening tool does not directly assess memory domains, its EF component measures essential cognitive processes impacted in MS [101].
Overall, these findings emphasize that TRACK-MS-R is a clinically feasible instrument for detecting CI in MS and highlight its importance for future long-term monitoring and research use.

4 Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust [S3]

4.1 Relevance

This study [S3] addressed the impact of non-motor symptoms, especially fatigue, on MS patients' capacity to psychosocially adapt to the mental impact of MS on patients' lives. The aim was to investigate psychosocial adjustment (PSA) in MS, with a particular focus on fatigue as a potential predictor. PSA is a complex and dynamic process along a disease trajectory. There is a vast discussion on how to best describe PSA. Among others, key indicators in the context of PSA are considered to include physical (PQoL), mental (MQoL), subjective QoL (SQoL), and the level of depressive symptoms [102, 103]. Measures of these constructs may allow for a snapshot in time of how well a patient facilitated PSA in the course of a disease. There is no consensus on how to best measure QoL in different diseases. According to an eudaimonic approach, HRQoL, which covers physical (PQoL) and mental aspects (MQoL), addresses a patient's capacity to achieve meaning and purpose in life according to physical fitness and capacity. Thus, measures of HRQoL often strongly correlate with disease severity. HRQoL approaches tend to overlook hedonic and emotional aspects of well-being, which are central to understanding PSA [104]. Contrary, SQoL, which reflects an individual's evaluation of life satisfaction and emotional well-being, rather refers to a hedonic approach. SQoL has been shown to be a stronger predictor of PSA than physical disability alone [24, 102, 103]. Using a comparative approach with Amyotrophic Lateral Sclerosis (ALS), the study further explored how different disease trajectories shape PSA outcomes. ALS, as a neurodegenerative disease, was chosen as a comparison group because, despite major differences in etiology and disease progression, it shares certain challenges with MS, such as motor impairment, cognitive decline in subgroups, and reduced HRQoL, providing a nuanced perspective on the role of non-motor symptoms. Further, the study aimed to address the question of whether the subjective burden in MS can be solely explained by physical disability or rather is affected by fatigue, depression, and QoL.

4.2 Materials and Methods

In this cross-sectional prospective study, seventy-seven patients with clinically confirmed MS according to the revised McDonald criteria [83] and thirty with ALS according to the revised El-Escorial criteria [105], all attending the out- and inpatient Neurology clinics at Ulm University, were consecutively recruited. Data collection periods spanned 12 months for MS (2024) and 7 months for ALS patients (2022). Inclusion criteria required a confirmed diagnosis of either MS or ALS, while exclusion criteria focused on significant language barriers and physical limitations

that would prevent participation. Ethical approval (No. 335/23, No. 381/19) was obtained from the Ethics Committee of Ulm University.
QoL was evaluated using validated PROMs: the Anamnestic Comparative Self-Assessment (ACSA) [80, 106] was used to measure SQoL. It is a global, generic, and widely used instrument that captures QoL independently of physical impairments. The Short-Form Survey 12 Questionnaire (SF-12) [107] was used to measure mental (MQoL) and physical (PQoL) components of HRQoL. Depression was assessed using the HADS-D [89] in MS and the ALS-specific ALS Depression Inventory (ADI-12) [108] in ALS. To allow comparison between groups, depression severity was expressed as a percentage of total scores. Fatigue was evaluated in the MS group using the FSMC [59], which measures both motor and cognitive fatigue aspects.
For statistical analysis, a confirmatory factor analysis (CFA) was conducted in R to test a latent PSA construct using depression and QoL as indicators. Additionally, group comparisons (MS vs. ALS) and multiple regressions were performed in SPSS version 29 to assess the predictive role of fatigue on PSA. Statistical significance was set at $p< 0.05$.

4.3 Results

4.3.1 Participant Characteristics and Clinical Parameters

Most MS patients had RRMS (64.9%), while 20.8% had SPMS and 14.3% PPMS. Compared to ALS patients, MS patients were significantly younger ($t(105)= -3.47$, $p< .001$), mostly female ($\chi^2(1)= 5.45$, $p= .020$), and had a longer disease duration ($t(104)= 5.11$, $p< .001$). Overall, MS patients showed mild physical disability, as indicated by lower EDSS scores [109] (mean EDSS ≤ 3.5). ALS patients showed moderate physical impairment according to ALS-FRS-R scores (mean ALS-FRS-R score = 36), suggesting a more advanced disease stage (ALS-FRS-R scores 34-41 correspond to King's stage 2 [110]).

4.3.2 Psychosocial Adjustment in MS

Confirmed by the fit indices Chi-squared ($\chi^2= 8.29$, $p= .016$), Root Mean Square Error of Approximation (RMSEA; 0.202, cut-off <0.05), and Comparative Fit Index (CFI; 0.933, cut-off >0.95), the CFA showed a poor fit for the PSA model. In particular, the RMSEA value surpassed the threshold, and the CFI fell slightly below the cut-off, indicating a poor model fit. However, the Standardized Root Mean Square Residual (SRMR; 0.059, cut-off <0.08) was within acceptable limits, suggesting that some aspects of the model residuals were reasonably accounted for [111]. Although the model fit was mainly poor, depression emerged as the most influential indicator of PSA ($\lambda= -0.93$, $p= .000$). Other significant indicators included SQoL ($\lambda= 0.60$, $p= .000$), MQoL ($\lambda= 0.75$, $p= .000$), and PQoL ($\lambda= 0.34$, $p= .006$).

4.3.3 *Predictors of Psychosocial Adjustment in MS*

The regression analyses revealed that both motor and cognitive fatigue significantly predicted depression and all dimensions of QoL. Therefore, motor fatigue was a significant predictor of depression (β= 0.190, t(75)= 5.37, p< .001, 27.8% explained variance), SQoL (β= −0.073, t(75)= −4.08, p< .001, 18.2% explained variance), MQoL (β= −0.441, t(75)= −4.40, p< .001, 20.5% explained variance), and PQoL (β= −0.643, t(75)= −8.57, p< .001, 49.5% explained variance). Similarly, cognitive fatigue predicted depression (β= 0.168, t(75)= 4.80, p< .001, 23.5% explained variance), SQoL (β= −0.059, t(75)= −3.30, p= .001, 12.7% explained variance), MQoL (β= −0.476, t(75)= −5.12, p< .001, 25.8% explained variance), and PQoL (β= −0.386, t(75)= −4.23, p< .001, 19.3% explained variance) (Figure 3).

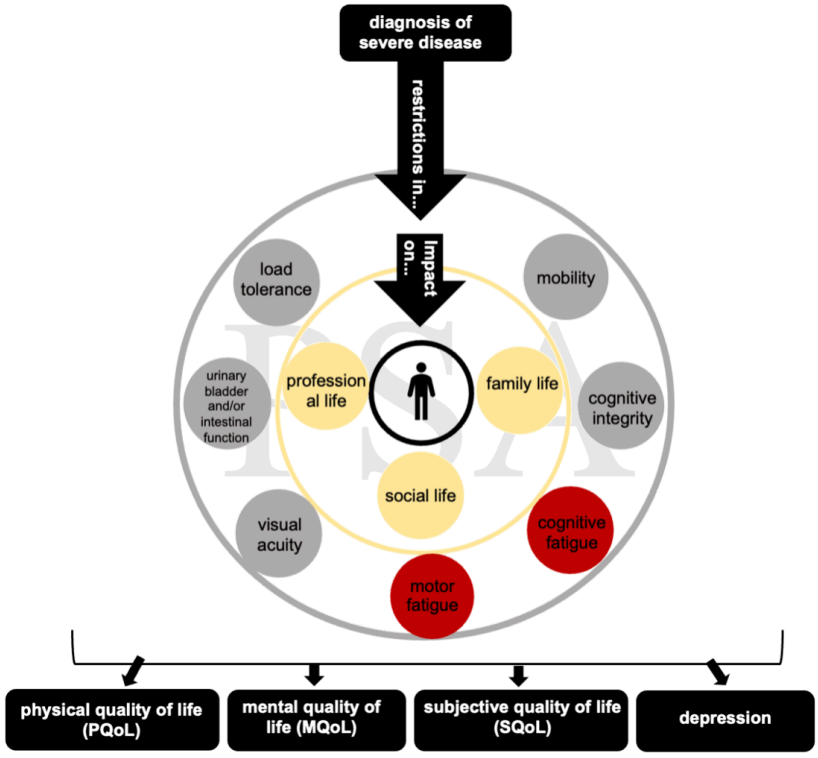


Figure 3. Psychosocial adjustment (PSA) in MS. Framework for PSA to a severe neurological diagnosis with potential outcomes (black squares). The gray/yellow rings illustrate the various stages patients must adjust to after receiving a diagnosis of a chronic neurological disease, like MS, or a fatal diagnosis, like ALS (outer ring: internal factors; inner ring: external factors; all characterized by the literature). The red circles indicate possible extra predictors of PSA that were examined in this study. Reprinted from Balz et al. (2025b) [S3], page 6, licensed under CC BY 4.0.

4.3.4 *Psychosocial Adjustment in MS vs. ALS*

MS patients exhibited significantly higher SQoL (t(41.735)= 2.10, p= .042; d= 0.50), significantly higher PQoL (t(105)= 3.64, p< .001; d= 0.78), and significantly reduced levels of depression (%) (t(105)= −6.18, p< .001; d= −1.33) in comparison to ALS

patients. No notable difference in MQoL ($t(105)= -0.90$, $p= 0.373$; $d= -0.19$) was observed between the groups.

4.4 Conclusion

In conclusion, this study [S3] deepened the understanding of PSA in MS patients, providing disease-specific insights and comparative findings with ALS. It showed that, despite MS being a chronic and disabling condition, many patients report surprisingly stable and neutral-to-positive outcomes regarding their SQoL and MQoL, at least in mild disease stages, as reported in the current study. These findings challenge previous assumptions in the literature [74, 78, 112, 113, 114, 115, 116], which often described a mainly decreased QoL in MS, primarily based on HRQoL and physical functioning (EDSS) measures. Further, the results indicate that to truly understand PSA in MS, subjective and hedonic aspects of QoL need to be more thoroughly incorporated into clinical assessments. Motor and cognitive fatigue also significantly contributed to PSA, negatively affecting all aspects of QoL and resulting in higher levels of depression, which in turn was the strongest indicator linked to poor PSA in MS. This supports including fatigue management and psychotherapy as essential elements of treatment in MS [20]. Compared to ALS patients, MS patients reported lower levels of depression and higher PQoL and SQoL. One explanation may lie in the differences in disease progression and treatment options: whereas ALS is characterized by a rapid and irreversible decline with only very limited treatment options of modest efficacy, MS typically shows a more moderate disease progression and benefits from a broad range of established DMTs. This relative stability may help preserve physical functioning and thereby facilitate a more positive subjective evaluation of QoL in MS. Interestingly, despite their fundamentally different disease trajectories and prognoses (MS is a chronic disease, and ALS is a fatal disease), MS and ALS patients showed similar levels of MQoL. This suggests that psychosocial burden is not only determined by disease severity or progression but also by the individual coping strategies that patients develop, which aligns with recent literature [80, 117, 118]. These coping strategies may be similar in different diseases, according to the current study.

In summary, this paper [S3] showed that PSA and maintaining high QoL are possible in MS despite visible physical disability, and they vary by disease progression, symptom burden, especially fatigue and depression. The study also highlighted that non-motor symptoms are crucial in shaping the lived experience of MS and warrant more focus in clinical practice and research. However, the current model of PSA in MS might be incomplete. The poor fit of the fit indices in the CFA suggests the need for a more comprehensive model that includes additional psychosocial resources, such as resilience or social support [119, 120, 121]. These resources may help reduce fatigue and depression and should be examined in future research and psychotherapeutic settings.

It is important to note that limitations such as the cross-sectional design of the study and the lack of assessment of cognitive functions in these patients highlight the need for longitudinal studies and comprehensive research that includes cognitive

functions. The dynamics and causal pathways of PSA in MS can only be fully understood through such approaches and subsequently effectively supported.

5 Synthesis and Outlook

This cumulative dissertation aimed to investigate the impact of MS on non-motor cerebral functions, like CI, fatigue, depression, and reduced QoL, and how these shape patients' lived experiences. Drawing on three interrelated studies [S1, S2, S3], this work offers consistent evidence that these symptoms are not just peripheral or reactive to physical disability, but are fundamental, inherent aspects of the disease process.

Cognitive deficits have emerged as a stable and clinically significant non-motor symptom of MS, impacting domains such as attention, memory, and EF in both RRMS and progressive subtypes (SPMS and PPMS). Notably, even without measurable physical decline over one year, cognitive deficits persisted. This challenges the traditional focus on motor symptoms as the leading indicator of disease burden and progression [15, 16, 39]. Instead, it shows that MS causes extensive brain damage with specific and lasting effects on cognition, which may slowly weaken daily functioning, employment status, and QoL long before visible physical disabilities appear [20, 26, 28, 30]. Therefore, early detection of impairment in cognitive functions is crucial. In response to the practical limitations (e.g., time constraints or a limited workforce) of comprehensive neuropsychological assessments in clinical and outpatient settings [44], this dissertation also evaluated the psychometric performance of a revised version of a brief cognitive screening tool designed for use in various healthcare settings. As a cognitive screening tool, TRACK-MS-R showed a high sensitivity using the gold-standard BICAMS-M as a reference, and demonstrated a good specificity as a cognitive marker of MS compared to HC. Its robust psychometric performance validates the integration of cognitive screening, particularly TRACK-MS-R, into clinical MS care, especially considering time and resource constraints in outpatient settings. Importantly, this contribution also highlights the general principle that early, resource-efficient detection of CI can guide timely pharmacological and psychotherapeutic interventions, before deficits consolidate or become functionally disabling [17, 28, 32, 40].

Beyond CI, the psychosocial impact and burden of MS became clear in the comparative analysis with ALS. Despite ALS being a fatal disease with a faster progression of physical disability, patients with MS reported similar MQoL. This intuitive paradoxical insight prompts a re-evaluation of how patients perceive living with chronic illness. The unpredictable nature of MS, along with its subjective and thus invisible to outsiders symptoms, especially fatigue, can gradually undermine psychological resilience in ways that are different from, but just as serious as, the challenges of an incurable diagnosis. Fatigue emerged as a key factor in decreased PSA, affecting both motor and cognitive areas and strongly linked to higher depression levels and lower QoL.

Taken together, these findings show that non-motor symptoms are not only common but also significant because they affect daily functioning, shape perceptions of the disease, and influence the ability to cope with and adapt to MS. More importantly, these symptoms may be parameterised using validated tools to provide evidence

for non-motor symptoms to evolve early and change during the disease course [8, 24, 28, 47]. The cumulative evidence presented in this dissertation redefines MS as a disease that goes beyond inflammation, demyelination, and physical disability; it is a cerebral, systemic condition with various non-motor symptoms, which require a multidimensional approach to care, further reinforcing its reputation as “the disease of a thousand faces” [122].

Several clinical and scientific implications arise from this work. First, non-motor symptoms should be regularly assessed in both clinical and non-clinical settings. Brief cognitive screening tools such as TRACK-MS-R provide accessible methods for early detection of cognitive deficits and can inform further diagnostic or therapeutic steps. Second, fatigue – primarily cognitive fatigue – should not just be seen as a bothersome complaint but as a possible disease-modifying symptom. Its widespread effects on cognition, mood, QoL [19, 21], and overall PSA make it a priority for therapeutic interventions. Third, the results highlight the need for integrated, multidisciplinary care models tailored to the individual symptom profile of each patient.

Future research should focus on longitudinal designs to track the natural progression of the non-motor burden of MS, particularly in response to DMTs, cognitive therapy, and psychotherapeutic interventions. There is also an urgent need for randomized trials that directly target these symptoms, using different therapeutic approaches, i.e., cognitive training, mindfulness-based interventions, psychotherapy, or structured fatigue management programs. Digital tools and ecological momentary assessment through Apps (i.e., Floodlight MS [123], MSCopilot [124]) could provide scalable, real-world monitoring of symptom changes, enabling new opportunities for personalized, data-driven care [125, 126]. Finally, the needs and perspectives of patients must remain central to all considerations. The lived experience, measured through PROMs, is crucial for creating care models that focus on what truly matters to patients with MS.

In summary, this dissertation emphasizes that the non-motor impact of MS is neither rare nor incidental – it is fundamental. Non-motor symptoms influence cognition, mood, and QoL in significant ways. It may thus be assumed that it deserves attention equal to that given to motor function or radiological evidence of MRI alterations. Recognizing, assessing, and managing these symptoms will not only improve clinical outcomes but also enhance independence, dignity, and well-being in patients living with MS.

6 Abstract

Multiple Sclerosis (MS) is characterized by demyelination and inflammation, leading to progressive physical disability. Historically, the medical community has conceptualized MS primarily as a motor disease. However, increasing evidence indicates that non-motor symptoms, especially cognitive impairment (CI), fatigue, and depression, are central features of the disease with a significant impact on quality of life (QoL). Yet, understanding and tracking these core features of MS is limited so far. This gap is approached by this cumulative dissertation. Non-motor cerebral functions and QoL were systematically analyzed to determine cerebral and psychosocial burden of MS. It integrates findings from three peer-reviewed studies that explored cognition, fatigue, and psychopathology (depression and anxiety) in MS over one year (S1), evaluate the diagnostic performance of a brief cognitive screening tool (TRACK-MS-R; S2), and analyze patient's capacity for psychosocial adjustment (PSA; S3) in MS in comparison to Amyotrophic Lateral Sclerosis (ALS).
S1: To investigate the progression of CI, fatigue, and psychopathology across different MS subtypes (relapsing-remitting MS, RRMS; secondary progressive MS, SPMS; primary progressive MS, PPMS), a one-year longitudinal study was conducted. The findings indicated that cognitive deficits in attention, memory, and executive functions were more pronounced in progressive subtypes (SPMS and PPMS), particularly in SPMS. At the same time, RRMS patients showed slight improvements, possibly due to cognitive reserve, disease stability, or disease-modifying therapies (DMTs). Notably, these cognitive deficits appeared largely independent of physical disability and psychopathology, indicating distinct underlying mechanisms. Fatigue and psychopathology were common across all subtypes and remained relatively stable over time. These findings emphasize the need for comprehensive, symptom-specific monitoring of non-motor symptoms in clinical MS care.
S2: To validate a revised version of the brief cognitive screening tool TRACK-MS (TRACK-MS-R), its psychometric performance was evaluated, showing a high sensitivity (97.44%) compared to the gold standard Brief International Cognitive Assessment for MS (BICAMS-M) and a good specificity (82.98%) in distinguishing MS patients from healthy controls (HC). TRACK-MS-R proved to be a quick (less than 5 minutes), reliable, and culturally adapted cognitive screening tool suitable for routine clinical and non-clinical settings. These findings highlight the clinical utility of accessible screening tools for early detection of CI in MS, particularly in settings with limited workforce and time constraints.
S3: PSA and QoL outcomes in MS patients were evaluated using patient-reported outcome measures (PROMs). PSA outcomes in MS were compared to those in ALS patients, with different etiology and disease course, but possible overlap in physical restrictions. Results showed that, despite physical disability and the ongoing burden of chronic illness, many MS patients reported neutral-to-positive subjective (SQoL) and mental QoL (MQoL). Both cognitive and motor fatigue were identified as key negative predictors of PSA. Interestingly, MS and ALS patients reported similar levels of MQoL, suggesting that disease progression and physical disability alone

do not determine how patients adapt to a severe diagnosis; coping strategies likely play a crucial role. The findings also highlight the need to revise existing PSA models in MS by including additional psychosocial resources, such as resilience and social support, and highlight the importance of mental health and fatigue management in clinical practice.

Overall, these findings challenge the common belief that MS-related disability is mainly physical. Instead, they provide a comprehensive view of MS as a cerebral and systemic disorder in which non-motor symptoms are central to the patient experience and clinical course. These symptoms are invisible to outsiders, persistent, and predictive of decreased QoL, even in the early stages of the disease. Due to time constraints and limited resources, these are often overlooked in routine care. The findings advocate for integrating cognitive and psychological screening into standard MS management, adopting multidisciplinary care models, and developing interventions that specifically target non-motor symptoms. By focusing on the non-motor impact of MS, this dissertation provides a more comprehensive understanding of the disease. It considers not only neurological damage but also the invisible burdens that impact daily life, resilience, and overall QoL.

7 References

International peer-reviewed journal articles included in this cumulative dissertation:

[S1] Taranu D., Balz L.T., Holbrook J., Tumani V., Schreiber H., Tumani H. & Uttner I. Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study. *Journal of Neurol*ogy 2025;272(6):398. doi:10.1007/s00415-025-13115-y

[S2] Balz, L. T., Uttner, I., Taranu, D., Erhart, D. K., Fangerau, T., Jung, S., Schreiber, H., Senel, M., Vardakas, I., Lule, D. E. & Tumani, H. Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis. *Biomedicines* 2025a;13(8):1902. doi: 10.3390/biomedicines13081902

[S3] Balz, L.T., Uttner, I., Weishaupt, J., Ludolph, A.C., Taranu, D., Vardakas, I., Jung, S., Fangerau, T., Erhart, D.K., Senel, M., Tumani, H. & Lulé, D. Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust. *Brain Sciences 2025b;15(7):745. doi:10.3390/brainsci15070745*

Articles cited in this cumulative dissertation:

1. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vecsei L, Milanov I. The epidemiology of multiple sclerosis in Europe. Eur J Neurol. 2006;13(7):700-22. doi: 10.1111/j.1468-1331.2006.01342.x

2. Ford H. Clinical presentation and diagnosis of multiple sclerosis. Clin Med (Lond). 2020;20(4):380-3. doi: 10.7861/clinmed.2020-0292

3. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018;391(10130):1622-36. doi: 10.1016/S0140-6736(18)30481-1

4. Elliott C, Belachew S, Wolinsky JS, Hauser SL, Kappos L, Barkhof F, Bernasconi C, Fecker J, Model F, Wei W, et al. Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. Brain. 2019;142(9):2787-99. doi: 10.1093/brain/awz212

5. Petracca M, Pontillo G, Moccia M, Carotenuto A, Cocozza S, Lanzillo R, Brunetti A, Brescia Morra V. Neuroimaging Correlates of Cognitive Dysfunction in Adults with Multiple Sclerosis. Brain Sci. 2021;11(3). doi: 10.3390/brainsci11030346

6. Chen Y, Haacke EM, Bernitsas E. Imaging of the Spinal Cord in Multiple Sclerosis: Past, Present, Future. Brain Sci. 2020;10(11). doi: 10.3390/brainsci10110857

7. Louapre C, Govindarajan ST, Gianni C, Madigan N, Nielsen AS, Sloane JA, Kinkel RP, Mainero C. The association between intra- and juxta-cortical pathology and cognitive impairment in multiple sclerosis by quantitative T(2)* mapping at 7 T MRI. Neuroimage Clin. 2016;12:879-86. doi: 10.1016/j.nicl.2016.11.001

8. Louapre C, Perlbarg V, Garcia-Lorenzo D, Urbanski M, Benali H, Assouad R, Galanaud D, Freeman L, Bodini B, Papeix C, et al. Brain networks disconnection in early multiple sclerosis cognitive deficits: an anatomofunctional study. Hum Brain Mapp. 2014;35(9):4706-17. doi: 10.1002/hbm.22505

9. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, Atzori M, Bernardi V, Barachino L, Rinaldi L, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol. 2009;66(9):1144-50. doi: 10.1001/archneurol.2009.174

10. Rocca MA, Valsasina P, Hulst HE, Abdel-Aziz K, Enzinger C, Gallo A, Pareto D, Riccitelli G, Muhlert N, Ciccarelli O, et al. Functional correlates of cognitive dysfunction in multiple sclerosis: A multicenter fMRI Study. Hum Brain Mapp. 2014;35(12):5799-814. doi: 10.1002/hbm.22586

11. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278-86 doi: 10.1212/WNL.0000000000000560

12. Brochet B, Ruet A. Cognitive Impairment in Multiple Sclerosis With Regards to Disease Duration and Clinical Phenotypes. Front Neurol. 2019;10:261. doi: 10.3389/fneur.2019.00261

13. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol. 2007;6:903-12. doi: 10.1016/S1474-4422(07)70243-0

14. Filippi M, Amato MP, Avolio C, Gallo P, Gasperini C, Inglese M, Marfia GA, Patti F. Towards a biological view of multiple sclerosis from early subtle to clinical progression: an expert opinion. J Neurol. 2025;272(2):179. doi: 10.1007/s00415-025-12917-4

15. Pearce JM. Historical descriptions of multiple sclerosis. Eur Neurol. 2005;54(1):49-53. doi: 10.1159/000087387

16. Nocentini U. Focus or Neglect on Cognitive Impairment Following the History of Multiple Sclerosis. NeuroSci. 2023;4(1):0. doi: 10.3390/neurosci4010008

17. Piacentini C, Argento O, Nocentini U. Cognitive impairment in multiple sclerosis: "classic" knowledge and recent acquisitions. Arq Neuropsiquiatr. 2023;81(6):585-96. doi: 10.1055/s-0043-1763485

18. Schild AK, Goereci Y, Scharfenberg D, Klein K, Lulling J, Meiberth D, Schweitzer F, Sturmer S, Zeyen P, Sahin D, et al. Multidomain cognitive impairment in non-hospitalized patients with the post-COVID-19 syndrome: results from a prospective monocentric cohort. J Neurol. 2023;270(3):1215-23. doi: 10.1007/s00415-022-11444-w

19. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult Scler. 2001;7:340-4. doi: 10.1177/135245850100700511

20. Oliva Ramirez A, Keenan A, Kalau O, Worthington E, Cohen L, Singh S. Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. BMC Neurol. 2021;21(1):468. doi: 10.1186/s12883-021-02396-1

21. Schmidt S, Jöstingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: Results of a cross-sectional study. Mult Scler Relat Disord. 2019;35:262-9. doi: 10.1016/j.msard.2019.07.029

22. Tranfa M, Iuzzolino VV, Perrella P, Carotenuto A, Pontillo G, Moccia M, Cocozza S, Elefante A, Lanzillo R, Brunetti A, et al. Exploring the relation between reserve and fatigue in multiple sclerosis. Mult Scler Relat Disord. 2023;76:104842. doi: 10.1016/j.msard.2023.104842

23. Kaya Aygunoglu S, Celebi A, Vardar N, Gursoy E. Correlation of Fatigue with Depression, Disability Level and Quality of Life in Patients with Multiple Sclerosis. Noro Psikiyatr Ars. 2015;52(3):247-51. doi: 10.5152/npa.2015.8714

24. Strober LB. Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model. Disabil Health J. 2018;11(4):555-61. doi: 10.1016/j.dhjo.2018.05.003

25. Matias-Guiu JA, Cortes-Martinez A, Valles-Salgado M, Oreja-Guevara C, Pytel V, Montero P, Moreno-Ramos T, Matias-Guiu J. Functional Components of Cognitive Impairment in Multiple Sclerosis: A Cross-Sectional Investigation. Front Neurol. 2017;8:643. doi: 10.3389/fneur.2017.00643

26. Macias Islas MA, Ciampi E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. Biomedicines. 2019;7(1). doi: 10.3390/biomedicines7010022

27. Huijbregts SC, Kalkers NF, De Sonneville LM, De Groot V, Reuling IE, Polman CH. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology. 2004;63:335-9. doi: 10.1212/01.wnl.0000129828.03714.90

28. Oset M, Stasiolek M, Matysiak M. Cognitive Dysfunction in the Early Stages of Multiple Sclerosis-How Much and How Important? Curr Neurol Neurosci Rep. 2020;20(7):22. doi: 10.1007/s11910-020-01045-3

29. Stavrogianni K, Giannopapas V, Kitsos DK, Christouli N, Smyrni V, Chasiotis AK, Akrivaki A, Dimitriadou EM, Tzartos JS, Tsivgoulis G, et al. Cognitive Impairment in Newly Diagnosed Patients with Multiple Sclerosis: A Systematic Review of Related Molecular Biomarkers and a Meta-Analysis of Associated Demographic and Disease-Related Characteristics. J Clin Med. 2025;14(8). doi: 10.3390/jcm14082630

30. Marrie RA, Patten SB, Berrigan LI, Tremlett H, Wolfson C, Warren S, Leung S, Fiest KM, McKay KA, Fisk JD, et al. Diagnoses of Depression and Anxiety Versus Current Symptoms and Quality of Life in Multiple Sclerosis. Int J MS Care. 2018;20(2):76-84. doi: 10.7224/1537-2073.2016-110

31. Chiaravalloti ND, De Luca J. Cognitive impairment in multiple sclerosis. Lancet Neurology. 2008;7:1139–51. doi: 10.1016/S1474-4422(08)70259-X

32. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020;19(10):860-71. doi: 10.1016/S1474-4422(20)30277-5

33. Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. J Neurol Sci. 2006;245(1-2):41-6. doi: 10.1016/j.jns.2005.08.019

34. Kavaliunas A, Danylaite Karrenbauer V, Binzer S, Hillert J. Systematic Review of the Socioeconomic Consequences in Patients With Multiple Sclerosis With Different Levels of Disability and Cognitive Function. Front Neurol. 2021;12:737211. doi: 10.3389/fneur.2021.737211

35. Brochet B, Clavelou P, Defer G, De Seze J, Louapre C, Magnin E, Ruet A, Thomas-Anterion C, Vermersch P. Cognitive Impairment in Secondary Progressive Multiple Sclerosis: Effect of Disease Duration, Age, and Progressive Phenotype. Brain Sci. 2022;12(2). doi: 10.3390/brainsci12020183

36. Comi G, Filippi M, Martinelli V, Campi A, Rodegher M, Alberoni M, Sirabian G, Canal N. Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. Journal of the Neurological Sciences. 1995;132:222-7 doi: 10.1016/0022-510x(95)00168-2

37. Ruet A, Deloire M, Charre-Morin J, Hamel D, Brochet B. Cognitive impairment differs between primary progressive and relapsing-remitting MS. Neurology. 2013;80:1501-8. doi: 0.1212/WNL.0b013e31828cf82f

38. Benedict RHB, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R, Consortium MSOA. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler. 2017;23:721-33. doi: 10.1177/1352458517690821

39. Migliore S, Ghazaryan A, Simonelli I, Pasqualetti P, Squitieri F, Curcio G, Landi D, Palmieri MG, Moffa F, Filippi MM, et al. Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis Patients with Very Mild Clinical Disability. Behav Neurol. 2017;2017:7404289. doi: 10.1155/2017/7404289

40. NICE. Multiple sclerosis in adults: management London: National Institute for Health and Care Excellence (NICE); 2022. Report No.: NICE Guideline, No. 220

41. Elwick H, Smith L, Mhizha-Murira JR, Topcu G, Leighton P, Drummond A, Evangelou N, Das Nair R. Cognitive assessment in multiple sclerosis clinical care: A qualitative evaluation of stakeholder perceptions and preferences. Neuropsychol Rehabil. 2021;32(7). doi: 10.1080/09602011.2021.1899942

42. Wills O, Probst Y. Towards new perspectives: A scoping review and meta-synthesis to redefine brain health for multiple sclerosis. Eur J Neurol. 2024;31(6):e16210. doi: 10.1111/ene.16210

43. Kalb R, Beier M, Benedict RH, Charvet L, Costello K, Feinstein A, Gingold J, Goverover Y, Halper J, Harris C, et al. Recommendations for cognitive screening and management in multiple sclerosis care. Mult Scler. 2018;24(13):1665-80. doi: 10.1177/1352458518803785

44. Lechner-Scott J, Agland S, Allan M, Darby D, Diamond K, Merlo D, van der Walt A. Managing cognitive impairment and its impact in multiple sclerosis: An Australian multidisciplinary perspective. Mult Scler Relat Disord. 2023;79:104952. doi: 10.1016/j.msard.2023.104952

45. Bakirtzis C, Ioannidis P, Messinis L, Nasios G, Konstantinopoulou E, Papathanasopoulos P, Grigoriadis N. The Rationale for Monitoring Cognitive Function in Multiple Sclerosis: Practical Issues for Clinicians. Open Neurol J. 2018;12:31-40. doi: 10.2174/1874205X01812010031

46. Gromisch ES, DeLuca J, Benedict RHB, Foley FW. Managing Cognitive Dysfunction in Multiple Sclerosis: A Snapshot of Changes in Screening, Assessment, and Treatment Practices. Int J MS Care. 2022;24(3):104-9. doi: 10.7224/1537-2073.2020-139

47. Meca-Lallana JE, Casanova B, Rodriguez-Antiguedad A, Eichau S, Izquierdo G, Duran C, Rio J, Hernandez MA, Calles C, Prieto-Gonzalez JM, et al. Consensus on early detection of disease progression in patients with multiple sclerosis. Front Neurol. 2022;13:931014. doi: 10.3389/fneur.2022.931014

48. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, Hamalainen P, Hartung HP, Krupp L, Penner IK, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler. 2012;18(6):891-8. doi: 10.1177/1352458511431076

49. Filser M, Schreiber H, Pottgen J, Ullrich S, Lang M, Penner IK. The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS): results from the German validation study. J Neurol. 2018;265(11):2587-93. doi: 10.1007/s00415-018-9034-1

50. Potticary H, Langdon D. A Systematic Review and Meta-Analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations. J Clin Med. 2023;12(2). doi: 10.3390/jcm12020703

51. Broch L, Flemmen HO, Simonsen CS, Berg-Hansen P, Ormstad H, Brunborg C, Celius EG. Fatigue in multiple sclerosis is associated with socioeconomic factors. Mult Scler Relat Disord. 2022;64:103955. doi: 10.1016/j.msard.2022.103955

52. Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, Janardhan V, Dubey N, Kinkel PR. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler. 2000;6:181-5. doi: 10.1177/135245850000600308

53. Zimek D, Miklusova M, Mares J. Overview of the Current Pathophysiology of Fatigue in Multiple Sclerosis, Its Diagnosis and Treatment Options - Review Article. Neuropsychiatr Dis Treat. 2023;19:2485-97. doi: 10.2147/NDT.S429862

54. Barbi C, Pizzini FB, Tamburin S, Martini A, Pedrinolla A, Laginestra FG, Giuriato G, Martignon C, Schena F, Venturelli M. Brain Structural and Functional Alterations in Multiple Sclerosis-Related Fatigue: A Systematic Review. Neurol Int. 2022;14(2):506-35. doi: 10.3390/neurolint14020042

55. Chalah MA, Riachi N, Ahdab R, Creange A, Lefaucheur JP, Ayache SS. Fatigue in Multiple Sclerosis: Neural Correlates and the Role of Non-Invasive Brain Stimulation. Front Cell Neurosci. 2015;9:460. doi: 10.3389/fncel.2015.00460

56. Kampaite A, Gustafsson R, York EN, Foley P, MacDougall NJJ, Bastin ME, Chandran S, Waldman AD, Meijboom R. Brain connectivity changes underlying depression and fatigue in relapsing-remitting multiple sclerosis: A systematic review. PLoS One. 2024;19(3):e0299634. doi: 10.1371/journal.pone.0299634

57. Braley TJ, Chervin RD. Fatigue in Multiple Sclerosis: Mechanisms, Evaluation, and Treatment. SLEEP. 2010;33(8):1061-7. doi: 10.1093/sleep/33.8.1061

58. Rudroff T, Kindred JH, Ketelhut NB. Fatigue in Multiple Sclerosis: Misconceptions and Future Research Directions. Front Neurol. 2016;7:122. doi: 10.3389/fneur.2016.00122

59. Penner IK, Raselli C, Stöcklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognition Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 2009;15(12):1509-17. doi: 10.1177/1352458509348519

60. Bruce JM, Bruce AS, Arnett PA. Response variability is associated with self-reported cognitive fatigue in multiple sclerosis. Neuropsychology. 2010;24:77-83. doi: 10.1037/a0015046

61. Fidao A, De Livera A, Nag N, Neate S, Jelinek GA, Simpson-Yap S. Depression mediates the relationship between fatigue and mental health-related quality of life in multiple sclerosis. Multiple Sclerosis and Related Disorders. 2021;47. doi: 10.1016/j.msard.2020.102620

62. Marrie RA, Cohen J, Stuve O, Trojano M, Sorensen PS, Reingold S, Cutter G, Reider N. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler. 2015;21(3):263-81. doi: 10.1177/1352458514564491

63. Young CA, Langdon D, Rog D, Chhetri SK, Tanasescu R, Kalra S, Webster G, Nicholas R, Ford HL, Woolmore J, et al. Prevalence, treatment and correlates of depression in multiple sclerosis. Mult Scler Relat Disord. 2024;87:105648. doi: 10.1016/j.msard.2024.105648

64. ICD–10 Kapitel V (F) – Klinisch–diagnostische Leitlinien. In: Dilling H, Mombour W, Schmidt MH, editors. ICD-10: Internationale Klassifikation psychischer Störungen. 10., überarbeitete Auflage. Göttingen: Hogrefe; 2015.

65. Janssens ACJW, van Doorn PA, de Boer JB, van der Meché FGA, Passchier J, Hintzen RQ. Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. Acta Neurol Scand. 2003;108:389-95. doi: 10.1034/j.1600-0404.2003.00166.x

66. Sullivan MJ, Weinshenker B, Mikail S, Edgley K. Depression before and after diagnosis of multiple sclerosis. Mult Scler. 1995;1:104-8. doi: 10.1177/135245859500100208

67. Possa MF, Minacapelli E, Canale S, Comi G, Martinelli V, Falautano M. The first year after diagnosis: psychological impact on people with multiple sclerosis. Psychol Health Med. 2017;22:1063-71. doi: 10.1080/13548506.2016.1274043

68. Weiss DB, Dyrud J, House RM, Beresford TP. Psychiatric manifestations of autoimmune disorders. Curr Treat Options Neurol. 2005;7:413-7. doi: 10.1007/s11940-005-0033-z

69. Sangster E, Lanka N, Acharya P, Virani S, Afreen S, Perthiani A, Nassar ST. Factors Contributing to the Development of Neuropsychiatric Manifestations in Persons With Multiple Sclerosis: A Systematic Review. Cureus. 2024;16(8):e66432. doi: 10.7759/cureus.66432

70. Pucak ML, Carroll KAL, Kerr DA, Kaplin AI. Neuropsychiatric manifestations of depression in multiple sclerosis: neuroinflammatory, neuroendocrine, and neurotrophic mechanisms in the pathogenesis of immune-mediated depression. Dialogues Clin Neurosci. 2007;9(2):125-39. doi: 10.31887/DCNS.2007.9.2/mpucak

71. Beal C, Stuifbergen AK, Sands DV, Brown A. Depression in Multiple Sclerosis: A Longitudinal Analysis. Arch Psychiatr Nurs. 2007;21:181-91. doi: 10.1016/j.apnu.2007.02.008

72. Freedman DE, Oh J, Kiss A, Puopolo J, Wishart M, Meza C, Feinstein A. The influence of depression and anxiety on cognition in people with multiple sclerosis: a cross-sectional analysis. J Neurol. 2024;271(8):4885-96. doi: 10.1007/s00415-024-12409-x

73. Kopchak OO, Odintsova TA. Cognitive impairment and depression in patients with relapsing-remitting multiple sclerosis depending on age and neuroimaging findings. Egypt J Neurol Psychiatr Neurosurg. 2021;57(1):119. doi: 10.1186/s41983-021-00376-3

74. Sehanovic A, Kunic S, Ibrahimagic OC, Smajlovic D, Tupkovic E, Mehicevic A, Zoletic E. Contributing Factors to the Quality of Life in Multiple Sclerosis. Med Arch. 2020;74(5):368-73. doi: 10.5455/medarh.2020.74.368-373

75. Bogosian A, Day F, Norton S, Silber E, Sakel M, Sharrack B, Moss-Morris R. Key demographics and psychological skills associated with adjustment to progressive Multiple Sclerosis early in the diagnosis. Front Rehabil Sci. 2022;3:966133. doi: 10.3389/fresc.2022.966133

76. Senders A, Bourdette D, Hanes D, Yadav V, Shinto L. Perceived stress in multiple sclerosis: the potential role of mindfulness in health and well-being. J Evid Based Complementary Altern Med. 2014;19(2):104-11. doi: 10.1177/2156587214523291

77. Batista AR, Silva S, Lencastre L, Guerra MP. Biopsychosocial Correlates of Quality of Life in Multiple Sclerosis Patients. Int J Environ Res Public Health. 2022;19(21). doi: 10.3390/ijerph192114431

78. Lysandropoulos AP, Havrdova E, Paradig MSG. 'Hidden' factors influencing quality of life in patients with multiple sclerosis. Eur J Neurol. 2015;22 Suppl 2:28-33. doi: 10.1111/ene.12801

79. Zwibel HL, Smrtka J. improving Quality of Life in multiple Sclerosis: An unmet Need. Am J Manag Care. 2011;17.

80. Bernheim JL. How to get serious answers to the serious question: “How have you been?”: Subjective Quality of Life (QOL) as an individual experiental emergent construct. Bioethics. 1999;13(3):272 - 87.

81. Penner IK. Evaluation of cognition and fatigue in multiple sclerosis: daily practice and future directions. Acta Neurol Scand. 2016;134 Suppl 200:19-23. doi: 10.1111/ane.12651

82. Feys P, Giovannoni G, Dijsselbloem N, Centonze D, Eelen P, Lykke Andersen S. The importance of a multi-disciplinary perspective and patient activation programmes in MS management. Mult Scler. 2016;22(2 Suppl):34-46. doi: 10.1177/1352458516650741

83. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-73. doi: 10.1016/S1474-4422(17)30470-2

84. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills. 1977;44:67-73. doi: 10.2466/pms.1977.44.2.367

85. Helmstaedter C, Lendt M, Lux S. Verbaler Lern-und Merk- fähigkeitstest: VLMT: manual. 1 ed. Göttingen: Hogrefe Verlag; 2001.

86. Benedict RHB, Schretlen DS, Groninger L, Dobraski M. Revision of the brief Visuospatial Memory Test: Studies of normal performance, reliability and validity. Psychological Assessment. 1996;8:145–53. doi: 10.1037/1040-3590.8.2.145

87. Ross TP, Calhoun E, Cox T, Wenner C, Kono W, Pleasant M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. Arch Clin Neuropsychol. 2007;22. doi: 10.1016/j.acn.2007.01.026

88. Wechsler D. WAIS-R Manual: Wechsler Adult Intelligence Scale-revised. New York: Psychological Corporation; 1981.

89. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes. 2003;1:1:29. doi: 10.1186/1477-7525-1-29

90. Cao H, Peyrodie L, Agnani O, Cavillon F, Hautecoeur P, Donzé C. Evaluation of an Expanded Disability Status Scale (EDSS) modeling strategy in multiple sclerosis. Med Biol Eng Comput. 2015;53:1141-51. doi: 0.1007/s11517-015-1383-7

91. Wachowius U, Talley M, Silver N, Heinze HJ, Sailer M. Cognitive impairment in primary and secondary progressive multiple sclerosis. J Clin Exp Neuropsychol. 2005;27:65-77. doi: 10.1080/138033990513645

92. Planche V, Gibelin M, Cregut D, Pereira B, Clavelou P. Cognitive impairment in a population-based study of patients with multiple sclerosis: differences between late relapsing-remitting, secondary progressive and primary progressive multiple sclerosis. European Journal of Neurology. 2016;23:282-9 doi: 10.1111/ene.12715

93. Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. Psychiatry Investig. 2019;16(12):877-88. doi: 10.30773/pi.2019.0106

94. Taranu D, Tumani H, Holbrook J, Tumani V, Uttner I, Fissler P. The TRACK-MS Test Battery: A Very Brief Tool to Track Multiple Sclerosis-Related Cognitive Impairment. Biomedicines. 2022;10(11). doi: 10.3390/biomedicines10112975

95. Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test (RWT). Göttingen: Hogrefe; 2000.

96. Elwood RW. The Wechsler Memory Scale-Revised: psychometric characteristics and clinical application. Neuropsychol Rev. 1991;2:179-201. doi: 10.1007/BF01109053

97. Zimmermann P, Fimm B. Testbatterie Zur Aufmerksamkeitsprufung (TAP). Freiburg: Psytest; 1992.

98. Petermann F. Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV). 4 ed. Frankfurt am Main: Pearson Assessment; 2012.

99. DeLuca J, Chiaravalloti ND, Sandroff BM. Treatment and management of cognitive dysfunction in patients with multiple sclerosis. Nat Rev Neurol. 2020;16(6):319-32. doi: 10.1038/s41582-020-0355-1

100. Villalobos D, Torres-Simon L, Pacios J, Paul N, Del Rio D. A Systematic Review of Normative Data for Verbal Fluency Test in Different Languages. Neuropsychol Rev. 2023;33(4):733-64. doi: 10.1007/s11065-022-09549-0

101. Delgado-Alvarez A, Matias-Guiu JA, Delgado-Alonso C, Hernandez-Lorenzo L, Cortes-Martinez A, Vidorreta L, Montero-Escribano P, Pytel V, Matias-Guiu J. Cognitive Processes Underlying Verbal Fluency in Multiple Sclerosis. Front Neurol. 2020;11:629183. doi: 10.3389/fneur.2020.629183

102. Lulé D, Pauli S, Altintas E, Singer U, Merk T, Uttner I, Birbaumer N, Ludolph AC. Emotional adjustment in amyotrophic lateral sclerosis (ALS). J Neurol. 2012;259(2):334-41. doi: 10.1007/s00415-011-6191-x

103. Vazquez Medrano CR, Aho-Ozhan HEA, Weiland U, Uttner I, Ludolph AC, Lule D. Disease progression but not physical state per se determines mental wellbeing in ALS. J Neurol. 2020;267(12):3593-601. doi: 10.1007/s00415-020-10027-x

104. Hosseini Z, Homayuni A, Etemadifar M. Barriers to quality of life in patients with multiple sclerosis: a qualitative study. BMC Neurol. 2022;22(1):174. doi: 10.1186/s12883-022-02700-7

105. Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, Shefner J, ALS/MND WFNRGO. A revision of the El Escorial criteria - 2015. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(5-6):291-2. doi: 10.3109/21678421.2015.1049183

106. Bernheim JL, Theuns P, Mazaheri M, Hofmans J, Fliege H, Rose M. The Potential of Anamnestic Comparative Self-Assessment (ACSA) to Reduce Bias in the Measurement of Subjective Well-Being. Journal of Happiness Studies. 2006;7(2):227-50. doi: 10.1007/s10902-005-4755-0

107. Ware JE, Kosinski M, Keller SD. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. In: The Health Institute NEMC, editor. Boston, Massachusetts;1995.

108. Kübler A, Winter S, Kaiser J, Birbaumer N, Hautzinger M. Das ALS-Depressionsinventar (ADI). Zeitschrift für Klinische Psychologie und Psychotherapie. 2005;34(1):19-26. doi: 10.1026/1616-3443.34.1.19

109. Conradsson D, Ytterberg C, von Koch L, Johansson S. Changes in disability in people with multiple sclerosis: a 10-year prospective study. Journal of Neurology 2018;265:119-26. doi: 10.1007/s00415-017-8676-8

110. Mani VE, Thomas J. A study of the clinical characteristics and severity of amyotrophic lateral sclerosis from North India. J Health Res. 2021;8:232-8. doi: 10.4103/cjhr.cjhr_67_20

111. Hu LT, Bentler PM. Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria versus New Alternatives. Structural Equation Modeling. 1999;6:1 - 55. doi: 10.1080/10705519909540118

112. Twork S, Wiesmeth S, Spindler M, Wirtz M, Schipper S, Pohlau D, Klewer J, Kugler J. Disability status and quality of life in multiple sclerosis: non-linearity of the Expanded Disability Status Scale (EDSS). Health Qual Life Outcomes. 2010;8:55. doi: 10.1186/1477-7525-8-55

113. Ghaem H, Haghighi AB. The impact of disability, fatigue and sleep quality on the quality of life in multiple sclerosis. Ann Indian Acad Neurol 2008;11:236-41. doi: 10.4103/0972-2327.44559

114. Alshubaili AF, Ohaeri JU, Awadalla AW, Mabrouk AA. Quality of life in multiple sclerosis: a Kuwaiti MSQOL-54 experience. Acta Neurol Scand. 2008;117:384-92. doi: 10.1111/j.1600-0404.2007.00960.x

115. Miller A, Dishon S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. Qual Life Res. 2006;15:259-71. doi: 0.1007/s11136-005-0891-6

116. Aymerich M, Guillamón I, Jovell AJ. health-related quality of life assessment in people with multiple sclerosis and their family caregivers. A multicenter study in catalonia (southern europe). Patient Prefer Adherence. 2009;3:311-21. doi: 10.2147/ppa.s6217

117. Bueno A, Sayao A, Yousefi M, Devonshire V, Traboulsee A, Tremlett H. Health-related quality of life in patients with longstanding 'benign multiple sclerosis'. Mult Scler Relat Disord. 2015;4:31-8. doi: 10.1016/j.msard.2014.09.211

118. Ratajska A, Glanz BI, Chitnis T, Weiner HL, Healy BC. Social support in multiple sclerosis: Associations with quality of life, depression, and anxiety. J Psychosom Res. 2020;138. doi: 10.1016/j.jpsychores.2020.110252

119. Kever A, Buyukturkoglu K, Riley CS, De Jager PL, Leavitt VM. Social support is linked to mental health, quality of life, and motor function in multiple sclerosis. J Neurol. 2021;268(5):1827-36. doi: 10.1007/s00415-020-10330-7

120. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MÁ. Quality of life in adults with multiple sclerosis: a systematic review. BMJ Open. 2020;10(11). doi: 10.1136/bmjopen-2020-041249

121. Rainone N, Chiodi A, Lanzillo R, Magri V, Napolitano A, Brescia Morra V, Valerio P, Freda MF. Affective disorders and Health-Related Quality of Life (HRQoL) in adolescents and young adults with Multiple Sclerosis (MS): the moderating role of resilience. Qual Life Res. 2017;26:727-36. doi: 10.1007/s11136-016-1466-4

122. Voigt I, Inojosa H, Dillenseger A, Haase R, Akgun K, Ziemssen T. Digital Twins for Multiple Sclerosis. Front Immunol. 2021;12:669811. doi: 10.3389/fimmu.2021.669811

123. Walter E, Traunfellner M, Meyer F, Enzinger C, Guger M, Bsteh C, Altmann P, Hegen H, Goger C, Mikl V. Cost-effectiveness of the Floodlight((R)) MS app in Austria. Unlocking the mystery of costs and outcomes of a digital health application for patients with multiple sclerosis. Digit Health. 2025;11:20552076251314550. doi: 10.1177/20552076251314550

124. Maillart E, Labauge P, Cohen M, Maarouf A, Vukusic S, Donze C, Gallien P, De Seze J, Bourre B, Moreau T, et al. MSCopilot, a new multiple sclerosis self-assessment digital solution: results of a comparative study versus standard tests. Eur J Neurol. 2020;27(3):429-36. doi: 10.1111/ene.14091

125. Podda J, Tacchino A, Ponzio M, Di Antonio F, Susini A, Pedulla L, Battaglia MA, Brichetto G. Mobile Health App (DIGICOG-MS) for Self-Assessment of Cognitive Impairment in People With Multiple Sclerosis: Instrument Validation and Usability Study. JMIR Form Res. 2024;8:e56074. doi: 10.2196/56074

126. Pless S, Woelfle T, Naegelin Y, Lorscheider J, Wiencierz A, Reyes O, Calabrese P, Kappos L. Assessment of cognitive performance in multiple sclerosis using smartphone-based training games: a feasibility study. J Neurol. 2023;270(7):3451-63. doi: 10.1007/s00415-023-11671-9

8 Appendix

Title of Publication

Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study

Taranu D.[†], **Balz L.T.**[†], Holbrook J., Tumani V., Schreiber H., Tumani H.* & Uttner I.* Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study. *Journal of Neurol*ogy 2025;272(6):398. doi:10.1007/s00415-025-13115-y

[†] Daniela Taranu and Luisa T. Balz contributed equally to this investigation.

*Hayrettin Tumani and Ingo Uttner are Co-senior authors.

Copyright

© The Author(s) 2025. This an open access article licensed under the terms of a Creative Commons Attribution 4.0 International License (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.

Own contributions

Formal Analysis, Methodology, Software, Validation, Visualization, Writing - Original Draft Preparation, Writing - Review and Editing

Journal of Neurology (2025) 272:398
https://doi.org/10.1007/s00415-025-13115-y

ORIGINAL COMMUNICATION

Cognitive impairment, mood, and fatigue in various multiple sclerosis subtypes: a one-year follow-up study

Daniela Taranu[1] · Luisa T. Balz[1] · Jill Holbrook[1] · Visal Tumani[2] · Herbert Schreiber[3] · Hayrettin Tumani[1] · Ingo Uttner[1]

Received: 17 February 2025 / Revised: 22 April 2025 / Accepted: 23 April 2025
© The Author(s) 2025

Abstract

Background Multiple sclerosis (MS) subtypes—relapsing–remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS) – have been associated with distinct cognitive impairment profiles, with progressive subtypes, in contrast to RRMS, showing additional deficits in more widespread domains. Research has largely focused on RRMS, leaving SPMS and PPMS underexplored due to their lower prevalence and limited therapeutic targeting. Data on the interplay between cognitive impairment, mood, and fatigue over time are also scarce. This study examined cognition, fatigue, and psychopathology over a period of one year to identify subtype-specific impairments and progression trajectories.

Methods Sixty-six MS patients (22 each with RRMS, SPMS, and PPMS) and 22 healthy controls (HC) were assessed using neuropsychological tests for attention, memory, processing speed, working memory, fluency and visuospatial functions. Patient-reported outcomes for depression, anxiety, and fatigue were also collected. Analyses included correlations, within-group comparisons (paired t-tests), and between-group comparisons (ANOVAs/ANCOVAs).

Results Progressive MS subtypes exhibited more severe cognitive impairments, fatigue, and mood disturbances than RRMS. Over one year, treated RRMS patients improved in various cognitive domains, while PPMS patients showed gains only in visuospatial abilities. On the other hand, SPMS patients exhibited no significant changes, suggesting more pronounced cognitive deficits.

Conclusions Cognitive impairments differed significantly across MS subtypes. While RRMS patients improved over one year and PPMS patients showed selective gains in one domain, SPMS showed no significant changes, indicating reduced cognitive reserve. These between-group differences suggest different cognitive trajectories. The findings underscore the need for tailored, holistic interventions for different MS subtypes.

Keywords Multiple Sclerosis · Cognitive Impairment · Disease Progression · Psychopathology · Fatigue · Neuropsychological Assessment

Introduction

Multiple sclerosis (MS), an immune-mediated disorder characterized by inflammation and neurodegeneration [1], is the most common inflammatory disease of the central nervous system and the leading cause of permanent disability in young adults. Cognitive impairment is a frequent and often overlooked sequel of MS, significantly affecting patients' daily functioning [1]. Cognitive deficits seem to vary across MS clinical phenotypes [2], which include relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). RRMS is the most common phenotype, affecting 80–85% of patients [3]. Approximately 25–40% of RRMS cases convert to SPMS within

Daniela Taranu and Luisa T. Balz contributed equally to this investigation.

Hayrettin Tumani and Ingo Uttner are Co-senior authors.

✉ Hayrettin Tumani
hayrettin.tumani@uni-ulm.de

[1] Department of Neurology, Faculty of Medicine, Ulm University, D-89071 Ulm, Germany

[2] Department of Psychiatry, Faculty of Medicine, Ulm University, D-89071 Ulm, Germany

[3] Neurological Practice Center, Neuropoint Academy & NTD, D-89073 Ulm, Germany

Published online: 14 May 2025

two decades [3, 4] despite modern treatment interventions. In RRMS, cognitive impairment is reported in 21%−45% of patients [1, 4], mainly including reduced information processing speed and deficits in verbal fluency and visuospatial memory [4, 5]. In SPMS cognitive impairment affects up to 80% of patients [1, 4], with widespread deficits in information processing speed, verbal fluency, episodic memory, working memory, visuospatial abilities, and executive functions having been found [6, 7]. PPMS, affecting about 10–15% of MS patients, is typically marked by an insidious progression of disability without apparent relapses [8]. PPMS patients have originally been thought to be spared from cognitive impairment [9], but more refined assessments in more recent studies have provided convincing evidence that 56%−91% of PPMS patients experience cognitive deficits, particularly in attention, working memory, executive function, and verbal episodic memory [5, 10]. Despite the prevalence and impact of cognitive impairment in SPMS and PPMS, these patients are often underrepresented in scientific studies [11, 12], mainly due to lack of therapeutic targets against the pathohysiological drivers of progression, but also due to physical challenges posed by the progressive nature of these subtypes, which can make participation in longitudinal studies difficult [12]. Therefore, most studies focus on RRMS patients [13, 14], who experience milder symptoms. This imbalance leaves gaps in our understanding of cognitive changes, especially in SPMS and PPMS.

Recent studies by van Dam et al.[15], De Meo et al.[16], and Podda et al.[17] have also highlighted the variability of cognitive impairment in MS, identifying distinct cognitive profiles, particularly in progressive forms of the disease. These findings fuel and expand ongoing discussions about cognitive deficits in MS and raise the important question of how cognitive phenotypes differ depending on the underlying MS disease course.

Our study aims to characterize specific cognitive trajectories across MS clinical subtypes at baseline and after a one-year follow-up, including comparisons with healthy controls (HC). We additionally explore the interplay between fatigue, depression, and cognitive function, aiming to clarify how these factors contribute to cognitive symptoms across MS phenotypes. This approach offers a more detailed understanding of cognitive changes in MS, including characterization of non-motor clinical and behavioral symptoms affecting patients' quality of life.

Materials and methods

Design and participants

Sixty-six MS patients (n = 22 each with RRMS, SPMS, and PPMS) were recruited from Ulm University's Neurology Department, along with 22 age- and sex-matched HCs, primarily caregivers. All participants provided informed consent. The study, approved by Ulm University's ethics committee (No.157/16), comprised a one-year prospective longitudinal design with data collected from 2017 to 2019. Inclusion criteria were confirmed MS diagnosis (revised McDonald criteria [18]), age 18–85, and ability to communicate during assessments. Exclusion criteria included motor, speech, or language impairments affecting test validity, complicating illnesses, psychiatric disorders, recent corticosteroid use (patients had to be stable for at least 30 days before data collection, with no corticosteroid treatment or relapse during this period), or unstable clinical status. No changes in symptomatic therapy (e.g., antidepressants or antispasmodics) were made in patients with psychological symptoms or fatigue, and no modifications were made to Disease-Modifying Therapies (DMTs) during the follow-up period.

Procedure

All MS patients underwent neurological and neuropsychological assessments targeting memory, attention, executive, and visuospatial functions at baseline (T0) and after one year (T1). Depression, anxiety, and fatigue were evaluated using standardized patient-reported measures. Demographics and clinical data were collected via semi-structured interviews. Physical impairment was assessed with the Expanded Disability Status Scale (EDSS), ranging from 0 (normal function) to 10 (death) [19]. Parallel versions of the Symbol Digit Modalities Test (SDMT) [20], Brief Visuospatial Memory Test (BVMT-R) [21], and Verbal Learning and Memory Test (VLMT) [22] were used at follow-up to reduce practice effects.

Cognitive assessments

The neuropsychological test battery included seven validated assessments: oral SDMT (information processing speed, attentional shift, visual scanning) [20], VLMT (verbal episodic memory), BVMT-R (visual episodic memory) [22], Paced Auditory Serial Addition Test (PASAT; auditory processing speed, working memory) [23], Controlled Oral Word Association Test (COWAT; verbal fluency) [24], and Block Design Test (BDT; visuospatial functions) [25].

Depression, anxiety and fatigue

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS), a tool for individuals with physical illnesses with 2 subscales of 7 items (total possible score of 21 points) and cut-off scores for mild (≥ 8), moderate (≥ 11), or severe (≥ 15) [26] depression and anxiety, respectively. Fatigue was measured using the Fatigue Scale for Motor and Cognitive Functions (FSMC), a 20-item

self-assessment questionnaire evaluating global, motor and cognitive fatigue, with subscale scores ranging from 10 to 50. Cut-off scores for global fatigue were ≥ 43 (mild), ≥ 53 (moderate), ≥ 63 (severe); for motor fatigue ≥ 22 (mild), ≥ 27 (moderate), ≥ 32 (severe); and for cognitive fatigue ≥ 22 (mild), moderate (≥ 28), severe (≥ 34) [27].

Statistical analysis

Statistical analyses were conducted using SPSS version 29 and R. A priori power calculations ensured 80% power to detect small to large effect sizes ($r = 0.1$–0.3; Cohen's $d = 0.70$) with $\alpha = 0.05$, resulting in a required total sample size of 88 participants, with 22 per group. Chi-square tests assessed gender matching between MS patients and HC. ANCOVA (with age and education as covariates) and ANOVA compared groups at baseline and follow-up, with post-hoc tests (Tukey or Games-Howell for variance violations). Paired t-tests analyzed within-group changes. Correlations examined links between psychopathology, fatigue, and cognition. Data were z-standardized using the data of the 22 HC at baseline. Composite scores for global cognition, psychopathology, and fatigue were calculated by averaging z-standardized subscores, with psychopathology and fatigue scores inverted. Global cognition refers to a composite score that includes all z-standardized cognitive tests used in the study, summarized into this single composite measure.

Results

Demographics and clinical data

In sum, 88 participants were included, consisting of 22 patients with RRMS, 22 patients with SPMS, 22 patients with PPMS, and 22 HC. A significant age difference was observed among the four groups, with patients diagnosed with PPMS being the oldest. The groups were comparable in terms of gender and education. As expected, both time since disease onset and since diagnosis varied significantly across the MS subtypes, with SPMS patients exhibiting the longest disease duration. SPMS patients also demonstrated the highest level of physical impairment, as indicated by an average EDSS score of 5.96, reflecting moderate to severe disability. Demographic and clinical data are summarized in Table 1.

Table 1 Demographics and clinical data of MS patients and HC

Characteristics	RRMS ($N = 22$)		SPMS ($N = 22$)		PPMS ($N = 22$)		HC ($N = 22$)		Statistics
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
Age (years)	40.23	10.00	51.41	8.78	53.27	6.64	49.82	14.81	**$F(3, 84) = 6.75$, $p < 0.001$**
Female	15	68.2%	12	54.5%	14	63.6%	11	50%	$\chi^2(3) = 1.88$, $p = .598$
Male	7	31.8%	10	45.5%	8	36.4%	11	50%	
Education (years)	10.32	2.53	10.09	2.71	11.18	1.89	11.82	2.22	$F(3, 84) = 2.51$, $p = .064$
EDSS	2.61	1.47	5.96	1.07	4.61	1.72			
EDSS 0–3.0	18	81.8%	0	0%	4	18.2%			
EDSS 3.5–6.0	3	13.6%	10	45.5%	11	50.0%			
EDSS ≥ 6.5	1	4.5%	12	54.5%	7	31.8%			
Time since onset (years)	11.82	8.75	18.23	8.30	10.82	7.25			**$F(2, 63) = 5.39$, $p = .007$**
Time since diagnosis (years)	8.18	6.22	14.64	8.09	6.14	4.49			**$F(2, 63) = 10.4$, $p < 0.001$**
Current therapy									
No therapy	5	22.7%	9	40.9%	12	54.6%			
First line	13	59.1%	5	22.7%					
Second line	4	18.2%	3	13.6%					
Third line			2	9.1%	7	31.8%			
Biotin			3	13.6%	3	13.6%			

First line therapies: interferons, glatiramer acetate, teriflunomide, dimethyl fumarate. Second line therapies: fingolimod, siponimod, cladribine. Third line therapies: natalizumab, ocrelizumab

RRMS Relapsing Remitting Multiple Sclerosis. *SPMS* Secondary Progressive Multiple Sclerosis. *PPMS* Primary Progressive Mulitple Sclerosis. *HC* Healthy Controls. *EDSS* Expanded Disability Status Scale

The use of bold formatting indicates statistical significance

Table 2 Cognitive assessment, psychopathology and fatigue of MS patients and HC (at baseline)

Cognitive domains/tests	RRMS ($N = 22$)		SPMS ($N = 22$)		PPMS ($N = 22$)		HC ($N = 22$)		Statistics	Statistics
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Unadjusted	adjusted for age, education
Verbal episodic memory										
VLMT total	53.41	9.46	49.77	12.47	50.73	9.87	59.32	8.36	**$F(3, 84) = 3.94, p = 0.011$, partial $\eta^2 = 0.123$**	$F(3, 82) = 2.48$, $p = 0.067$, partial $\eta^2 = 0.083$
VLMT delayed recall	11.00	2.81	9.23	3.61	10.64	3.27	12.82	1.92	**$F(3, 84) = 5.44, p = 0.002$, partial $\eta^2 = 0.163$**	**$F(3, 82) = 3.73, p = 0.014$, partial $\eta^2 = 0.120$**
VLMT recognition	14.18	1.22	13.86	1.75	13.41	1.74	14.00	1.27	$F(3, 84) = 1.04$, $p = .379$, partial $\eta^2 = 0.036$	$F(3, 82) = 0.51$, $p = .677$, partial $\eta^2 = 0.018$
Visual episodic memory										
BVMT-R total	24.18	6.23	20.09	8.23	18.95	7.27	26.45	5.71	**$F(3, 84) = 5.62, p = 0.001$, partial $\eta^2 = 0.167$**	**$F(3, 82) = 3.68, p = 0.015$, partial $\eta^2 = 0.119$**
BVMT-R delayed recall	9.32	2.21	7.55	2.99	8.09	2.47	10.50	1.66	**$F(3, 84) = 6.76, p < 0.001$, partial $\eta^2 = 0.194$**	**$F(3, 82) = 4.70, p = 0.004$, partial $\eta^2 = 0.147$**
Attentional functions										
PASAT-3 total	46.18	8.84	40.33	15.17	37.27	15.45	47.95	6.29	**$F(3, 83) = 3.74, p = 0.014$, partial $\eta^2 = 0.119$**	**$F(3, 81) = 2.84, p = 0.043$, partial $\eta^2 = 0.095$**
SDMT	53.09	9.86	41.91	15.08	42.95	13.00	56.45	8.21	**$F(3, 84) = 8.29, p < 0.001$, partial $\eta^2 = 0.228$**	**$F(3, 82) = 5.54, p = 0.002$, partial $\eta^2 = 0.168$**
Executive functions										
COWAT	30.91	9.17	26.95	9.10	28.18	9.90	39.45	7.28	**$F(3, 84) = 8.79, p < 0.001$, partial $\eta^2 = 0.239$**	**$F(3, 82) = 7.78, p < 0.001$, partial $\eta^2 = 0.222$**
Visuospatial functions										
BDT	50.23	9.35	40.64	10.91	38.55	10.67	52.00	10.24	**$F(3, 84) = 9.42, p < 0.001$, partial $\eta^2 = 0.252$**	**$F(3, 82) = 6.17, p < 0.001$, partial $\eta^2 = 0.184$**
Global Fatigue (FSMC)	54.95	19.52	73.95	13.49	64.86	21.45	37.77	14.79	**$F(3, 84) = 17.01, p < 0.001$, partial $\eta^2 = 0.378$**	
Mild	2	9.1%	2	9.1%	3	13.6%	4	18.2%		
Moderate	2	9.1%	3	13.6%	3	13.6%	3	13.6%		
Severe	10	45.5%	17	77.3%	13	59.1%	1	4.5%		
Cognitive Fatigue (FSMC)	27.09	10.11	34.45	9.23	29.18	11.96	19.23	7.18	**$F(3, 84) = 9.21, p < 0.001$, partial $\eta^2 = 0.247$**	
Mild	3	13.6%	3	13.6%	3	13.6%	4	18.2%		
Moderate	4	18.2%	6	27.3%	5	22.7%	3	13.6%		
Severe	7	31.8%	11	50%	8	36.4%	1	4.5%		
Motor Fatigue (FSMC)	27.86	9.81	39.50	5.36	35.68	10.92	18.55	8.02	**$F(3, 84) = 24.49, p < 0.001$, partial $\eta^2 = 0.467$**	
Mild	2	9.1%	0	0%	1	4.5%	4	18.2%		
Moderate	1	4.5%	2	9.1%	4	18.2%	2	9.1%		
Severe	11	50%	20	90.9%	15	68.2%	1	4.5%		
Depression (HADS-D)	3.36	2.48	6.91	3.99	5.55	3.13	3.82	3.26	**$F(3, 84) = 5.52, p = 0.002$, partial $\eta^2 = 0.165$**	
Mild	1	4.5%	6	27.3%	8	36.4%	3	13.6%		
Moderate	0	0%	5	22.7%	0	0%	0	0%		
Severe	0	0%	0	0%	0	0%	0	0%		
Anxiety (HADS-A)	5.82	3.30	6.68	3.86	6.64	3.43	4.73	3.25	$F(3, 84) = 1.53$, $p = 0.212$, partial $\eta^2 = 0.052$	

Table 2 (continued)

Cognitive domains/tests	RRMS ($N = 22$)		SPMS ($N = 22$)		PPMS ($N = 22$)		HC ($N = 22$)		Statistics	Statistics
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Unadjusted	adjusted for age, education
Mild	4	18.2%	7	31.8%	2	9.1%	2	9.1%		
Moderate	2	9.1%	3	13.6%	4	18.2%	1	4.5%		
Severe	0	0%	0	0%	0	0%	0	0%		

RRMS Relapsing Remitting Multiple Sclerosis. *SPMS* Secondary Progressive Multiple Sclerosis. *PPMS* Primary Progressive Mulitple Sclerosis. *HC* Healthy Controls. *VLMT* Verbal Learning Memory Test. *BVMT-R* Brief Visuospatial Memory Test – Revised. *COWAT* Controlled Oral Word Association Test. *PASAT-3* Paced Auditory Serial Addition Test – 3 s version. *SDMT* Symbol Digit Modalities Test. *BDT* Block Design Test. *FSMC* Fatigue Scale for Motor and Cognitive Functions. *HADS* Hospital Anxiety and Depression Scale

The use of bold formatting indicates statistical significance

Between-group comparison and correlations at baseline

HC outperformed all MS subtypes across most cognitive domains, even after adjusting for age and education (Table 2). Composite z-scores revealed significant group differences when comparing RRMS with a combined group of progressive MS forms (SPMS and PPMS, N = 44). Patients with progressive MS performed significantly worse than those with RRMS in global cognition, visual episodic memory, attentional functions, visuospatial functions, global fatigue, and psychopathology (Δ [− 1.26, − 0.57], p [0.001, 0.049]). When analyzing at the subtype level and considering SPMS and PPMS separately (N = 22 respectively) SPMS ($\Delta = -1.32$, $p < 0.001$) and PPMS (PPMS: $\Delta = -1.29$, $p < 0.001$) showed significantly worse global cognition than HC, but not RRMS. Additionally, PPMS ($\Delta = -0.77$, $p = 0.040$) scored lower than RRMS. With respect to cognitive profile, RRMS ($\Delta = -1.04$, $p = 0.015$) and both progressive forms (SPMS: $\Delta = -1.45$, $p = 0.002$; PPMS: $\Delta = -1.39$, $p = 0.003$) performed poorly in verbal and visual episodic memory in comparison with HC. Attention deficits were prominent in SPMS ($\Delta = -1.54$, $p = 0.009$) and PPMS ($\Delta = -1.67$, $p = 0.002$) compared with HC, with PPMS ($\Delta = -1.33$, $p = 0.027$) scoring lower than RRMS. SPMS patients ($\Delta = 0.77$, $p = 0.030$) reported higher psychopathology. Fatigue was pronounced across all MS subtypes (SPMS: $\Delta = 2.37$, $p < 0.001$; PPMS: $\Delta = 1.76$, $p < 0.001$; RRMS: $\Delta = 1.13$, $p = 0.010$), and SPMS showed higher fatigue than RRMS ($\Delta = -1.24$, $p = 0.004$). Executive function deficits were significant in all MS groups, but visuospatial impairments were more severe in progressive forms (SPMS: $\Delta = -1.11$, $p = 0.002$; PPMS: $\Delta = -1.31$, $p < 0.001$) (Fig. 1).

Between-group comparison and correlations at follow-up

Overall, 87 out of the initial 88 participants remained in the study from T0 to T1 (drop-out rate 1.14%). At follow-up, HC generally outperformed all MS subtypes, the most substantial differences being observed in verbal and visual episodic memory, attention, executive, and visuospatial functions (Table 3; Fig. 2). Even after adjustments for age and education, many of these differences persisted, particularly between HC and progressive forms of MS. Additionally, levels of cognitive and motor fatigue and depressive symptoms were significantly higher in progressive MS subtypes compared with HC (Table 3).

Follow-up comparisons of z-standardized composite scores, initially conducted at the group level by combining SPMS and PPMS into a progressive MS group (N = 44) and comparing it to RRMS, revealed that patients with

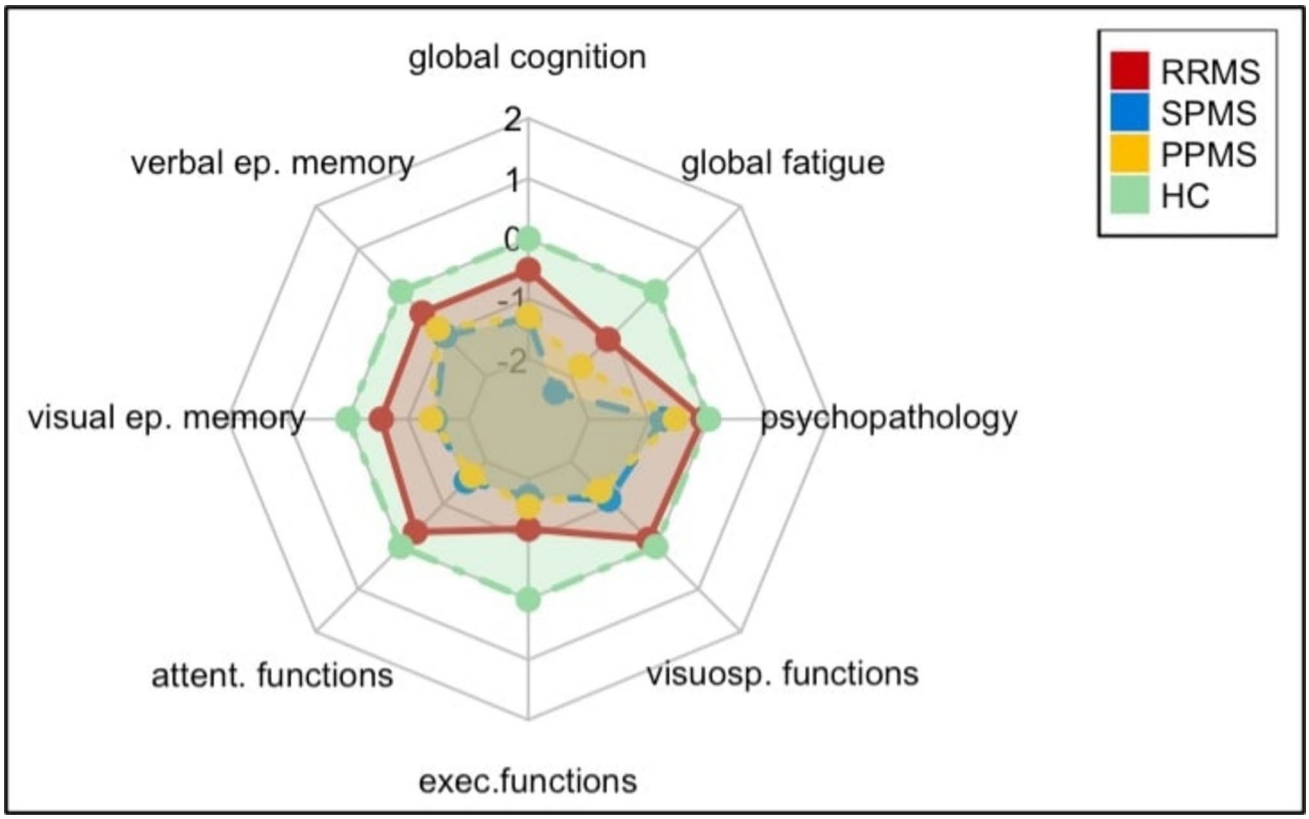


Fig. 1 Between-group comparison at baseline

progressive MS exhibited significantly poorer performance across multiple domains. These included global cognition, visual and verbal episodic memory, attentional functions, visuospatial functions, and global fatigue (Δ [− 1.41, − 0.71], *p* [0.001, 0.022]). When analyzing at the subtype level, separating SPMS and PPMS and comparing each to RRMS, both SPMS (Δ = − 1.03, $p = 0.007$) and PPMS (Δ = − 0.85, $p = 0.010$) patients showed significantly lower global cognition scores than those with RRMS. Additionally, SPMS patients performed significantly worse in verbal episodic memory compared to RRMS (Δ = − 1.08, $p = 0.009$). With respect to attention, both SPMS (Δ = − 1.47, $p = 0.022$) and PPMS (Δ = − 1.35, $p = 0.009$) patients had significantly poorer results than RRMS patients. Psychopathology was also higher in the SPMS group (Δ = 0.82, $p = 0.030$) compared with RRMS. Visuospatial functions were impaired in patients with progressive MS, with SPMS patients (Δ = − 0.99, $p = 0.010$) showing lower scores than those with RRMS. Finally, fatigue levels were higher in SPMS patients (Δ = 1.21, $p = 0.005$) compared with RRMS (Fig. 2).

Correlation analyses in MS subtypes at baseline and follow-up

At baseline, correlation analyses on data from RRMS patients revealed significant positive associations between psychopathology and fatigue ($r = 0.57$, $p = 0.005$) and between fatigue and global cognition ($r = 0.45$, $p = 0.035$). In PPMS patients, a significant correlation was likewise observed between psychopathology and fatigue ($r = 0.66$, $p < 0.001$), but not between fatigue and global cognition. For SPMS patients, no significant correlations were found ($p > 0.05$) between these domains.

At follow-up, correlation analyses indicated a significant association between fatigue and psychopathology for RRMS ($r = 0.46$, $p = 0.030$), SPMS ($r = 0.51$, $p = 0.015$), and PPMS ($r = 0.86$, $p < 0.001$). However, no significant correlations were found between global cognition and fatigue or psychopathology for any of the MS subtypes (all $p > 0.05$).

Within-group comparison from baseline to follow-up

For within-group comparisons at one year compared with baseline, significant improvements were observed in the RRMS group in several cognitive domains. Specifically,

Table 3 Cognitive test results of MS patients and HC – follow-up (after 12 months)

Cognitive domains/tests	RRMS ($N = 22$)		SPMS ($N = 22$)		PPMS ($N = 21$)		HC ($N = 22$)		Statistics	
	Mean/N	SD/%	Mean/N	SD/%(sample size)	Mean/N	SD/%	Mean/N	SD/%	Unadjusted	Adjusted for age, education
Verbal episodic memory										
VLMT total	58.77	6.23	50.55	12.37	53.76	10.28	63.09	7.87	**$F(3, 83) = 7.46, p < .001$, partial $\eta^2 = .212$**	**$F(3, 81) = 5.17, p = .003$, partial $\eta^2 = .161$**
VLMT delayed recall	12.50	1.99	9.82	3.58	10.67	2.87	13.55	1.77	**$F(3, 83) = 8.97, p < .001$, partial $\eta^2 = .245$**	**$F(3, 81) = 6.23, p < .001$, partial $\eta^2 = .187$**
VLMT recognition	14.64	0.79	13.55	1.79	13.43	1.91	14.59	0.73	**$F(3, 83) = 4.65, p = .005$, partial $\eta^2 = .144$**	**$F(3, 81) = 3.60, p = .017$, partial $\eta^2 = .118$**
Visual episodic memory										
BVMT-R total	24.27	3.97	20.86	6.46 *(21)*	20.52	4.71	25.86	6.52	**$F(3, 82) = 4.82, p = .004$, partial $\eta^2 = .150$**	**$F(3, 80) = 2.96, p = .037$, partial $\eta^2 = .100$**
BVMT-R delayed recall	9.09	1.38	7.67	2.35 *(21)*	7.90	1.90	9.59	1.74	**$F(3, 82) = 5.29, p = .002$, partial $\eta^2 = .162$**	**$F(3, 80) = 3.15, p = .030$, partial $\eta^2 = .106$**
attentional functions										
PASAT-3 total	48.45	8.41	40.33	14.10 *(21)*	41.43	12.45	47.82	7.38	**$F(3, 82) = 3.23, p = .026$, partial $\eta^2 = .106$**	$F(3, 80) = 1.90$, $p = .137$, partial $\eta^2 = .066$
SDMT	56.77	10.73	43.29	15.89 *(21)*	43.76	10.75	55.50	9.29	**$F(3, 82) = 8.11, p < .001$, partial $\eta^2 = .229$**	**$F(3, 80) = 4.82, p = .004$, partial $\eta^2 = .153$**
Executive functions										
COWAT	31.73	9.49	27.82	8.51	29.52	9.21	40.55	7.22	**$F(3, 83) = 9.39, p < .001$, partial $\eta^2 = .253$**	**$F(3, 81) = 7.69, p < .001$, partial $\eta^2 = .222$**
Visuospatial functions										
BDT	51.77	9.40	41.62	11.54 *(21)*	44.00	11.15	52.41	9.42	**$F(3, 82) = 5.91, p = .001$, partial $\eta^2 = .178$**	**$F(3, 80) = 3.00, p = .035$, partial $\eta^2 = .101$**
Global Fatigue (FSMC)	54.00	17.85	72.59	17.71	64.90	20.67	38.73	14.61	**$F(3, 83) = 14.92, p < .001$, partial $\eta^2 = .350$**	
Mild	5	22.7%	2	9.1%	3	13.6%	3	13.6%		
Moderate	2	9.1%	3	13.6%	4	18.2%	0	0%		
Severe	9	40.9%	16	72.7%	11	50.0%	3	13.6%		
Cognitive Fatigue (FSMC)	26.27	9.10	33.64	10.63	29.00	12.54	19.59	7.16	**$F(3, 83) = 7.54, p < .001$, partial $\eta^2 = .214$**	
Mild	5	22.7%	3	13.6%	4	18.2%	4	18.2%		
Moderate	3	13.6%	3	13.6%	2	9.1%	2	9.1%		
Severe	7	31.8%	13	59.1%	9	40.9%	1	4.5%		
Motor Fatigue (FSMC)	27.73	9.18	38.95	7.93	35.90	9.72	19.14	7.88	**$F(3, 83) = 22.89, p < .001$, partial $\eta^2 = .453$**	
Mild	2	9.1%	0	0%	1	4.5%	2	9.1%		
Moderate	4	18.2%	3	13.6%	4	18.2%	1	4.5%		
Severe	10	45.5%	18	81.8%	14	63.6%	3	13.6%		
Depression (HADS-D)	3.59	2.67	8.09	3.78	5.71	3.32	3.05	2.40	**$F(3, 83) = 12.17, p < .001$, partial $\eta^2 = .306$**	

Table 3 (continued)

Cognitive domains/tests	RRMS ($N = 22$)		SPMS ($N = 22$)		PPMS ($N = 21$)		HC ($N = 22$)		Statistics	
	Mean/N	SD/%	Mean/N	SD/%(sample size)	Mean/N	SD/%	Mean/N	SD/%	Unadjusted	Adjusted for age, education
Mild	1	4.5%	10	45.5%	6	27.3%	0	0%		
Moderate	1	4.5%	3	13.6%	2	9.1%	0	0%		
Severe	0	0%	1	4.5%	0	0%	0	0%		
Anxiety (HADS-A)	5.91	3.85	6.73	4.23	5.90	4.16	3.82	3.29	$F(3, 83) = 2.23$, $p = .090$, partial $\eta^2 = .075$	
Mild	5	22.7%	1	4.5%	1	4.5%	0	0%		
Moderate	3	13.6%	7	31.8%	5	22.7%	0	0%		
Severe	0	0%	0	0%	0	0%	1	4.5%		

RRMS Relapsing Remitting Multiple Sclerosis. *SPMS* Secondary Progressive Multiple Sclerosis. *PPMS* Primary Progressive Mulitple Sclerosis. *HC* Healthy Controls. *VLMT* Verbal Learning Memory Test. *BVMT-R* Brief Visuospatial Memory Test – Revised. *COWAT* Controlled Oral Word Association Test. *PASAT-3* Paced Auditory Serial Addition Test – 3 s version. *SDMT* Symbol Digit Modalities Test. *BDT* Block Design Test. *FSMC* Fatigue Scale for Motor and Cognitive Functions. *HADS* Hospital Anxiety and Depression Scale

The use of bold formatting indicates statistical significance

RRMS patients showed significant gains in verbal episodic memory subtests, including total learning score (VLMT total: $t(21) = -3.75$, $p = 0.001$, $d = -0.799$) and delayed recall (VLMT recall: $t(21) = -3.05$, $p = 0.006$, $d = -0.651$). Additionally, a significant improvement was noted in attentional function (PASAT: $t(21) = -3.52$, $p = 0.002$, $d = -0.751$). Composite scores showed RRMS patients achieving significant gains in global cognition ($t(21) = -5.09$, $p < 0.001$, $d = -1.09$), verbal episodic memory ($t(21) = -4.00$, $p < 0.001$, $d = -0.852$), and attentional functions ($t(21) = -3.38$, $p = 0.003$, $d = -0.72$).

For the PPMS subgroup, significant improvements from baseline to follow-up were observed in visuospatial functions (BDT: $t(20) = -3.72$, $p = 0.001$, $d = -0.812$) and in global cognition ($t(20) = -2.13$, $p = 0.045$, $d = -0.466$). In contrast, SPMS patients showed no significant changes from baseline to follow-up ($p > 0.05$) (Fig. 3).

RRMS patients achieved the greatest improvement from baseline to follow-up, particularly in VLMT total and VLMT recall scores (statistically significant). PPMS patients exhibited the most pronounced learning effect in the visuospatial BDT test (significant change in within-group comparison; Fig. 4).

Discussion

Our study examined the cognitive and psycho-behavioral trajectories of clinically defined MS subtypes over one year. The findings highlight significant differences in cognitive functioning, psychopathology, and fatigue among patients with different MS subtypes compared to HC and among MS subtypes themselves. Moreover, our results indicate that the subtype of MS is associated with () specific kinds of cognitive deficits, suggesting the need for subtype-specific therapeutic interventions.

Between-group comparison of cognition, psychopathology and fatigue at baseline

Cognitive impairment was evident in all MS subtypes at baseline, with patients in the SPMS and PPMS subgroups exhibiting poorer cognitive performance compared with HC. Even in early relapsing–remitting MS (RRMS), impairment was observed in executive functions. Our findings align with the existing literature indicating that cognitive decline is an early and prevalent symptom of MS that is often more severe and more extensive in progressive forms of MS [2, 28]. Deficits in verbal episodic memory, processing speed, attention, and executive function were particularly pronounced in progressive MS. These impairments were evident both at the group level, when SPMS and PPMS were combined into a progressive MS group, and at the subtype level, when distinct patterns of cognitive dysfunction emerged for SPMS

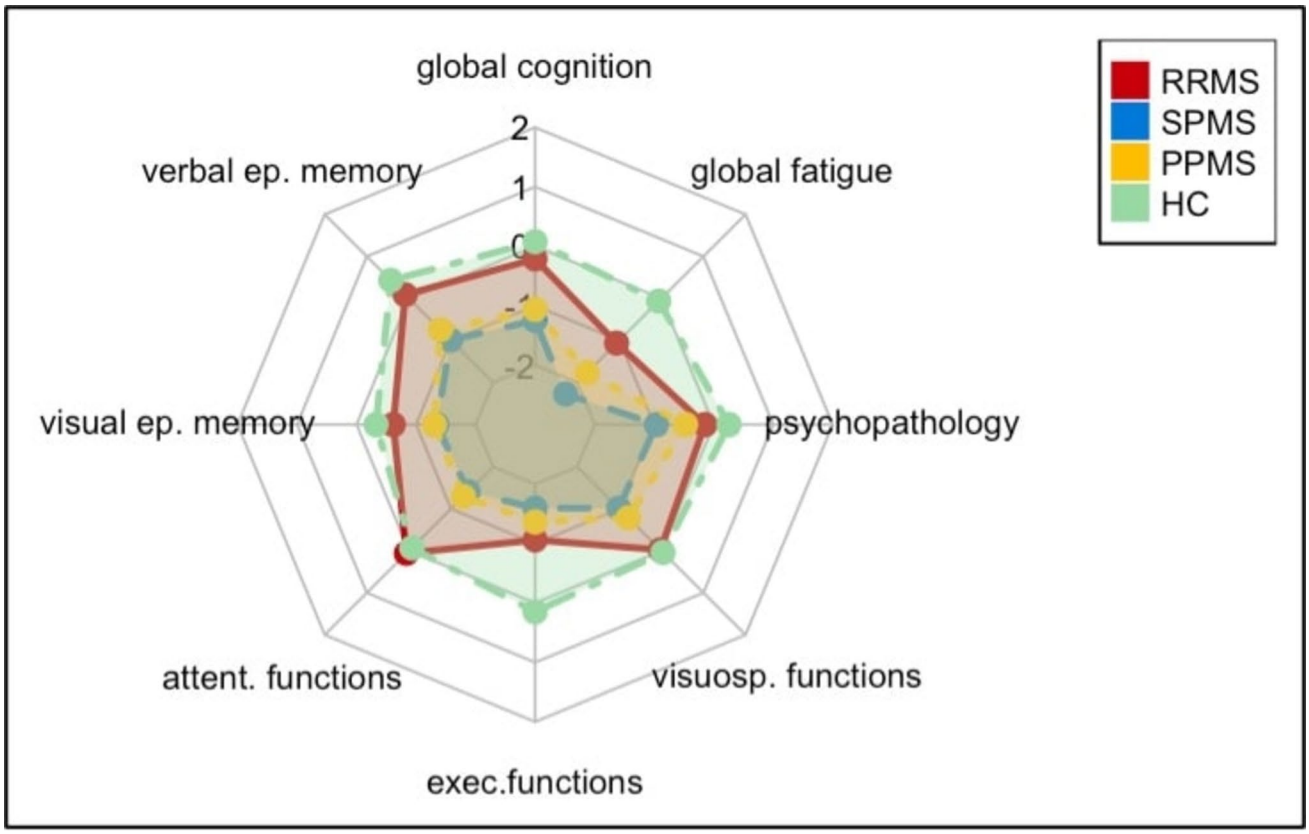


Fig. 2 Between-group comparison at follow-up

and PPMS. Our data suggest an urgent need for early cognitive assessments and targeted interventions for SPMS and PPMS patients, as they may experience more significant neuronal loss and cognitive decline [29] affecting quality of life. Psychopathological symptoms at baseline, especially depression and anxiety, were also significantly elevated in the SPMS group compared with HC, which is in line with previous studies [30]. The complex interrelationship between cognitive impairment and psychological factors suggests that stabilizing mental health and fatigue may attenuate cognitive decline in MS. Elevated fatigue levels were reported across all MS subtypes at baseline, with SPMS patients experiencing the highest levels, aligning with the existing literature on fatigue prevalence and severity[31]. Moreover, our data reinforces the pervasive nature of fatigue in MS and its detrimental impact on quality of life and brain function.

Between-group comparison of cognition, psychopathology and fatigue at follow-up

Drop-out rate was minimal (1.14%), providing a remarkably complete data set. Specifically, only one participant withdrew from the study due to the long travel distance to the clinic and a reluctance to undergo another round of cognitive testing. Importantly, this participant did not differ significantly from the overall group in terms of psychiatric conditions or other relevant factors. At one year, HC consistently outperformed all MS subtypes, particularly in verbal and visual episodic memory, attentional, executive, and visuospatial functions. The persistent cognitive differences observed between HC and patients with progressive forms of MS highlight the significant cognitive deficits associated with progressive disease. This aligns with existing literature suggesting more pronounced and extensive cognitive impairments in SPMS and PPMS compared with RRMS (at combined group level and subtype level) and HC [2, 10, 28]. Additionally, elevated levels of depressive symptoms and fatigue reported in the progressive MS groups suggest that combined treatment approaches should address both cognitive rehabilitation and emotional well-being [32]. The high fatigue levels reported among all MS subtypes at follow-up highlight the necessity of fatigue management interventions.

Relationship between cognition, psychopathology and fatigue among MS subtypes

In our study, cognitive function did not consistently correlate with fatigue or psychopathology scores, other than a

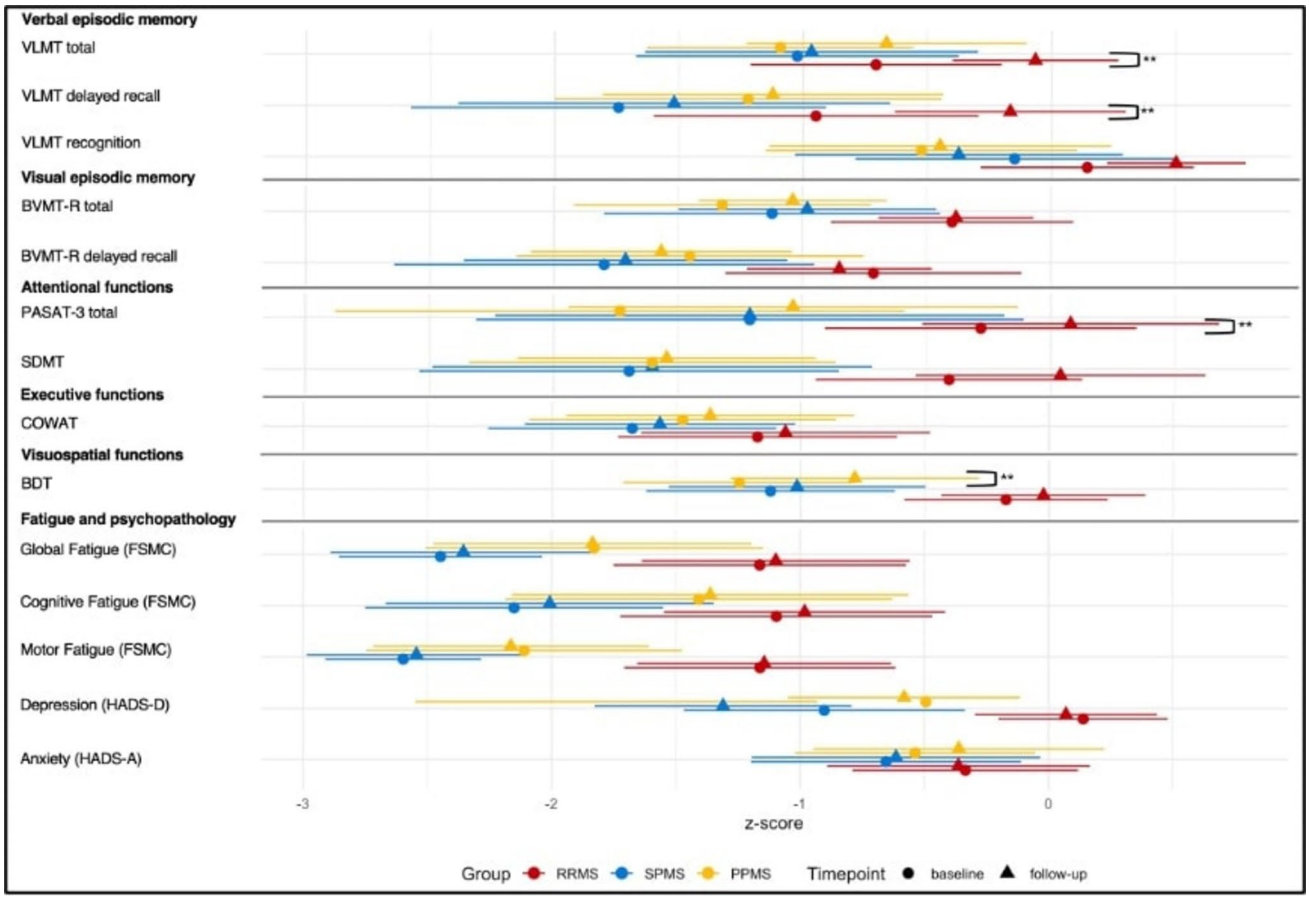


Fig. 3 Between-group comparison from baseline to follow-up

baseline association observed in RRMS. Our results contrast with an earlier study that showed an association between fatigue and global cognition [35]. However, two other studies also did not show relationships between depression and specific cognitive functions including memory, language, and visuospatial functions [36, 37]. The absence of consistent correlations between cognition and fatigue or psychopathology suggests that heterogenous mechanisms associated with intrinsic disease processes and neurodegeneration may influence cognition, particularly in progressive forms of MS. In contrast to the lack of correlation with cognition, consistent associations between fatigue and psychopathology were observed across all MS subtypes at follow-up, suggesting that these factors may potentiate each other. These results align with existing literature [33, 34]. It may therefore be hypothesized that the relationship between cognitive and psychopathological factors is more complex than previously assumed.

Within-group comparison of cognition, psychopathology and fatigue from baseline to follow-up

Within-group comparisons from baseline to follow-up showed that the RRMS group displayed cognitive improvement, particularly in tasks assessing verbal episodic memory and attention. The reason for this improvement is unclear and confirmatory data are required. Possible hypotheses include (1) Cognitive recovery may occur in RRMS patients during periods in which MS is stable, particularly as cognitive fatigue showed a slight, though non-significant, decrease from baseline to follow-up. (2) Improvements in the RRMS group might indicate a higher cognitive reserve, as these patients potentially benefitted from repetition effects. (3) The RRMS group might have particularly benefitted from stabilizing treatment effects. In contrast, SPMS and PPMS patients showed no significant improvement, suggesting that disease progression may have influenced their cognitive reserve, impairing their ability to benefit from repetition effects. Additionally, the stability of psychological symptoms and fatigue levels between baseline and follow-up

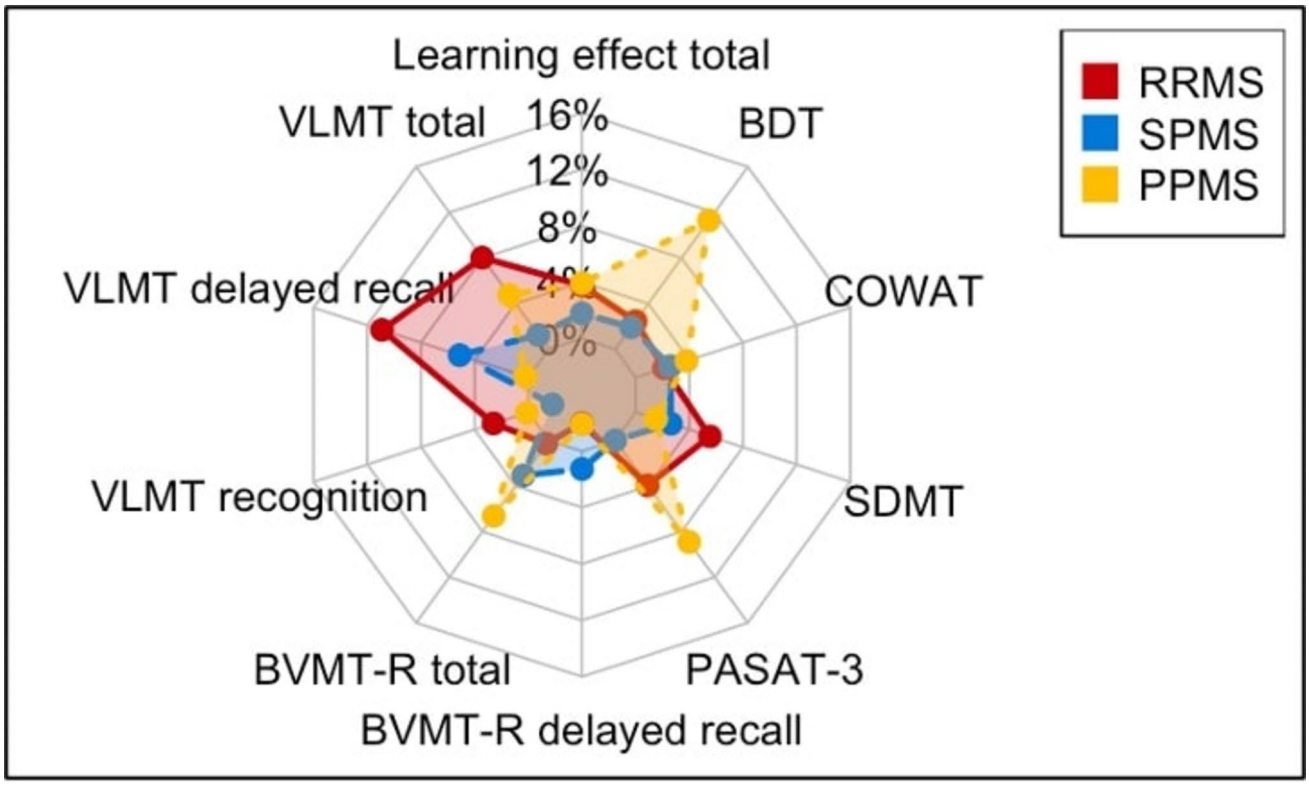


Fig. 4 Between-group comparison of learning effects in cognitive domain subtests

for all groups may indicate that these factors might be entrenched in the disease process, a finding that aligns with existing literature [38].

While our study offers valuable insights, some limitations should be acknowledged. The sample size of 88 participants prevents us from drawing general conclusions from our results. Variations in age among groups at baseline necessitated statistical adjustment; however, age did not significantly correlate with changes over the one-year study period, indicating that it likely did not influence our findings. The one-year follow-up duration may have constrained our ability to detect more pronounced MS-related changes, particularly given the overall low disease activity as reflected by stable EDSS scores. Possible confounding factors such as comorbidities, medications, and lifestyle could not be statistically addressed in this small study. Although parallel test versions were used to mitigate practice effects, a learning effect may have persisted, particularly within the RRMS group, potentially affecting the accuracy of long-term cognitive assessments. In this context, any residual learning effects may primarily be interpreted as a measure of cognitive reserve, which differed between groups. Future research with longer follow-up periods is necessary to provide deeper insights into the long-term progression of cognitive symptoms.

Overall, our study addresses an important gap in the literature by focusing on underrepresented SPMS and PPMS patient groups. By jointly examining cognitive function, fatigue, and psychopathology across all MS subtypes over a one-year period, we were able to make direct comparisons between MS subtypes and offer new insights into the neuropsychological and psychopathological profiles of each subtype. Progressive MS forms exhibited more pronounced and widespread cognitive impairments than RRMS. Fatigue and psychopathological symptoms were present at moderate to high levels and remained stable at the one-year follow-up in all MS groups.

Given the probable interplay between cognitive and psychopathological factors in MS patients, interventions should prioritize both cognitive rehabilitation and psychological support, particularly for progressive MS. Extended follow-up studies are needed to understand long-term cognitive trajectories and refine subtype-specific management and treatment strategies.

Acknowledgements The authors thank all patients and their caregivers for their participation.

Funding Open Access funding enabled and organized by Projekt DEAL. Author(s) received no financial support for research, authorship, and/or publication of this article.

Data availability Anonymized data will be shared upon reasonable request from a qualified investigator.

Declarations

Conflicts of interest H.S. received grants from Bayer, Biogen, Novartis, Roche and Sanofi and consultancy and speaker`s honoraria from Almirall, Bayer, Biogen, Bristol-Myers-Squibb, Janssen, Novartis, Roche, Sanofi and Teva. H.T. received honoraria as a consultant/speaker and/or for events sponsored by Alexion, Bayer, Biogen, Bristol-Myers Squibb, Celgene, Diamed, Fresenius, Fujirebio, GlaxoSmithKline, Horizon, Janssen-Cilag, Merck, Novartis, Roche, Sanofi-Genzyme, Siemens, Teva and Viatris. No conflicts are relevant to the study. D.T., L.T.B., J.H., V.T. and I.U. declared no conflicts of interest.

Ethical approval/consent This study was approved by the Ethics Committee of Ulm University (Ethics Code: 157/16) on Sept. 13, 2016. All participants provided written informed consent prior to enrolment in the study. This research was conducted ethically in accordance with the Declaration of Helsinki.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Benedict RHB et al (2020) Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol 19(10):860–871
2. Huijbregts SC et al (2004) Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology 63:335–339
3. Lublin FD et al (2014) Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83:278–286
4. Brochet B, Ruet A (2019) Cognitive impairment in multiple sclerosis with regards to disease duration and clinical phenotypes. Front Neurol 10:261
5. Macias Islas MA, Ciampi E (2019) Assessment and impact of cognitive impairment in multiple sclerosis: an overview. Biomedicines 7(1):22
6. Delgado-Alvarez A et al (2020) Cognitive processes underlying verbal fluency in multiple sclerosis. Front Neurol 11:629183
7. Matias-Guiu JA et al (2017) Functional components of cognitive impairment in multiple sclerosis: a cross-sectional investigation. Front Neurol 8:643
8. Miller DH, Leary SM (2007) Primary-progressive multiple sclerosis. Lancet Neurol 6:903–912
9. Comi G et al (1995) Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. J Neurol Sci 132:222–227
10. Ruet A et al (2013) Cognitive impairment differs between primary progressive and relapsing-remitting MS. Neurology 80:1501–1508
11. Brochet B et al (2022) Cognitive impairment in secondary progressive multiple sclerosis: effect of disease duration, age, and progressive phenotype. Brain Sci 12(2):183
12. Jakimovski D et al (2024) Cognitive function in severe progressive multiple sclerosis. Brain Commun 6(4):fcae226
13. Migliore S et al (2017) Cognitive impairment in relapsing-remitting multiple sclerosis patients with very mild clinical disability. Behav Neurol 2017:7404289
14. Altieri M et al (2020) Cognitive performance in relapsing-remitting multiple sclerosis: at risk or impaired? Dement Geriatr Cogn Disord 49(6):539–543
15. van Dam M et al (2024) Identifying and understanding cognitive profiles in multiple sclerosis: a role for visuospatial memory functioning. J Neurol 271(5):2195–2206
16. De Meo E et al (2021) Identifying the distinct cognitive phenotypes in multiple sclerosis. JAMA Neurol 78(4):414–425
17. Podda J et al (2024) A taxonomy of cognitive phenotypes in Multiple Sclerosis: a 1-year longitudinal study. Sci Rep 14(1):20362
18. Thompson AJ et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162–173
19. Cao H et al (2015) Evaluation of an expanded disability status scale (EDSS) modeling strategy in multiple sclerosis. Med Biol Eng Comput 53:1141–1151
20. Benedict RHB et al (2017) Validity of the symbol digit modalities test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 23:721–733
21. Benedict RHB et al (1996) Revision of the brief visuospatial memory test: studies of normal performance, reliability and validity. Psychol Assess 8:145–153
22. Helmstaedter C, Lendt M, Lux S (2001) Verbaler Lern-und Merkfähigkeitstest: VLMT: manual, 1st edn. Hogrefe Verlag, Göttingen
23. Gronwall DM (1977) Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 44:67–73
24. Ross TP et al (2007) The reliability and validity of qualitative scores for the controlled oral word association test. Arch Clin Neuropsychol 22:475–488
25. Wechsler D (1981) WAIS-R manual: wechsler adult intelligence scale-revised. Psychological Corporation, New York
26. Snaith RP (2003) The hospital anxiety and depression scale. Health Qual Life Outcomes 1(1):29
27. Penner IK et al (2009) The fatigue scale for motor and cognition functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler 15(12):1509–1517
28. Wachowius U et al (2005) Cognitive impairment in primary and secondary progressive multiple sclerosis. J Clin Exp Neuropsychol 27:65–77
29. Planche V et al (2016) Cognitive impairment in a population-based study of patients with multiple sclerosis: differences between late relapsing-remitting, secondary progressive and primary progressive multiple sclerosis. Eur J Neurol 23:282–289
30. Silveira C et al (2019) Neuropsychiatric Symptoms of multiple sclerosis: state of the art. Psychiatry Investig 16(12):877–888
31. Oliva Ramirez A et al (2021) Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. BMC Neurol 21(1):468
32. Leavitt VM et al (2020) Dissociable cognitive patterns related to depression and anxiety in multiple sclerosis. Mult Scler 26(10):1247–1255
33. Bakshi R et al (2000) Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 6:181–185
34. Tranfa M et al (2023) Exploring the relation between reserve and fatigue in multiple sclerosis. Mult Scler Relat Disord 76:104842
35. Stenager E, Knudsen L, Jensen K (1994) Multiple sclerosis: correlation of anxiety, physical impairment and cognitive dysfunction. Ital J Neurol Sci 15:97–101

36. Bruce JM, Bruce AS, Arnett PA (2010) Response variability is associated with self-reported cognitive fatigue in multiple sclerosis. Neuropsychology 24:77–83
37. Lehmann P et al (2013) Self-reported sleep problems, but not fatigue, lead to decline in sustained attention in MS patients. Mult Scler 19:490–497
38. Beal C et al (2007) Depression in multiple sclerosis: a longitudinal analysis. Arch Psychiatr Nurs 21:181–191

Title of Publication

Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis

---

Balz, L. T., Uttner, I., Taranu, D., Erhart, D. K., Fangerau, T., Jung, S., Schreiber, H., Senel, M., Vardakas, I., Lule, D. E.[†] & Tumani, H.[†] Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis. Biomedicines 2025;13(8):1902. doi: 10.3390/biomedicines13081902

[†] These authors contributed equally to this work.

Copyright

© The Author(s) 2025. This an open access article licensed under the terms of a Creative Commons Attribution 4.0 International License (CC BY 4.0), http://creativecommons.org/licenses/by/4.0/.

Own contributions

Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – Original Draft, Writing – Review and Editing

biomedicines

Article

Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis

Luisa T. Balz [1], Ingo Uttner [1], Daniela Taranu [1], Deborah K. Erhart [1], Tanja Fangerau [1], Stefanie Jung [1], Herbert Schreiber [2], Makbule Senel [1], Ioannis Vardakas [1], Dorothée E. Lulé [1,*,†] and Hayrettin Tumani [1,*,†]

[1] Department of Neurology, Faculty of Medicine, Ulm University, D-89081 Ulm, Germany; luisa.balz@uni-ulm.de (L.T.B.); ingo.uttner@uni-ulm.de (I.U.); daniela.taranu@uni-ulm.de (D.T.); deborah.erhart@uni-ulm.de (D.K.E.); tanja.fangerau@rku.de (T.F.); stefanie.jung@rku.de (S.J.); makbule.senel@uni-ulm.de (M.S.); ioannis.vardakas@uni-ulm.de (I.V.)
[2] Neurological Practice Center, Neuropoint Academy & NTD, D-89073 Ulm, Germany; schreiber@neurologie-ulm.de
* Correspondence: dorothee.lule@uni-ulm.de (D.E.L.); hayrettin.tumani@uni-ulm.de (H.T.); Tel.: +49-7311775267 (D.E.L.); +49-7311775206 (H.T.)
† These authors contributed equally to this work.

Abstract

Background/Objectives: Cognitive impairment is one of the most common and debilitating clinical features of Multiple Sclerosis (MS). Neuropsychological assessment, however, is time-consuming and requires personal resources, so, due to limited resources in daily clinical practice, information on cognitive profiles is often lacking, despite its high prognostic relevance. Time-saving and effective tools are required to bridge this gap. This study evaluates the sensitivity and specificity of a revised version of TRACK-MS (TRACK-MS-R), a recently published screening tool to identify cognitive impairment in MS in a fast and reliable way, offering a balance between efficiency and diagnostic yield for the individual patient. **Methods**: In this prospective cross-sectional study, 102 MS patients and 94 age-, sex-, and education-matched healthy controls (HC) completed an extensive neuropsychological assessment, including TRACK-MS-R, to test for cognitive processing speed (Symbol Digit Modalities Test, SDMT) and verbal fluency (Regensburger Word Fluency Test, RWT). Sensitivity of TRACK-MS-R was assessed by using the BICAMS-M battery as a reference, and specificity was determined by comparing MS patients to HC. **Results**: TRACK-MS-R demonstrated high sensitivity (97.44%) when compared to the gold standard as represented by BICAMS-M for early and accurately detecting cognitive impairment in MS patients. Additionally, as a potential cognitive marker, TRACK-MS-R showed a specificity of 82.98% in distinguishing MS patients from healthy controls. **Conclusions**: TRACK-MS-R proves to be a highly sensitive and time-efficient screening tool for detecting cognitive impairment in patients with MS, while demonstrating good specificity compared to HC. Whereas high sensitivity is a prerequisite for a valid screening tool, its relatively modest specificity compared to BICAMS-M (62.9%) calls for caution in interpreting standalone results but instead indicates more extensive neuropsychological testing. Its briefness and diagnostic accuracy support its implementation in routine clinical practice, particularly in time-constrained settings.

Keywords: multiple sclerosis; cognitive screening; sensitivity; specificity

check for updates

Academic Editor: Simone Battaglia

Received: 9 July 2025
Revised: 29 July 2025
Accepted: 31 July 2025
Published: 4 August 2025

Citation: Balz, L.T.; Uttner, I.; Taranu, D.; Erhart, D.K.; Fangerau, T.; Jung, S.; Schreiber, H.; Senel, M.; Vardakas, I.; Lulé, D.E.; et al. Sensitivity and Specificity of a Revised Version of the TRACK-MS Screening Battery for Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis. *Biomedicines* **2025**, *13*, 1902. https://doi.org/10.3390/biomedicines13081902

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Cognitive impairment is considered one of the most common and debilitating sequelae of Multiple Sclerosis (MS), affecting approximately 40–70% of patients throughout the disease course [1–3]. It closely interferes with various fields of daily life, including quality of life [4], employment status, and social functioning [5]. Furthermore, tracking cognitive functioning is crucial for monitoring disease progression [6–12]. Yet, cognitive screening is still underutilized and often not implemented in daily clinical MS care due to time constraints and limited workforce [13]. Current efforts highlight the need to incorporate routine cognitive assessment into MS clinics and practices, including clinical trials [14–16]. However, there are gaps in standardized methodological approaches applicable to both clinical and non-clinical settings. Country-specific versions of the Brief International Cognitive Assessment for MS (BICAMS-M) screening battery are the current gold standard for cognitive screening in MS and have been proposed as a practical and validated tool in clinical settings [17,18]. BICAMS-M consists of the Verbal Learning and Memory Test (VLMT; episodic memory) [19], the revised version of the Brief Visuospatial Memory Test (BVMT-R; visual episodic memory) [20], and the Symbol Digit Modalities Test (SDMT; cognitive processing speed) [21] and takes approximately 15–20 min to administer. Yet, even this relatively short test battery may pose challenges in high-throughput clinical settings and out-of-hospital neurologist's offices in town. Even more, BICAMS-M does not fully capture all cognitive domains relevant to MS, particularly lacking measures of cognitive flexibility as part of executive functions. Executive functions, including planning, problem solving, inhibition, working memory, cognitive flexibility, and strategic thinking [22,23], are a key cognitive domain affected in MS, with evidence of early impairment in the course of the disease [22,24]. Considering the clinical implications, executive functions are often neglected in brief cognitive screening tests, as they usually require more time for administration. One of the briefest and most widely used executive function measurements is the verbal fluency test for one or two minutes. It is considered a sensitive and valid measure of cognitive flexibility and executive control, which is especially true for the 2nd minute of performance [22,25–28].

To address these issues, a preliminary study by Taranu et al. [29] recently introduced TRACK-MS, a very brief (approximately 5 min to administer) cognitive screening tool designed to detect cognitive impairment in MS patients. TRACK-MS concentrates on the SDMT and the Controlled Oral Word Association Test (COWAT; verbal fluency) [30], two subtests shown to correlate strongly with the Expanded Disability Status Scale (EDSS) in a German MS cohort [29]. TRACK-MS also distinguished MS patients from healthy controls (HC), demonstrating its potential for efficient cognitive monitoring. However, in the first step of TRACK-MS development, the validation was based on a small clinical sample. Moreover, for the application in German-speaking patients, there is a lack of appropriate normative data for the COWAT, as it is not validated for this language. Finally, there was limited evidence with regard to diagnostic validity, despite sensitivity and specificity being key criteria for a valid and reliable diagnostic marker of cognition in MS [29].

We hereby present a revised version of TRACK-MS, which also uses the SDMT but replaces the original verbal fluency measure with a well-validated, language-adapted German verbal fluency task [31,32]. This adapted version, referred to as TRACK-MS Revised (TRACK-MS-R), preserves the original version's brevity while incorporating information processing and executive function through a 2 min verbal fluency task, for which many different language-specific norms are available. With this approach a combination of a non-culturally dependent screening battery for cognitive processing speed (SDMT) and fluency task with an additional time-related flexibility factor in executive functioning (2 min verbal fluency) is provided for cross-national comparison. It may thus provide an executive

function and language-specific compound marker as a valuable supplement to the current gold standard BICAMS-M (with its major focus on memory domain functioning). While replacing the COWAT with the RWT mainly ensures linguistic and normative appropriateness for German speakers, both tests measure the same fundamental aspect of phonemic verbal fluency. Importantly, the extended 2-min version of the RWT improves sensitivity to executive dysfunction by detecting changes in word production over time, thereby preserving the construct validity and diagnostic accuracy of the original TRACK-MS approach.

We evaluated the diagnostic utility of TRACK-MS-R by (1) assessing its sensitivity and specificity as a cognitive screening tool in MS patients, using the established gold standard BICAMS-M as a reference, and (2) by additionally examining its ability to distinguish MS patients from HC, thereby exploring its potential as a cognitive marker.

2. Materials and Methods

2.1. Design and Participants

One hundred and two MS patients attending the out- and inpatient clinic at the Department of Neurology at Ulm University were consecutively enrolled in this prospective cross-sectional study, with a 24-month data collection period (2023–2025). Also, ninety-four age-, sex-, and education-matched HC were recruited via advertisements in sports facilities and public locations. Inclusion criteria for patients were a diagnosis of clinically and laboratory-confirmed definite MS according to revised McDonald's criteria [33], and for all subjects, the ability to comprehend and communicate during assessments. Exclusion criteria included motor, speech, or language impairments affecting test validity; severe psychiatric or cognitive disorders; recent corticosteroid use (patients had to be stable for at least 30 days before data collection, with no corticosteroid treatment or relapse interfering during this period); or unstable clinical status. The study was approved by the ethics committee of the University of Ulm (No. 335/23). All participants gave informed consent prior to their inclusion in the study.

2.2. Procedure

All MS patients underwent a comprehensive clinical neurological examination by a trained physician in the clinical setting. Subsequently, participants completed a detailed neuropsychological assessment focusing on memory, attention, executive, and visuospatial functions. In addition, participants reported outcome measures on depression, anxiety, and fatigue, while demographics and clinical data were collected via semi-structured interviews. Physical impairment was measured using the Expanded Disability Status Scale (EDSS with values from 0 = normal neurological function to 10 = death) [34].

2.3. Detailed Neuropsychological Assessment

To exclude severe cognitive impairment and to provide a benchmark scale for cognitive function, an extensive neuropsychological assessment was conducted, targeting a broad range of cognitive domains. Verbal short-term and working memory were evaluated using the Digit Span Test from the Wechsler Memory Scale-Revised (WMS-R) [35], while nonverbal short-term and working memory were assessed with the Block-Tapping Test (WMS-R). Verbal and visual episodic memory were addressed using the Verbal Learning and Memory Test (VLMT) [19] and the revised version of the Brief Visuospatial Memory Test (BVMT-R) [20]. Attention domains, including divided attention and incompatibility, were evaluated with the German "Testbatterie zur Aufmerksamkeitsprüfung" (TAP) [36]. Logical reasoning and concept formation were assessed using the Matrices subtest of the German version of the Wechsler Adult Intelligence Scale (WAIS) [37].

2.4. TRACK-MS and TRACK-MS-R

The Symbol Digit Modalities Test (SDMT) [21] was employed to measure information processing speed as well as divided and selective attention. Verbal fluency was assessed using both the Controlled Oral Word Association Test (COWAT) [30] and the Regensburger Wortflüssigkeitstest (RWT, phonematic fluency letter "S"), the most widely used German adaptation of verbal fluency measures [31,32].

The ultrashort screening tool TRACK-MS (SDMT + COWAT) was established as a very brief repeatable cognitive tracking tool with comparable test quality criteria as BICAMS-M [29], combining the two tests with the highest validity for MS-specific cognitive changes—the Controlled Oral Word Association Test (COWAT) and SDMT—with an administration time of 5 min.

The revised version of TRACK-MS (TRACK-MS-R, SDMT + RWT, letter "S") replaces the COWAT with the RWT, which is the German equivalent, and allows a 2-min word generation period using the letter "S". In contrast, the COWAT requires participants to generate words using the letters "F-A-S" for one minute each. TRACK-MS-R is thus slightly shorter than the original version (about 4 min). Most importantly, normative data for the German-speaking population are available.

2.5. MS-Specific Cognitive Screening Batteries

The current gold standard for cognitive screening in MS, the Brief International Cognitive Assessment for MS (BICAMS-M), which was established by the international expert consensus committee to promote and facilitate an international standard, was used in its validated German version [38]. It includes tests of cognitive processing speed (SDMT) and verbal and non-verbal memory (VLMT learning and BVMT-R learning) [17] and takes approximately 20 min to administer.

2.6. Depression and Anxiety

Depression and anxiety were documented as patient-reported measures using the Hospital Anxiety and Depression Scale (HADS; 7 items, range 0 to 21 for depression and anxiety, respectively), which is specifically aimed at people with physical illnesses or physical complaints, with cut-off scores for mild ($\geq$8), moderate ($\geq$11), or severe ($\geq$15) [39] depression and anxiety, respectively.

2.7. Fatigue

Fatigue was measured using the Fatigue Scale for Motor and Cognitive Functions (FSMC), a 20-item questionnaire evaluating motor and cognitive fatigue. Each item is rated on a 5-point Likert scale (1–5), with cut-offs for motor fatigue: mild ($\geq$22), moderate ($\geq$27), severe ($\geq$32); for cognitive fatigue: mild ($\geq$22), moderate ($\geq$28), severe ($\geq$34) [40].

2.8. Statistical Analysis

Statistical analyses were performed using SPSS version 29 (IBM Corp., Armonk, NY, USA). A priori power calculations ensured 80% power to detect medium to large effect sizes (partial η^2 = 0.06–0.14) with α = 0.05, requiring N = 94 MS patients and N = 94 HC. Gender matching was assessed using the chi-square test. Group differences in cognition, depression, anxiety, and fatigue were analyzed via ANOVA/ANCOVA. A normal distribution can be assumed due to the sample size of N > 30 [41]. Composite scores for BICAMS-M and TRACK-MS-R were calculated by averaging z-standardized subtest scores. Z-standardization was performed using data from 94 HC. Sensitivity and specificity were calculated using a standard 2 $\times$ 2 contingency table (TN = true negative,

TP = true positive, FP = false positive, FN = false negative), with the following formulas: specificity = TN/(TN + FP) and sensitivity = TP/(TP + FN).

3. Results

3.1. Demographics and Clinical Data

A total of 196 participants were included, comprising 102 patients with MS and 94 HC. The groups were comparable in terms of age and education. A significantly higher proportion of females was observed in the HC group compared to the MS patients. The majority of MS patients were diagnosed with relapsing-remitting MS (RRMS), and overall patients showed only minor physical impairment, as indicated by a mean EDSS score $\leq$ 3.5 [42]. Participant characteristics are summarized in Table 1.

Table 1. Demographics and clinical data.

Characteristics	MS Patients (N = 102)		HC * (N = 94)		Statistics [a]
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	45.49 (13.29)		47.13 (14.11)		$F(1, 194) = 0.70$, $p = 0.404$
Female/Male		61/41 (59.8/40.2)		69/25 (73.4/26.6)	$\chi^2(1) = 4.05$, $p = 0.044$
Years of education	14.61 (2.92)		14.91 (2.85)		$F(1, 194) = 0.56$, $p = 0.457$
EDSS *	2.79 (1.82)				
Time since diagnosis (years)	9.97 (8.09)				
Phenotype					
RRMS *		73 (71.6)			
PPMS *		11 (10.8)			
SPMS *		17 (16.7)			

* EDSS = Expanded Disability Status Scale; RRMS = Relapsing Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; PPMS = Primary Progressive Multiple Sclerosis; HC = Healthy Controls. [a] ANOVA or Chi-square test for group comparison; threshold for significant difference with $p < 0.05$.

3.2. Neuropsychological Assessment

After controlling for gender, significant differences between MS patients and HC were observed across most cognitive domains assessed in the extensive neuropsychological test battery (see Table 2). MS patients showed significantly lower performance compared to HC in verbal and nonverbal short-term memory, verbal working memory, verbal and visual episodic memory, attentional functions (including visual divided attention, incompatibility, and cognitive processing speed), and executive functions. No significant group differences were found for nonverbal working memory (Block-Tapping Test backwards), the recognition task of visual episodic memory (BVMT-R recognition), and auditory divided attention (all $F < 2.56$ and $p > 0.05$). These specific subtests are not included in core cognitive test batteries such as TRACK-MS-R or BICAMS-M and are therefore not considered further in the subsequent sensitivity and specificity analyses.

Table 2. Neuropsychological profile, affective state, and fatigue.

Cognitive Domains/PROMs *		MS Patients		HC *		Statistics [a]		
Tests	**N (Cohort)**	**Mean (SD)**	**N (%)**	**Mean (SD)**	**N (%)**	***F***	***p*-Value**	**Partial η^2**
Verbal short-term memory								
digit span forward	196	7.00 (1.85)		8.11 (1.65)		9.77	**<0.001**	0.092
Nonverbal short-term memory								
block-tapping-test forward	196	8.17 (1.83)		9.39 (1.77)		11.82	**<0.001**	0.109
Verbal working memory								
digit span backwards	196	5.75 (1.97)		6.81 (1.86)		8.15	**<0.001**	0.78
Nonverbal working memory								
block-tapping-test backwards	196	8.45 (6.70)		10.59 (10.89)		1.40	0.248	0.014
Verbal episodic memory								
VLMT * total	196	50.55 (11.45)		59.31 (8.05)		30.16	**<0.001**	0.238
VLMT * delayed recall	196	10.14 (3.94)		12.78 (2.64)		21.10	**<0.001**	0.179
VLMT * recognition	196	13.37 (2.60)		14.48 (0.86)		7.89	**<0.001**	0.076
Visual episodic memory								
BVMT-R * total	196	24.55 (8.04)		28.20 (5.49)		6.94	**0.001**	0.067
BVMT-R * delayed recall	196	9.73 (2.88)		10.85 (1.73)		5.96	**0.003**	0.058
BVMT-R * recognition	196	5.65 (0.94)		5.87 (0.42)		2.56	0.080	0.026
Attentional functions								
TAP * divided attention (auditory)	190	657.82 (159.65)		613.09 (111.74)		2.47	0.087	0.026
TAP * divided attention (visual)	190	871.54 (214.88)		757.03 (95.60)		11.41	**<0.001**	0.109
TAP * incompatibility	190	573.99 (180.83)		501.68 (109.98)		5.47	**0.005**	0.055
SDMT *	196	50.13 (13.31)		59.77 (9.33)		17.05	**<0.001**	0.150
Executive functions								
phonemic verbal fluency (RWT * S)	196	18.99 (7.16)		24.47 (7.01)		14.95	**<0.001**	0.135
phonemic verbal fluency (COWAT *)	196	34.25 (9.95)		43.77 (12.11)		19.22	**<0.001**	0.166
matrices (WAIS *)	193	17.16 (4.81)		19.51 (3.13)		8.38	**<0.001**	0.081
Cognitive fatigue (FSMC *)	196	30.12 (12.05)		18.46 (7.50)		32.46	**<0.001**	0.253
mild			13 (12.7)		18 (19.1)			
moderate			17 (16.7)		9 (9.6)			
severe			44 (43.1)		3 (3.2)			
Motor fatigue (FSMC *)	196	31.83 (11.60)		18.34 (7.31)		46.19	**<0.001**	0.325
mild			10 (9.8)		16 (17)			
moderate			11 (10.8)		10 (10.6)			
severe			57 (55.9)		4 (4.3)			

Table 2. *Cont.*

Cognitive Domains/PROMs *		MS Patients		HC *		Statistics [a]		
Depression (HADS-D *)	196	5.81 (4.20)		2.96 (2.64)		16.26	**<0.001**	0.144
mild			20 (19.6)		7 (7.4)			
moderate			14 (13.7)		0 (0)			
severe			2 (2)		0 (0)			
Anxiety (HADS-A *)	196	7.19 (4.48)		4.29 (2.55)		15.06	**<0.001**	0.135
mild			19 (18.6)		7 (7.4)			
moderate			15 (14.7)		0 (0)			
severe			9 (8.8)		0 (0)			

* PROMs = Patient-Reported Outcome Measures; HC = Healthy Controls; VLMT = Verbal Learning Memory Test; BVMT-R = Brief Visuospatial Memory Test—Revised; TAP = Testbatterie zur Aufmerksamkeitsprüfung; SDMT = Symbol Digit Modalities Test; RWT = Regensburger Wortflüssigkeitstest (German Version of Verbal Fluency); COWAT = Controlled Oral Word Association Test; WAIS = Wechsler Adult Intelligence Scale; FSMC = Fatigue Scale for Motor and Cognitive Functions; HADS = Hospital Anxiety and Depression Scale. [a] ANCOVA for group comparison, adjusted for gender; threshold for significant difference with $p < 0.05$ (significant results are highlighted in bold).

3.3. Affective State and Fatigue

MS patients reported significantly greater symptoms of depression and anxiety and higher levels of cognitive and motor fatigue (see Table 2).

3.4. Sensitivity and Specificity of TRACK-MS-R vs. Gold Standard BICAMS-M

To evaluate the utility as a screening tool for cognitive impairment within the MS population, the sensitivity and specificity of TRACK-MS-R were determined using BICAMS-M as the gold standard. The classification was based on the standard 2 × 2 contingency table (see Figure 1). Based on these data, TRACK-MS-R demonstrated a sensitivity of 97.44% and a specificity of 62.90% when compared to the gold standard BICAMS-M (see Figure 1).

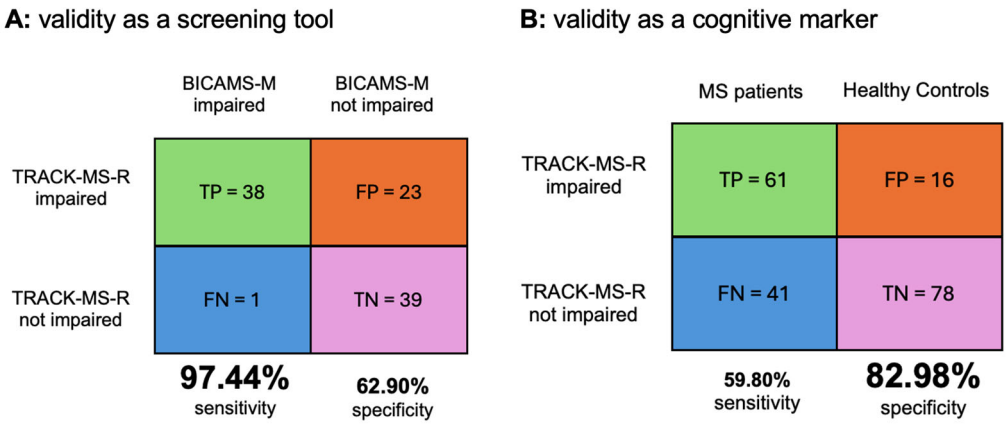


Figure 1. Validity of TRACK-MS-R. Standard 2 × 2 contingency tables illustrating the validity of TRACK-MS-R as a screening tool (**A**) and as a cognitive marker (**B**). The matrices display true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) to determine sensitivity and specificity. (**A**): classification of MS patients by TRACK-MS-R compared to the gold standard BICAMS-M. (**B**): classification performance of TRACK-MS-R in differentiating MS patients from Heathy Controls. Colors are used solely for visual clarity: green = TP, orange = FP, blue = FN, purple = TN.

3.5. Sensitivity and Specificity of TRACK-MS-R as a Cognitive Marker of MS

To further assess the utility of TRACK-MS-R as a potential cognitive marker to classify MS patients as impaired in comparison to HC, a 2 × 2 contingency table was again applied to calculate sensitivity and specificity relative to HC classification (see Figure 1). Based on this classification, TRACK-MS-R yielded a specificity of 82.98% in distinguishing MS patients from HC (see Figure 1) and a sensitivity of 59.80%.

4. Discussion

This study evaluated the diagnostic utility of the revised version of the very short test battery TRACK-MS (TRACK-MS-R) for detecting cognitive impairment in patients with MS in routine clinical and doctor practice. We hereby present diagnostic performance metrics such as sensitivity and specificity for the German-speaking population. Results indicate that TRACK-MS-R is a highly sensitive screening tool (97.44%) for identifying cognitive impairment in MS patients, which is often a result of cortical involvement/lesions and more prevalent in progressive disease states [2,43]. TRACK-MS-R demonstrates good specificity (82.98%) when distinguishing MS patients from healthy controls, which allows a more precise definition of MS-specific cognitive changes. The short administration time of a maximum of 5 min further underscores its potential for implementation in clinical routine in hospitals and medical practices, i.e., time-constrained settings [44] compared to the current gold standard BICAMS-M. By confirming and broadening the applicability of TRACK-MS-R in a larger and more representative German-speaking cohort of MS patients and HC, these findings build upon and extend the previous work by Taranu et al. [29], who introduced the original TRACK-MS as a brief and clinically feasible alternative to standard cognitive assessments such as the current gold standard BICAMS-M [17]. In contrast to the initial validation, the current study incorporates a language-adapted verbal fluency task [31], for which extensive normative data for many different languages, including the German-speaking population, are available. The hereby presented diagnostic validation of TRACK-MS-R represents a critical step toward clinical utility, as it allows for reliable and time-efficient identification of cognitively impaired individuals in everyday practice, without sacrificing diagnostic accuracy. As a compound marker of cognitive processing speed and executive functioning, it substantially adds to the current gold standard BICAMS-M. The inclusion of information processing speed and executive functioning as key domains in TRACK-MS-R emphasizes its clinical importance and accounts for its ability to detect early cognitive changes in MS. These functions are closely related to the integrity of frontal and subcortical white matter pathways, which are often affected by inflammatory lesions and neurodegenerative changes typical of MS [45–49]. Neuroimaging studies consistently show that cognitive impairment in MS is linked to both cortical lesions and the disruption of fronto-subcortical circuits involved in executive control and mental flexibility [50–52]. Processing speed in particular is one of the most sensitive cognitive domains affected in MS and correlates strongly with lesion burden, white matter disconnection, and regional atrophy in these networks [50–52]. These pathophysiological insights strengthen the construct validity of TRACK-MS-R and support its use as a practically feasible screening tool that targets neural systems affected early in MS-related cognitive decline.

As emphasized in recent literature [2,6,53–61], our findings align with the urgent need to implement more time-efficient cognitive screening instruments into routine clinical care for MS patients. Due to its high sensitivity, TRACK-MS-R ensures that cognitively impaired MS patients are correctly identified. In clinical practice, this makes TRACK-MS-R particularly useful for "ruling in" individuals who may benefit from more comprehensive neuropsychological evaluation or early cognitive interventions [62,63]. Its greatest utility may lie in early-stage screening, where subtle cognitive changes can guide timely diag-

nostic clarification or therapeutic adjustments [5,55,58,64]. Moreover, this high sensitivity significantly reduces the risk of underdiagnosis, an ongoing challenge in MS care, where cognitive symptoms often remain unrecognized and thus untreated [3,54,65,66].

While the high sensitivity of TRACK-MS-R supports its utility as an early detection tool, its moderate specificity (62.9% compared to BICAMS-M) indicates that some MS patients without relevant cognitive impairment may screen positive. In routine clinical care, this trade-off may be acceptable when the main goal is early detection of cognitive impairment. However, clinicians should be aware that a positive TRACK-MS-R result may require additional, more elaborate neuropsychological assessment to confirm impairment and determine appropriate interventions.

The good specificity of TRACK-MS-R compared to HC indicates that MS patients are accurately classified as cognitively impaired, minimizing false-negative results. This strengthens the tool's reliability in distinguishing MS-related cognitive impairment from normal cognitive functioning. As such, TRACK-MS-R holds promise not only for individual-level screening but also as a supportive tool in research contexts. These findings are in line with those reported by Taranu et al. [29], who also demonstrated significant group-level differences using the original TRACK-MS battery in a German MS sample, thereby further validating the clinical and research utility of the TRACK-MS approach.

From a methodological standpoint, replacing the Controlled Oral Word Association Test (COWAT) [30] with the RWT strengthened the construct validity of the verbal fluency domain while enhancing its linguistic and cultural appropriateness for German-speaking populations in specific. Many different language-specific adaptations of the verbal fluency measure are available and may be implemented as required, substantially increasing the wide application of Track-MS-R and making it especially important for international studies. Building on this, the RWT improves the diagnostic validity of TRACK-MS-R by incorporating a full two-minute word generation period. This captures the decline in verbal output associated with controlled retrieval and executive function [67]. In the future, other subtests of the RWT, in addition to assessing formal-lexical fluency, may be added, as the RWT also offers subtests to assess semantic fluency and both formal-lexical and semantic category switching. This allows for a more comprehensive evaluation of executive domains without substantially extending the test administration time. While TRACK-MS-R was validated in a German-speaking population using an adapted and linguistically validated verbal fluency task, future research is needed to evaluate its applicability in broader linguistic and cultural contexts. Given that language-specific versions of the verbal fluency task do exist, TRACK-MS-R could be adapted in a modular way to support cross-national comparisons while maintaining strong psychometric properties. This approach would enable testing and potentially implementing TRACK-MS-R in various international healthcare settings.

The implications of these findings are two-fold. First, due to its brevity and ease of administration, TRACK-MS-R is suitable not only for neuropsychologists or neurologists but also for other healthcare professionals involved in MS care, such as general practitioners or nurses. This broadens its applicability in interdisciplinary settings. Second, the reliable group-level differentiation between MS patients and healthy controls supports its potential use as a cognitive marker in clinical research.

However, certain limitations must be acknowledged: (a) While the sample size was sufficient for cross-sectional diagnostic analyses, future studies need to examine the longitudinal sensitivity of TRACK-MS-R to detect subtle cognitive decline over time, which would provide further evidence for its utility in disease monitoring; (b) Unlike more comprehensive cognitive screening batteries like BICAMS-M, TRACK-MS-R does not directly assess memory functions, so it is not an integral cognitive screening tool. However, the

RWT verbal fluency task indirectly captures memory-relevant processes: retrieving words from long-term memory is essential to completing the task. Also, working memory is addressed since patients have to monitor their verbal output to avoid repetition. Therefore, although there are no explicit memory subtests, certain memory-related mechanisms (e.g., working and episodic memory) are still involved [26]; (c) Participants were recruited from a single university hospital and by public advertisements. This convenience sampling may limit the generalizability of findings to broader MS populations, particularly those with lower education levels or more severe physical disability; (d) Although TRACK-MS-R combines a well-known verbal fluency measure (RWT) with existing normative data for the German-speaking population, there are currently no separate normative data for the complete TRACK-MS-R screening tool. This approach was chosen to enable early clinical application and feasibility testing. However, we are currently conducting longitudinal follow-up studies within a German MS cohort to evaluate TRACK-MS and TRACK-MS-R over time. These studies aim to evaluate the sensitivity of TRACK-MS-R in detecting subtle cognitive changes at different disease stages and treatment intervals. As part of this, we are validating both tools across inpatient and outpatient settings and are currently developing specific normative data for TRACK-MS-R. This will enable the creation of reliable change indices, which are crucial for interpreting within-subject changes across different time points. Developing these normative data will further strengthen its diagnostic validity and clinical applicability for future studies.

5. Conclusions

In conclusion, TRACK-MS-R emerges as a psychometrically robust, time-efficient, and clinically feasible cognitive screening instrument for MS patients. By demonstrating excellent sensitivity and solid specificity, TRACK-MS-R provides a valid screening alternative to more time-consuming test batteries such as BICAMS-M, without compromising diagnostic accuracy. It may as well be used in addition to BICAMS-M to extend the BICAMS-M memory domain related findings by the executive function domain of Track-MS-R. Its brief administration time, cultural adaptability through validated language-specific norms, and focus on core cognitive domains relevant to MS—namely, processing speed and verbal fluency—render it highly suitable for routine implementation in a broad spectrum of clinical settings, including outpatient care and non-specialist environments. Furthermore, its potential application as a cognitive marker may support its integration into longitudinal monitoring protocols and research frameworks. Future longitudinal studies are warranted to confirm its utility in tracking cognitive trajectories and informing therapeutic decisions over the course of the disease. Overall, TRACK-MS-R represents a significant contribution to the practical assessment of cognitive function in MS, also addressing an unmet need in time-constrained clinical practice.

Author Contributions: Conceptualization, L.T.B., I.U., H.S., D.E.L. and H.T.; Data curation, L.T.B.; Formal analysis, L.T.B. and D.E.L.; Investigation, L.T.B.; Methodology, L.T.B. and D.E.L.; Project administration, D.E.L. and H.T.; Resources, D.E.L. and H.T.; Software, L.T.B.; Supervision, I.U., D.E.L. and H.T.; Validation, L.T.B., D.E.L. and H.T.; Visualization, L.T.B. and D.E.L.; Writing—original draft, L.T.B. and D.E.L.; Writing—review and editing, L.T.B., I.U., D.T., D.K.E., T.F., S.J., H.S., M.S., I.V., D.E.L. and H.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ulm University (File number 335/23, 19 December 2023).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgments: The authors thank all participants, including patients and healthy controls, for their valuable contribution to this study.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MS	Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
EDSS	Expanded Disability Status Scale
HC	Healthy Controls
BICAMS	Brief International Cognitive Assessment for MS
VLMT	Verbal Learning and Memory Test
BVMT-R	Brief Visuospatial Memory Test—Revised Version
SDMT	Symbol Digit Modalities Test
COWAT	Controlled Oral Word Association Test
WAIS	Wechsler Adult Intelligence Scale
RWT	Regensburger Wortflüssigkeitstest
TAP	Testbatterie zur Aufmerksamkeitsprüfung
WMS-R	Wechsler Memory Scale-Revised
HADS	Hospital Anxiety and Depression Scale
FSMC	Fatigue Scale for Motor and Cognitive Functions
TN	True negative
TP	True positive
FP	False positive
FN	False negative

References

1. Chiaravalloti, N.D.; De Luca, J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* **2008**, *7*, 1139–1151. [CrossRef] [PubMed]
2. Benedict, R.H.B.; Amato, M.P.; DeLuca, J.; Geurts, J.J.G. Cognitive impairment in multiple sclerosis: Clinical management, MRI, and therapeutic avenues. *Lancet Neurol.* **2020**, *19*, 860–871. [CrossRef]
3. Amato, M.P.; Zipoli, V.; Portaccio, E. Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *J. Neurol. Sci.* **2006**, *245*, 41–46. [CrossRef]
4. Eijlers, A.J.C.; van Geest, Q.; Dekker, I.; Steenwijk, M.D.; Meijer, K.A.; Hulst, H.E.; Barkhof, F.; Uitdehaag, B.M.J.; Schoonheim, M.M.; Geurts, J.J.G. Predicting cognitive decline in multiple sclerosis: A 5-year follow-up study. *Brain* **2018**, *141*, 2605–2618. [CrossRef]
5. Macias Islas, M.A.; Ciampi, E. Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines* **2019**, *7*, 22. [CrossRef]
6. Kalb, R.; Beier, M.; Benedict, R.H.; Charvet, L.; Costello, K.; Feinstein, A.; Gingold, J.; Goverover, Y.; Halper, J.; Harris, C.; et al. Recommendations for cognitive screening and management in multiple sclerosis care. *Mult. Scler.* **2018**, *24*, 1665–1680. [CrossRef]
7. Benito-Leon, J.; Morales, J.M.; Rivera-Navarro, J.; Mitchell, A. A review about the impact of multiple sclerosis on health-related quality of life. *Disabil. Rehabil.* **2003**, *25*, 1291–1303. [CrossRef]
8. Morrow, S.A.; Rosehart, H.; Pantazopoulos, K. Anxiety and Depressive Symptoms Are Associated with Worse Performance on Objective Cognitive Tests in MS. *J. Neuropsychiatry Clin. Neurosci.* **2016**, *28*, 118–123. [CrossRef]
9. Ruet, A.; Deloire, M.; Hamel, D.; Ouallet, J.C.; Petry, K.; Brochet, B. Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: A 7-year longitudinal study. *J. Neurol.* **2013**, *260*, 776–784. [CrossRef]

10. De Meo, E.; Portaccio, E.; Giorgio, A.; Ruano, L.; Goretti, B.; Niccolai, C.; Patti, F.; Chisari, C.G.; Gallo, P.; Grossi, P.; et al. Identifying the Distinct Cognitive Phenotypes in Multiple Sclerosis. *JAMA Neurol.* **2021**, *78*, 414–425. [CrossRef]
11. Wills, O.; Probst, Y. Towards new perspectives: A scoping review and meta-synthesis to redefine brain health for multiple sclerosis. *Eur. J. Neurol.* **2024**, *31*, e16210. [CrossRef] [PubMed]
12. Delgado-Alvarez, A.; Delgado-Alonso, C.; Goudsmit, M.; Gil, M.J.; Diez-Cirarda, M.; Valles-Salgado, M.; Montero-Escribano, P.; Hernandez-Lorenzo, L.; Matias-Guiu, J.; Matias-Guiu, J.A. Validation of a brief cross-cultural cognitive screening test in Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2022**, *67*, 104091. [CrossRef] [PubMed]
13. Lechner-Scott, J.; Agland, S.; Allan, M.; Darby, D.; Diamond, K.; Merlo, D.; van der Walt, A. Managing cognitive impairment and its impact in multiple sclerosis: An Australian multidisciplinary perspective. *Mult. Scler. Relat. Disord.* **2023**, *79*, 104952. [CrossRef] [PubMed]
14. Sumowski, J.F.; Benedict, R.; Enzinger, C.; Filippi, M.; Geurts, J.J.; Hamalainen, P.; Hulst, H.; Inglese, M.; Leavitt, V.M.; Rocca, M.A.; et al. Cognition in multiple sclerosis: State of the field and priorities for the future. *Neurology* **2018**, *90*, 278–288. [CrossRef]
15. van Dongen, L.; Westerik, B.; van der Hiele, K.; Visser, L.H.; Schoonheim, M.M.; Douw, L.; Twisk, J.W.R.; de Jong, B.A.; Geurts, J.J.G.; Hulst, H.E. Introducing Multiple Screener: An unsupervised digital screening tool for cognitive deficits in MS. *Mult. Scler. Relat. Disord.* **2020**, *38*, 101479. [CrossRef]
16. Wojcik, C.M.; Beier, M.; Costello, K.; DeLuca, J.; Feinstein, A.; Goverover, Y.; Gudesblatt, M.; Jaworski, M., 3rd; Kalb, R.; Kostich, L.; et al. Computerized neuropsychological assessment devices in multiple sclerosis: A systematic review. *Mult. Scler.* **2019**, *25*, 1848–1869. [CrossRef]
17. Langdon, D.W.; Amato, M.P.; Boringa, J.; Brochet, B.; Foley, F.; Fredrikson, S.; Hamalainen, P.; Hartung, H.P.; Krupp, L.; Penner, I.K.; et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult. Scler.* **2012**, *18*, 891–898. [CrossRef]
18. Potticary, H.; Langdon, D. A Systematic Review and Meta-Analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations. *J. Clin. Med.* **2023**, *12*, 703. [CrossRef]
19. Helmstaedter, C.; Lendt, M.; Lux, S. *Verbaler Lern-Und Merk-Fähigkeitstest: VLMT: Manual*, 1st ed.; Hogrefe Verlag: Göttingen, Germany, 2001.
20. Benedict, R.H.B.; Schretlen, D.S.; Groninger, L.; Dobraski, M. Revision of the brief Visuospatial Memory Test: Studies of normal performance, reliability and validity. *Psychol. Assess.* **1996**, *8*, 145–153. [CrossRef]
21. Benedict, R.H.B.; DeLuca, J.; Phillips, G.; LaRocca, N.; Hudson, L.D.; Rudick, R.; Consortium, M.S.O.A. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult. Scler.* **2017**, *23*, 721–733. [CrossRef]
22. Henry, J.D.; Beatty, W.W. Verbal fluency deficits in multiple sclerosis. *Neuropsychologia* **2006**, *44*, 1166–1174. [CrossRef]
23. Godefroy, O.; Azouvi, P.; Robert, P.; Roussel, M.; LeGall, D.; Meulemans, T.; Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group. Dysexecutive syndrome: Diagnostic criteria and validation study. *Ann. Neurol.* **2010**, *68*, 855–864. [CrossRef]
24. Cerezo Garcia, M.; Martin Plasencia, P.; Aladro Benito, Y. Alteration profile of executive functions in multiple sclerosis. *Acta Neurol. Scand.* **2015**, *131*, 313–320. [CrossRef] [PubMed]
25. Meca-Lallana, V.; Gascon-Gimenez, F.; Ginestal-Lopez, R.C.; Higueras, Y.; Tellez-Lara, N.; Carreres-Polo, J.; Eichau-Madueno, S.; Romero-Imbroda, J.; Vidal-Jordana, A.; Perez-Miralles, F. Cognitive impairment in multiple sclerosis: Diagnosis and monitoring. *Neurol. Sci.* **2021**, *42*, 5183–5193. [CrossRef] [PubMed]
26. Delgado-Alvarez, A.; Matias-Guiu, J.A.; Delgado-Alonso, C.; Hernandez-Lorenzo, L.; Cortes-Martinez, A.; Vidorreta, L.; Montero-Escribano, P.; Pytel, V.; Matias-Guiu, J. Cognitive Processes Underlying Verbal Fluency in Multiple Sclerosis. *Front. Neurol.* **2020**, *11*, 629183. [CrossRef] [PubMed]
27. Blecher, T.; Miron, S.; Schneider, G.G.; Achiron, A.; Ben-Shachar, M. Association Between White Matter Microstructure and Verbal Fluency in Patients with Multiple Sclerosis. *Front. Psychol.* **2019**, *10*, 1607. [CrossRef] [PubMed]
28. Robinson, G.; Shallice, T.; Bozzali, M.; Cipolotti, L. The differing roles of the frontal cortex in fluency tests. *Brain* **2012**, *135*, 2202–2214. [CrossRef]
29. Taranu, D.; Tumani, H.; Holbrook, J.; Tumani, V.; Uttner, I.; Fissler, P. The TRACK-MS Test Battery: A Very Brief Tool to Track Multiple Sclerosis-Related Cognitive Impairment. *Biomedicines* **2022**, *10*, 2975. [CrossRef]
30. Ross, T.P.; Calhoun, E.; Cox, T.; Wenner, C.; Kono, W.; Pleasant, M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. *Arch. Clin. Neuropsychol.* **2007**, *22*, 475–488. [CrossRef]
31. Aschenbrenner, S.; Tucha, O.; Lange, K.W. *Regensburger Wortflüssigkeits-Test (RWT)*; Hogrefe Verlag: Göttingen, Germany, 2000.
32. Shao, Z.; Janse, E.; Visser, K.; Meyer, A.S. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front. Psychol.* **2014**, *5*, 772. [CrossRef]
33. Thompson, A.J.; Banwell, B.L.; Barkhof, F.; Carroll, W.M.; Coetzee, T.; Comi, G.; Correale, J.; Fazekas, F.; Filippi, M.; Freedman, M.S.; et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet. Neurol.* **2018**, *17*, 162–173. [CrossRef]

34. Cao, H.; Peyrodie, L.; Agnani, O.; Cavillon, F.; Hautecoeur, P.; Donzé, C. Evaluation of an Expanded Disability Status Scale (EDSS) modeling strategy in multiple sclerosis. *Med. Biol. Eng. Comput.* **2015**, *53*, 1141–1151. [CrossRef] [PubMed]
35. Elwood, R.W. The Wechsler Memory Scale-Revised: Psychometric characteristics and clinical application. *Neuropsychol. Rev.* **1991**, *2*, 179–201. [CrossRef] [PubMed]
36. Zimmermann, P.; Fimm, B. *Testbatterie Zur Aufmerksamkeitsprufung (TAP)*; Psytest: Freiburg, Germany, 1992.
37. Petermann, F. *Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV)*, 4th ed.; Pearson Assessment: Frankfurt am Main, Germany, 2012.
38. Filser, M.; Schreiber, H.; Pottgen, J.; Ullrich, S.; Lang, M.; Penner, I.K. The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS): Results from the German validation study. *J. Neurol.* **2018**, *265*, 2587–2593. [CrossRef]
39. Snaith, R.P. The Hospital Anxiety And Depression Scale. *Health Qual. Life Outcomes* **2003**, *1*, 29. [CrossRef] [PubMed]
40. Penner, I.K.; Raselli, C.; Stöcklin, M.; Opwis, K.; Kappos, L.; Calabrese, P. The Fatigue Scale for Motor and Cognition Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult. Scler.* **2009**, *15*, 1509–1517. [CrossRef]
41. Lix, L.M.; Keselman, J.C.; Keselman, H.J. Consequences of Assumption Violations Revisited: A Quantitative Review of Alternatives to the One-Way Analysis of Variance F Test. *Rev. Educ. Res.* **1996**, *66*, 579–619. [CrossRef]
42. Conradsson, D.; Ytterberg, C.; von Koch, L.; Johansson, S. Changes in disability in people with multiple sclerosis: A 10-year prospective study. *J. Neurol.* **2018**, *265*, 119–126. [CrossRef]
43. Brochet, B.; Ruet, A. Cognitive Impairment in Multiple Sclerosis with Regards to Disease Duration and Clinical Phenotypes. *Front. Neurol.* **2019**, *10*, 261. [CrossRef]
44. Portaccio, E.; Amato, M.P. Cognitive Impairment in Multiple Sclerosis: An Update on Assessment and Management. *NeuroSci* **2022**, *3*, 667–676. [CrossRef]
45. Louapre, C.; Perlbarg, V.; Garcia-Lorenzo, D.; Urbanski, M.; Benali, H.; Assouad, R.; Galanaud, D.; Freeman, L.; Bodini, B.; Papeix, C.; et al. Brain networks disconnection in early multiple sclerosis cognitive deficits: An anatomofunctional study. *Hum. Brain Mapp.* **2014**, *35*, 4706–4717. [CrossRef]
46. Rocca, M.A.; Valsasina, P.; Hulst, H.E.; Abdel-Aziz, K.; Enzinger, C.; Gallo, A.; Pareto, D.; Riccitelli, G.; Muhlert, N.; Ciccarelli, O.; et al. Functional correlates of cognitive dysfunction in multiple sclerosis: A multicenter fMRI Study. *Hum. Brain Mapp.* **2014**, *35*, 5799–5814. [CrossRef]
47. Akaike, S.; Okamoto, T.; Kurosawa, R.; Onodera, N.; Lin, Y.; Sato, W.; Yamamura, T.; Takahashi, Y. Exploring the Potential of the Corpus Callosum Area as a Predictive Marker for Impaired Information Processing in Multiple Sclerosis. *J. Clin. Med.* **2023**, *12*, 6948. [CrossRef] [PubMed]
48. Gregorio, F.D.; Battaglia, S. The intricate brain-body interaction in psychiatric and neurological diseases. *Adv. Clin. Exp. Med.* **2024**, *33*, 321–326. [CrossRef]
49. Calabrese, M.; Agosta, F.; Rinaldi, F.; Mattisi, I.; Grossi, P.; Favaretto, A.; Atzori, M.; Bernardi, V.; Barachino, L.; Rinaldi, L.; et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Arch. Neurol.* **2009**, *66*, 1144–1150. [CrossRef] [PubMed]
50. Petracca, M.; Pontillo, G.; Moccia, M.; Carotenuto, A.; Cocozza, S.; Lanzillo, R.; Brunetti, A.; Brescia Morra, V. Neuroimaging Correlates of Cognitive Dysfunction in Adults with Multiple Sclerosis. *Brain Sci.* **2021**, *11*, 346. [CrossRef] [PubMed]
51. Burggraaff, J.; Liu, Y.; Prieto, J.C.; Simoes, J.; de Sitter, A.; Ruggieri, S.; Brouwer, I.; Lissenberg-Witte, B.I.; Rocca, M.A.; Valsasina, P.; et al. Manual and automated tissue segmentation confirm the impact of thalamus atrophy on cognition in multiple sclerosis: A multicenter study. *Neuroimage Clin.* **2021**, *29*, 102549. [CrossRef]
52. Rocca, M.A.; Amato, M.P.; De Stefano, N.; Enzinger, C.; Geurts, J.J.; Penner, I.K.; Rovira, A.; Sumowski, J.F.; Valsasina, P.; Filippi, M.; et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol.* **2015**, *14*, 302–317. [CrossRef]
53. Piacentini, C.; Argento, O.; Nocentini, U. Cognitive impairment in multiple sclerosis: "classic" knowledge and recent acquisitions. *Arq. Neuropsiquiatr.* **2023**, *81*, 585–596. [CrossRef]
54. Elwick, H.; Topcu, G.; Allen, C.M.; Drummond, A.; Evangelou, N.; Nair, R.D. Cognitive measures used in adults with multiple sclerosis: A systematic review. *Neuropsychol. Rehabil.* **2022**, *32*, 2464–2481. [CrossRef]
55. Oset, M.; Stasiolek, M.; Matysiak, M. Cognitive Dysfunction in the Early Stages of Multiple Sclerosis-How Much and How Important? *Curr. Neurol. Neurosci. Rep.* **2020**, *20*, 22. [CrossRef]
56. Elwick, H.; Smith, L.; Mhizha-Murira, J.R.; Topcu, G.; Leighton, P.; Drummond, A.; Evangelou, N.; Das Nair, R. Cognitive assessment in multiple sclerosis clinical care: A qualitative evaluation of stakeholder perceptions and preferences. *Neuropsychol. Rehabil.* **2021**, *32*, 1456–1474. [CrossRef]
57. Stavrogianni, K.; Giannopapas, V.; Kitsos, D.K.; Christouli, N.; Smyrni, V.; Chasiotis, A.K.; Akrivaki, A.; Dimitriadou, E.M.; Tzartos, J.S.; Tsivgoulis, G.; et al. Cognitive Impairment in Newly Diagnosed Patients with Multiple Sclerosis: A Systematic Review of Related Molecular Biomarkers and a Meta-Analysis of Associated Demographic and Disease-Related Characteristics. *J. Clin. Med.* **2025**, *14*, 2630. [CrossRef] [PubMed]

58. Pless, S.; Woelfle, T.; Naegelin, Y.; Lorscheider, J.; Wiencierz, A.; Reyes, O.; Calabrese, P.; Kappos, L. Assessment of cognitive performance in multiple sclerosis using smartphone-based training games: A feasibility study. *J. Neurol.* **2023**, *270*, 3451–3463. [CrossRef] [PubMed]
59. Ruano, L.; Branco, M.; Severo, M.; Sousa, A.; Castelo, J.; Araujo, I.; Pais, J.; Cerqueira, J.; Amato, M.P.; Lunet, N.; et al. Tracking cognitive impairment in multiple sclerosis using the Brain on Track test: A validation study. *Neurol. Sci.* **2020**, *41*, 183–191. [CrossRef]
60. Meca-Lallana, J.E.; Prieto-Gonzalez, J.M.; Jimenez-Veiga, J.; Carreon-Guarnizo, E.; Jimenez-Martin, I.; Hernandez-Clares, R.; Sistiaga-Berrondo, A.; Carles-Dies, R.; Garcia-Molina, E.; Cerdan-Sanchez, M.; et al. Development and validation of a brief electronic screening test for cognitive impairment in multiple sclerosis (SCI-MS Test). *Mult. Scler. Relat. Disord.* **2019**, *28*, 50–56. [CrossRef]
61. National Institute for Health and Care Excellence (NICE). *Multiple Sclerosis in Adults: Management*; NICE Guideline NG220; NICE: London, UK, 2022; Available online: https://www.nice.org.uk/guidance/ng220 (accessed on 29 July 2025).
62. Carotenuto, A.; Costabile, T.; Pontillo, G.; Moccia, M.; Falco, F.; Petracca, M.; Petruzzo, M.; Russo, C.V.; Di Stasi, M.; Paolella, C.; et al. Cognitive trajectories in multiple sclerosis: A long-term follow-up study. *Neurol. Sci.* **2022**, *43*, 1215–1222. [CrossRef]
63. Chen, O.Y.; Lipsmeier, F.; Phan, H.; Dondelinger, F.; Creagh, A.; Gossens, C.; Lindemann, M.; de Vos, M. Personalized Longitudinal Assessment of Multiple Sclerosis Using Smartphones. *IEEE J. Biomed. Health Inform.* **2023**, *27*, 3633–3644. [CrossRef]
64. Podda, J.; Tacchino, A.; Ponzio, M.; Di Antonio, F.; Susini, A.; Pedulla, L.; Battaglia, M.A.; Brichetto, G. Mobile Health App (DIGICOG-MS) for Self-Assessment of Cognitive Impairment in People with Multiple Sclerosis: Instrument Validation and Usability Study. *JMIR Form. Res.* **2024**, *8*, e56074. [CrossRef]
65. Patti, F.; Amato, M.P.; Trojano, M.; Bastianello, S.; Tola, M.R.; Goretti, B.; Caniatti, L.; Di Monte, E.; Ferrazza, P.; Brescia Morra, V.; et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: Baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Mult. Scler. J.* **2009**, *15*, 779–788. [CrossRef]
66. DeLuca, J.; Chiaravalloti, N.D.; Sandroff, B.M. Treatment and management of cognitive dysfunction in patients with multiple sclerosis. *Nat. Rev. Neurol.* **2020**, *16*, 319–332. [CrossRef]
67. Crowe, S.F. Decrease in performance on the verbal fluency test as a function of time: Evaluation in a young healthy sample. *J. Clin. Exp. Neuropsychol.* **1998**, *20*, 391–401. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Title of Publication

Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust

---

Balz, L.T., Uttner, I., Weishaupt, J., Ludolph, A.C., Taranu, D., Vardakas, I., Jung, S., Fangerau, T., Erhart, D.K., Senel, M., Tumani, H.† & Lulé, D.† Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust. *Brain Sciences 2025;15(7):745. doi:10.3390/brainsci15070745*

† These authors contributed equally to this work.

Copyright

© 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license, https://creativecommons.org/licenses/by/4.0/.

Own contributions

Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing - Original Draft Preparation, Writing - Review and Editing, Visualization

brain sciences

MDPI

Article

Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust

Luisa T. Balz, Ingo Uttner, Jochen Weishaupt, Albert C. Ludolph, Daniela Taranu, Ioannis Vardakas, Stefanie Jung, Tanja Fangerau, Deborah K. Erhart, Makbule Senel, Hayrettin Tumani † and Dorothée E. Lulé *,†

Department of Neurology, Faculty of Medicine, Ulm University, D-89081 Ulm, Germany; luisa.balz@uni-ulm.de (L.T.B.); ingo.uttner@uni-ulm.de (I.U.); jochen.weishaupt@uni-ulm.de (J.W.); albert-c.ludolph@uni-ulm.de (A.C.L.); daniela.taranu@uni-ulm.de (D.T.); ioannis.vardakas@uni-ulm.de (I.V.); stefanie.jung@rku.de (S.J.); tanja.fangerau@rku.de (T.F.); deborah.erhart@uni-ulm.de (D.K.E.); makbule.senel@uni-ulm.de (M.S.); hayrettin.tumani@uni-ulm.de (H.T.)

* Correspondence: dorothee.lule@uni-ulm.de; Tel.: +49-731-1775267

† These authors contributed equally to this work.

Abstract

Background/Objectives: Multiple sclerosis (MS) is a complex neurological disease that is associated with a broad spectrum of physical and psychological symptoms. Psychosocial adjustment (PSA) refers to the ability to cope with these challenges, which influence quality of life (QoL) and depressiveness in ways not yet fully understood. This study explores the relationship of PSA and disease-specific symptoms in MS, including fatigue, a prominent MS symptom. Additionally, PSA was compared to Amyotrophic Lateral Sclerosis (ALS) to disentangle the impact of disease trajectory on PSA. **Methods**: We interviewed 77 MS patients using patient-reported outcome measures on QoL and depression and compared them to 30 ALS patients. Confirmatory factor analysis and regression analysis were used to identify PSA indicators and predictors in MS, while *t*-tests assessed PSA differences across diseases. **Results**: Key PSA indicators in MS included physical (PQoL), mental (MQoL), and subjective (SQoL) quality of life, as well as depressiveness, with cognitive and motor fatigue emerging as significant predictors. MS patients had higher PQoL and SQoL and lower levels of depression compared to ALS patients, while both groups were comparable with regard to MQoL. **Conclusions**: PSA in MS is supported by high QoL and low depression levels, with fatigue being a significant predictor. Despite different disease trajectories, patients with MS and ALS showed comparable MQoL, indicating that both diseases similarly impact mental QoL, reflecting a partial overlap in psychosocial adjustment. Overall, psychosocial adjustment was more favorable in MS, likely due to its slower disease progression compared to ALS.

Keywords: multiple sclerosis; psychosocial adjustment; quality of life; depression; fatigue

check for updates

Academic Editors: Nicoletta Ciccarelli and Elisa Pini

Received: 23 June 2025
Revised: 4 July 2025
Accepted: 9 July 2025
Published: 11 July 2025

Citation: Balz, L.T.; Uttner, I.; Weishaupt, J.; Ludolph, A.C.; Taranu, D.; Vardakas, I.; Jung, S.; Fangerau, T.; Erhart, D.K.; Senel, M.; et al. Quality of Life in Multiple Sclerosis Compared to Amyotrophic Lateral Sclerosis: Fatigue and Fast Disease Progression Interferes with the Ability to Psychosocially Adjust. *Brain Sci.* **2025**, *15*, 745. https://doi.org/10.3390/brainsci15070745

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Multiple sclerosis (MS) is characterized by inflammation, demyelination, and axonal degeneration, leading to a wide range of neurological symptoms such as visual disturbances, limb weakness, and gait problems [1]. Over time, the disease can cause irreversible disability, affecting multiple body systems and significantly impairing psychological, cognitive, and occupational functions [1,2]. Consequently, the diagnosis of MS is a highly

stressful life event, necessitating psychosocial adjustment (PSA), which then determines patient's wellbeing. PSA in MS patients involves adapting to significant changes caused by the disease's severity and its extensive impact [2–4]. As the process of adjustment to a severe disease is complex, multi-faceted, and dynamic, defining successful PSA is challenging. One option to address PSA in the clinical context is to measure consequences of PSA, including psychological wellbeing. As there is a lack of a universal definition of PSA outcome measures, many researchers traditionally focus on quality of life (QoL) and depression in cross-sectional studies to report outcome measures of PSA in MS [2,5–7]. QoL is a multidimensional construct, which encompasses physical, psychological, and social dimensions, not merely physical integrity [8,9]. QoL can be broadly divided into health-related QoL—which itself includes physical and mental QoL components—and subjective QoL, which reflects an individual's personal evaluation of life satisfaction and emotional wellbeing. Research indicates that MS patients experience lower QoL and higher levels of depression compared to other disabled populations, which may be attributed to disease-specific factors that hamper successful psychosocial adjustment in MS. Current research provides evidence that among these, psychosocial factors may provide the strongest impact on QoL and the level of depression, even more than the disease's severity itself [3,6,10–12]. Yet, most research in MS—and, notably, as shown in studies on neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS)—focuses on health-related quality of life, which by definition interferes with disease severity [13,14]. Mental aspects of quality of life may be less interrelated with disease progression, but this interaction is so far poorly understood [15]. What has been known is the close interaction of subjective QoL and depression in MS [15]. Depression is a prevalent comorbidity in MS, with studies indicating that it affects approximately 27% of patients at any given time and up to 50% over their lifetime [6,16–18]. This risk is notably higher in the years immediately following diagnosis, where patients often experience elevated levels of depression and anxiety [19–21]. Depression in MS is not only more common than in other neurological disorders but also tends to impair both the mental and physical components of QoL [3,7,22–24]. The persistent nature of depression in MS highlights its significance as a major contributor to the overall burden of the disease, further exacerbating the challenges faced by patients. Fatigue is prevalent among MS patients, with reported rates ranging from 18.2% to 97% [25], it is characterized by a profound sense of tiredness and lack of energy that disrupts normal activities, distinct from feelings of sadness or weakness [26]. Fatigue has been shown to predict lower QoL and is closely associated with the severity of depressive symptoms in MS patients [1,11,22,26–33]. These findings highlight the critical role of fatigue in the overall disease burden, making it a key factor in both the psychological and physical wellbeing of MS patients. Overall, poor PSA is commonly reported in MS patients [34], and so far, little is understood about PSA in MS, especially with regard to clinical course and severity. While MS, as a chronic inflammatory disease of the central nervous system, shares some clinical features—such as movement impairment and QoL decline—with neurodegenerative diseases like ALS, its slower disease progression and specific symptoms like fatigue may uniquely affect PSA. Importantly, while PSA has already been investigated in ALS [35], it remains underexplored in MS. This study therefore focuses on describing PSA in MS and identifying fatigue as a predictor, while additionally drawing comparisons with PSA in ALS to explore how different disease trajectories shape PSA outcomes. Factors indicating successful PSA in these diseases are, among others, physical (PQoL), mental (MQoL), and subjective (SQoL) quality of life, as well as the level of depression.

2. Materials and Methods

2.1. Design and Participants

Seventy-seven MS patients and thirty ALS patients were recruited from the Department of Neurology at Ulm University and gave informed consent prior to their inclusion in the study. The study was approved by the Ethics Committee of the University of Ulm (No. 335/23, No. 381/19). We used a prospective cross-sectional survey design, with a 12-month data collection period for MS patients (2024) and 7 months for ALS patients (2022). The analyses presented in this study are post hoc and exploratory in nature. The inclusion criterion for patients was either a diagnosis of MS with clinically and laboratory definite MS according to McDonald's criteria [36] or ALS according to the revised El-Escorial criteria [37]. Exclusion criteria were insufficient skills of the German language and physical constraints preventing task completion. Physical impairment was measured using the Expanded Disability Status Scale (EDSS with values from 0 = normal neurological function to 10 = death [38]) in MS and the ALS functional rating scale (revised form, ALS-FRS-R [39] with values from 0 = complete paralysis to 48 = normal physical function) in ALS.

2.2. Quality of Life and Depression as Outcome Measures of PSA

Patient-reported questionnaires were selected to assess important outcomes and indicators of PSA that are relevant to people with MS, such as subjective and health-related quality of life, and the severity of depression. SQoL was assessed with the Anamnestic Comparative Self-Assessment (ACSA; range −5 for as bad as possible and +5 as good as possible [8,40]), a widely used instrument capturing SQoL independently of physical impairments. MQoL and PQoL were assessed using the mental and physical component score (MCS and PCS; a range of 0 to 50 +/−10 points corresponds one standard deviation (SD)) of the Short-Form Survey 12 Questionnaire (SF-12), which describes health-related QoL and is commonly applied in MS research [41]. In MS, depression was measured using the Hospital Anxiety and Depression Scale—Depression (HADS-D; 7 items, a range of 0 to 21 for depression), which is specifically aimed at people with physical illnesses or physical complaints and commonly used to screen for depression in patients with MS. A cut-off ≥ 8 was used to identify patients with all degrees of depression [42]. In ALS, depression was assessed using the ALS Depression Inventory (ADI-12), an instrument specially developed for ALS patients, which takes into account their special life situation (a range of 12 to 48). A cut-off ≥ 22 was used to identify patients with all degrees of depression [43]. Due to different measures for depression, a depression rate was calculated as a percentage ((raw score/maximum achievable score on the scale) $\times$ 100) for better comparability of the values.

2.3. Fatigue

Fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions (FSMC), which is a diagnostic method for clarifying motor and cognitive fatigue symptoms in MS patients. The FSMC is a measure of self-assessment and comprises 20 items, which are made up of subscales for the assessment of motor and cognitive fatigue (5-point Likert scale range from 1 = 'does not apply at all' to 5 = 'applies completely'; a range of 10 to 50 per subscale) [44]. The following cut-offs were used:

FSMC motor score: ≥22 mild motor fatigue, ≥27 moderate motor fatigue, and ≥32 severe motor fatigue [44];
FSMC cognition score: ≥22 mild cognitive fatigue, ≥28 moderate cognitive fatigue, and ≥34 severe cognitive fatigue [44].

2.4. Statistical Analysis

Statistical analyses were performed using SPSS version 29 (IBM Corp., Armonk, NY, USA) and R (lavaan package). Statistical significance was set at $\alpha < 0.05$. A confirmatory factor analysis (CFA) was performed with R using the maximum likelihood method for N = 77 MS patients. The quality of the measurement model was evaluated using the Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR) criteria [45]. In addition, the factor loadings of each indicator variable (HADS-D, ACSA, MCS, and PCS of SF-12) were calculated and tested for significance, with the variance of PSA fixed at 1 to provide a metric for the latent factor. Multiple regression analyses were performed to assess the predictive relationship of cognitive and motor fatigue with all PSA indicator variables. *t*-tests for independent samples were performed to assess differences in PSA between MS and ALS. A normal distribution can be assumed due to the sample size of $N \geq 30$ (N = 77 MS patients, N = 30 ALS patients) and the robustness of the *t*-test [46,47].

3. Results

3.1. Demographics and Clinical Data

Regarding the MS phenotypes, the majority of MS patients presented with the relapsing–remitting form (RRMS, 64.9%), followed by secondary progressive MS (SPMS, 20.8%) and primary progressive MS (PPMS, 14.3%). MS patients were predominantly female, younger, and had longer disease duration than ALS patients. MS Patients showed minor physical impairment according to EDSS (EDSS $\leq$ 3.5 indicates minor physical impairment [27]) and therefore presented with a less progressed disease stage compared to ALS, who were moderately impaired according to ALS-FRS-R (ALS-FRS-R score 34–41 indicates King's stage 2 [48]) (Table 1).

Table 1. Demographics and clinical data of MS patients compared to ALS.

Characteristics	MS Patients (N = 77)		ALS Patients (N = 30)		Statistics
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	46.83 (13.64)		56.60 (11.45)		$t(105) = -3.47$, $p < 0.001$
Female/Male		45/32 (58.4/41.6)		10/20 (33.3/66.7)	$\chi^2(1) = 5.45$, $p = 0.020$
Years of education	14.50 (2.82)		14.60 (3.33)		$t(105) = -0.16$, $p = 0.876$
EDSS *	2.90 (1.84)				
ALS-FRS-R *			35.97 (9.02)		
Time since onset (years)	10.34 (9.30)		1.62 (0.87)		$t(104) = 5.11$, $p < 0.001$
PPMS *		11 (14.3)			
SPMS *		16 (20.8)			
RRMS *		50 (64.9)			

* EDSS = Expanded Disability Status Scale; ALS-FRS-R = ALS Functional Rating Scale—Revised; PPMS = primary progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis.

3.2. Indicators of Psychosocial Adjustment in MS: CFA

There was a significant difference between the PSA model and the saturated model it was tested against ($\chi^2 = 8.29$, $p = 0.016$), indicating a bad model fit, and the RMSEA (0.202) was above the limit of <0.05, which did not indicate a good model fit. The value of the

SRMR (0.059) did not exceed the cut-off (SRMR < 0.08), indicating a good model fit. Further, the CFI (0.933) fell below the cut-off value (CFI > 0.95) (see Table 2).

Table 2. Confirmatory factor analysis (CFA) model fit indices and cut-off criteria.

Fit Index	Observed Value	Cut-off Criterion	Interpretation
χ^2 *	8.29, $p = 0.016$	$p > 0.05$	poor fit (interpretation based on p-value)
RMSEA *	0.202	<0.05 (good), <0.08 (acceptable)	poor fit (interpretation based on index value)
SRMR *	0.059	<0.08	good fit (interpretation based on index value)
CFI *	0.933	>0.95	marginal fit (interpretation based on index value)

* χ^2 = Chi-squared; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual; CFI = Comparative Fit Index.

Overall, most fit indices did not show a good fitting of the PSA model, which indicates that the model needs to be adapted [45]. Despite the bad model fit, depression (λ = −0.93, $p = 0.000$) was found to be the strongest predictor of PSA, in addition to SQoL (λ = 0.60, $p = 0.000$), MQoL (λ = 0.75, $p = 0.000$), and PQoL (λ = 0.34, $p = 0.006$) (Figure 1).

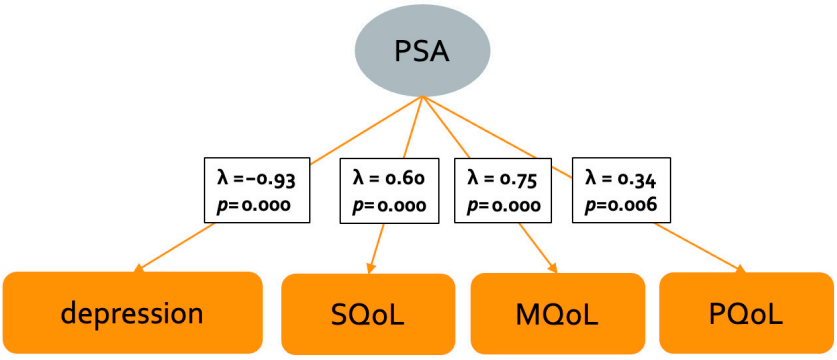


Figure 1. CFA model of PSA in MS. Psychosocial adjustment and its possible outcomes (orange squares). The significant indicators of PSA are highlighted in bold.

3.3. Predictors of Psychosocial Adjustment in MS: Regression Analyses

The Shapiro–Wilk test revealed no deviation from normality, and the assumption of homogeneity of variance was not breached. Motor fatigue was found to be a significant predictor of depression (β = 0.190, $t(75) = 5.37$, $p < 0.001$, explaining 27.8% of its variance), SQoL (β = −0.073, $t(75) = -4.08$, $p < 0.001$, explaining 18.2% of its variance), MQoL (β = −0.441, $t(75) = -4.40$, $p < 0.001$, explaining 20.5% of its variance), and PQoL (β = −0.643, $t(75) = -8.57$, $p < 0.001$, explaining 49.5% of its variance). Cognitive fatigue was identified as a significant predictor of depression (β = 0.168, $t(75) = 4.80$, $p < 0.001$, explaining 23.5% of its variance), SQoL (β = −0.059, $t(75) = -3.30$, $p = 0.001$, explaining 12.7% of its variance), MQoL (β = −0.476, $t(75) = -5.12$, $p < 0.001$, explaining 25.8% of its variance), and PQoL (β = −0.386, $t(75) = -4.23$, $p < 0.001$, explaining 19.3% of its variance) (see Figure 2).

3.4. Psychosocial Adjustment Comparison to ALS

A t-test for independent samples was performed to compare PSA (depression, SQoL, MQoL, and PQoL) in MS to ALS. The requirement for homogeneity of variance, tested by the Levene test, was not met for SQoL ($p < 0.05$), which is why the corrected t-test for unequal variances was calculated for SQoL. MS patients had a significantly higher SQoL ($t(41.735) = 2.10$, $p = 0.042$; d = 0.50), higher PQoL ($t(105) = 3.64$, $p < 0.001$; d = 0.78), and lower level of depression (%) ($t(105) = -6.18$, $p < 0.001$; d = −1.33) compared to ALS

patients. No significant difference compared to ALS was found for MQoL ($t(105) = -0.90$, $p = 0.373$; d = −0.19) (see Table 3).

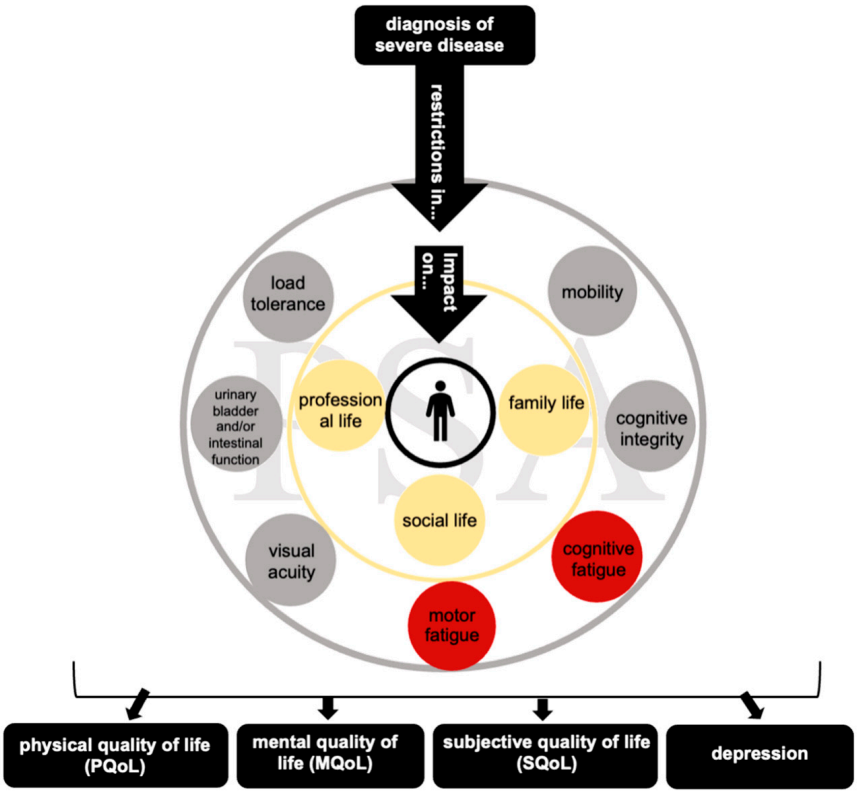


Figure 2. Psychosocial adjustment in MS. Model of psychosocial adjustment to a severe diagnosis with possible outcome variables (black squares). The gray/yellow rings represent the different levels patients have to adapt following a chronic diagnosis, such as MS, or a fatal neurological diagnosis, such as ALS (outer ring: internal factor; inner ring: external factors; all defined by the literature). The red circles represent potential additional predictors of PSA, which were evaluated in this study.

Table 3. Determinants of psychosocial adjustment in MS and ALS.

Patient-Reported Outcome Measures	MS Patients (N = 77)		ALS Patients (N = 30)
	Mean (SD)	N (%)	Mean (SD)
HADS-D *	5.58 (4.21)		
ADI-12 *			24.97 (7.91)
Level of depression (%)	26.59 (20.05)		52.01 (16.48)
ACSA *	0.75 (2.01)		−0.40 (2.74)
SF-12 MCS *	45.79 (11.36)		47.98 (11.41)
SF-12 PCS *	42.64 (10.67)		33.74 (13.01)
FSMC motor *	30.60 (11.67)		
mild (≥22)		9 (11.7)	
moderate (≥27)		10 (13)	
severe (≥32)		38 (49.4)	
FSMC cognition *	29.05 (12.12)		
mild (≥22)		7 (9.1)	
moderate (≥28)		14 (18.2)	
severe (≥34)		31 (40.3)	

* HADS-D = Hospital Anxiety and Depression Scale—Depression; ADI-12 = ALS Depression Inventory; ACSA = Anamnestic Comparative Self-Assessment; SF-12 = Short-Form Survey 12 Items; SF-12 MCS = mental component score; SF-12 PCS = physical component score; FSMC = Fatigue Scale for Motor and Cognitive Functions.

4. Discussion

4.1. Psychosocial Adjustment in MS

Our findings emphasize the complexity of PSA in MS, highlighting key factors that influence successful adaptation. Despite the challenges posed by MS, QoL measures revealed a positive outlook, with neutral-to-high scores in different QoL measures. These results suggest that many patients maintain a reasonable QoL, particularly in the subjective and mental domains. This finding may not be in line with the existing literature, as most studies have reported a moderate-to-poor QoL in MS patients but primarily focused on health-related QoL [5,7,49–53]. However, some QoL measures, particularly those based on eudaimonic concepts—such as physical health and economic status—often fail to capture the subjective and emotional dimensions of QoL, which are crucial for understanding PSA [5,8,29,40]. As physical health declines, these measures often indicate low QoL [49,52], as numerous studies have reported a correlation between physical function and health-related QoL in MS [3,7,22,54]. This highlights the need for PSA models to account for the subjective/hedonic aspects of wellbeing. Further, depression emerged as a central determinant, with a moderate prevalence of 26.59% in MS patients, which is consistent with previous research [6,16–18]. The persistent nature of depression in MS patients significantly impairs both mental and physical QoL [3,7,22–24], making it a critical issue that requires urgent attention in clinical practice.

The poor model fit in the CFA suggests that the PSA model in MS may benefit from refinement, potentially by integrating resilience, social support, self-esteem, and self-efficacy to better understand patient adjustment [55–58].

Fatigue, both motor and cognitive, played a key role in PSA, aligning with previous findings [2]. Many MS patients experienced severe motor and cognitive fatigue, highlighting its significant burden. Motor fatigue was closely linked to high levels of depression and a reduced quality of life, particularly in the physical domain. Cognitive fatigue showed similar effects, contributing to emotional distress and overall lower wellbeing. These findings suggest that cognitive fatigue plays a notable role in affecting not only mood (depression) but also overall QoL, with its strongest effect observed in mental QoL. The lower explained variance in subjective QoL (12.7%) implies that cognitive fatigue might have a more indirect or less pronounced effect compared to physical and mental components. In summary, these findings underscore the dual burden of fatigue in MS—as reported in previous studies—where both motor and cognitive aspects contribute to worse psychosocial outcomes [10,25,26,29,31,59], further complicating the adjustment process. Addressing fatigue in clinical practice is therefore essential for improving PSA and overall QoL in MS patients.

Importantly, our sample of MS patients included all phenotypes (PPMS, SPMS, and RRMS) without stratification, with a predominance of RRMS. Psychosocial adjustment may therefore differ in progressive subtypes, and future research should aim to examine these phenotypes separately to capture course-specific patterns more accurately. Importantly, patients with SPMS and patients with later stages of PPMS often experience more significant neurological and neurocognitive deficits, which are likely correlated with greater challenges in psychosocial adjustment.

4.2. Psychosocial Adjustment Compared to ALS

Despite distinct differences in etiology, clinical progression, and fatality between MS and ALS (one is fatal, the other is not), our findings suggest a notable convergence in PSA outcomes, particularly in terms of mental QoL. While the specific trajectory and symptoms of each disease vary, the psychological and emotional burdens they impose are similar, requiring comparable approaches to psychosocial adaptation. In examining single

parameters of PSA, patients with MS and ALS displayed comparable mental QoL and maintained a neutral-to-positive subjective QoL. Notably, MS patients reported nearly half the levels of depression compared to ALS patients, which indicates a more favorable PSA outcome in MS patients, despite differences in disease stages and trajectories. This may be partly attributed to the moderate disease progression and the wide range of available disease-modifying treatments in MS, compared to the rapid decline seen in ALS and the limited number of treatment options, for which evidence for efficacy is very much limited [60,61]. Furthermore, the high progression rate in ALS, marked by significantly lower physical QoL, is known to disrupt PSA to a greater extent, highlighting the added challenge faced by ALS patients [13,14,35]. The lack of significant differences in mental QoL between MS and ALS suggests that both groups face similar mental health challenges, likely stemming from the chronic and incurable nature of their conditions.

4.3. Limitations

This study has several important limitations that should be acknowledged. First, the CFA indicated a poor model fit, as reflected by an elevated RMSEA and suboptimal CFI values, suggesting that the latent construct of perceived psychosocial adjustment may not be adequately captured by the current indicator set. Second, depression was assessed using non-equivalent instruments across diagnostic groups—HADS-D for MS and ADI-12 for ALS—introducing possible measurement bias despite normalization efforts. This compromises the comparability of depressive symptom scores and may affect interpretation of associations with PSA. Third, the cross-sectional design inherently limits the ability to infer causal relationships. While associations between fatigue, depression, and PSA are evident, temporal directionality remains unclear. Longitudinal data would be essential to elucidate dynamic changes and potential causal pathways. Finally, the study did not account for cognitive functioning, a particularly relevant omission given that cognitive impairment affects up to 40–70% of patients with multiple sclerosis [62–64]. Without cognitive metrics, interpretations of PSA across groups remain incomplete.

5. Conclusions

Our study offers valuable insights into the psychosocial adjustment of patients with MS compared to ALS. It is important to emphasize that psychosocial adjustment is an ongoing and dynamic process. In this study, depression and quality of life were used as outcome measures to indicate PSA in a cross-sectional study. With this, only a condition report of a highly complex process is presented. For future studies, longitudinal and multi-faceted measures of PSA in these severe conditions (MS and ALS) are needed to provide a deep understanding of the full scope of PSA over time. Our research significantly contributes to the existing understanding of coping with the emotional, psychological, and social consequences of chronic illness with a more comprehensive understanding of the challenges each group faces. MS patients face some unique challenges, including a high prevalence of depression and its pervasive impact of fatigue on quality of life in this population. Unlike ALS, where rapid disease progression severely impacts PSA, MS patients experience a longer, less predictable course, with fatigue emerging as a dominant factor. This adds complexity to the adjustment process, further underscoring the need for tailored interventions. Integrating mindfulness-based interventions and resilience training into care plans can be particularly effective, helping patients maintain a good quality of life [4,65–68] even in the face of severe physical challenges.

Author Contributions: Conceptualization, L.T.B., H.T. and D.E.L.; methodology, L.T.B. and D.E.L.; software, L.T.B.; validation, L.T.B., H.T. and D.E.L.; formal analysis, L.T.B. and D.E.L.; investigation, L.T.B.; resources, H.T. and D.E.L.; data curation, L.T.B.; writing—original draft preparation, L.T.B. and

D.E.L.; writing—review and editing, L.T.B., D.E.L., H.T., I.U., J.W., A.C.L., D.T., I.V., S.J., T.F., D.K.E. and M.S.; visualization, L.T.B. and D.E.L.; supervision, D.E.L., H.T. and I.U.; project administration, D.E.L. and H.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ulm University (File number 335/23 and 381/19).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgments: The authors thank all patients for their participation.

Conflicts of Interest: The authors report no conflict of interest related to this work.

Abbreviations

The following abbreviations are used in this manuscript:

MS	Multiple sclerosis
ALS	Amyotrophic Lateral Sclerosis
PSA	Psychosocial adjustment
QoL	Quality of life
PQoL	Physical quality of life
MQoL	Mental quality of life
SQoL	Subjective quality of life
EDSS	Expanded Disability Status Scale
RRMS	Relapsing–remitting multiple sclerosis
PPMS	Primary progressive multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
ALS-FRS-R	ALS Functional Rating Scale—Revised
ACSA	Anamnestic Comparative Self-Assessment
SF-12	Short-Form Survey 12 Questionnaire
MCS	Mental component score
PCS	Physical component score
HADS-D	Hospital Anxiety and Depression Scale—Depression
ADI-12	ALS Depression Inventory
FSMC	Fatigue Scale for Motor and Cognitive Functions
SD	Standard deviation
CFA	Confirmatory factor analysis
CFI	Comparative Fit Index
SRMR	Standardized Root Mean Square Residual
RMSEA	Root Mean Square Error of Approximation

References

1. Pugliatti, M.; Rosati, G.; Carton, H.; Riise, T.; Drulovic, J.; Vecsei, L.; Milanov, I. The epidemiology of multiple sclerosis in Europe. *Eur. J. Neurol.* **2006**, *13*, 700–722. [CrossRef]
2. Bogosian, A.; Day, F.; Norton, S.; Silber, E.; Sakel, M.; Sharrack, B.; Moss-Morris, R. Key demographics and psychological skills associated with adjustment to progressive Multiple Sclerosis early in the diagnosis. *Front. Rehabil. Sci.* **2022**, *3*, 966133. [CrossRef]
3. Batista, A.R.; Silva, S.; Lencastre, L.; Guerra, M.P. Biopsychosocial Correlates of Quality of Life in Multiple Sclerosis Patients. *Int. J. Environ. Res. Public Health* **2022**, *19*, 14431. [CrossRef]
4. Senders, A.; Bourdette, D.; Hanes, D.; Yadav, V.; Shinto, L. Perceived stress in multiple sclerosis: The potential role of mindfulness in health and well-being. *J. Evid. Based Complement. Altern. Med.* **2014**, *19*, 104–111. [CrossRef] [PubMed]

5. Lysandropoulos, A.P.; Havrdova, E.; Paradig, M.S.G. 'Hidden' factors influencing quality of life in patients with multiple sclerosis. *Eur. J. Neurol.* **2015**, *22* (Suppl. S2), 28–33. [CrossRef]
6. Zwibel, H.L.; Smrtka, J. Improving quality of life in multiple Sclerosis: An unmet need. *Am. J. Manag. Care* **2011**, *17*, S139–S145. [PubMed]
7. Sehanovic, A.; Kunic, S.; Ibrahimagic, O.C.; Smajlovic, D.; Tupkovic, E.; Mehicevic, A.; Zoletic, E. Contributing Factors to the Quality of Life in Multiple Sclerosis. *Med. Arch.* **2020**, *74*, 368–373. [CrossRef] [PubMed]
8. Bernheim, J.L. How to get serious answers to the serious question: "How have you been?": Subjective Quality of Life (QOL) as an individual experiental emergent construct. *Bioethics* **1999**, *13*, 272–287. [CrossRef]
9. Harper, A.; Power, M. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. *Psychol. Med.* **1998**, *28*, 551–558.
10. Hosseini, Z.; Homayuni, A.; Etemadifar, M. Barriers to quality of life in patients with multiple sclerosis: A qualitative study. *BMC Neurol.* **2022**, *22*, 174. [CrossRef]
11. Strober, L.B. Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model. *Disabil. Health J.* **2018**, *11*, 555–561. [CrossRef] [PubMed]
12. Szilasiova, J.; Krokavcova, M.; Gdovinova, Z.; Rosenberger, J.; van Dijk, J.P. Quality of life in patients with multiple sclerosis in Eastern Slovakia. *Disabil. Rehabil.* **2011**, *33*, 1587–1593. [CrossRef] [PubMed]
13. Lulé, D.; Pauli, S.; Altintas, E.; Singer, U.; Merk, T.; Uttner, I.; Birbaumer, N.; Ludolph, A.C. Emotional adjustment in amyotrophic lateral sclerosis (ALS). *J. Neurol.* **2012**, *259*, 334–341. [CrossRef] [PubMed]
14. Vazquez Medrano, C.R.; Aho-Ozhan, H.E.A.; Weiland, U.; Uttner, I.; Ludolph, A.C.; Lule, D. Disease progression but not physical state per se determines mental wellbeing in ALS. *J. Neurol.* **2020**, *267*, 3593–3601. [CrossRef]
15. Bueno, A.; Sayao, A.; Yousefi, M.; Devonshire, V.; Traboulsee, A.; Tremlett, H. Health-related quality of life in patients with longstanding 'benign multiple sclerosis'. *Mult. Scler. Relat. Disord.* **2015**, *4*, 31–38. [CrossRef]
16. Marrie, R.A.; Cohen, J.; Stuve, O.; Trojano, M.; Sorensen, P.S.; Reingold, S.; Cutter, G.; Reider, N. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. *Mult. Scler. J.* **2015**, *21*, 263–281. [CrossRef]
17. Young, C.A.; Langdon, D.; Rog, D.; Chhetri, S.K.; Tanasescu, R.; Kalra, S.; Webster, G.; Nicholas, R.; Ford, H.L.; Woolmore, J.; et al. Prevalence, treatment and correlates of depression in multiple sclerosis. *Mult. Scler. Relat. Disord.* **2024**, *87*, 105648. [CrossRef]
18. Weiss, D.B.; Dyrud, J.; House, R.M.; Beresford, T.P. Psychiatric manifestations of autoimmune disorders. *Curr. Treat. Options Neurol.* **2005**, *7*, 413–417. [CrossRef]
19. Janssens, A.C.J.W.; van Doorn, P.A.; de Boer, J.B.; van der Meché, F.G.A.; Passchier, J.; Hintzen, R.Q. Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners. *Acta Neurol. Scand.* **2003**, *108*, 389–395. [CrossRef]
20. Sullivan, M.J.; Weinshenker, B.; Mikail, S.; Edgley, K. Depression before and after diagnosis of multiple sclerosis. *Mult. Scler. J.* **1995**, *1*, 104–108. [CrossRef]
21. Possa, M.F.; Minacapelli, E.; Canale, S.; Comi, G.; Martinelli, V.; Falautano, M. The first year after diagnosis: Psychological impact on people with multiple sclerosis. *Psychol. Health Med.* **2017**, *22*, 1063–1071. [CrossRef] [PubMed]
22. Marrie, R.A.; Patten, S.B.; Berrigan, L.I.; Tremlett, H.; Wolfson, C.; Warren, S.; Leung, S.; Fiest, K.M.; McKay, K.A.; Fisk, J.D.; et al. Diagnoses of Depression and Anxiety Versus Current Symptoms and Quality of Life in Multiple Sclerosis. *Int. J. MS Care* **2018**, *20*, 76–84. [CrossRef]
23. Schubert, D.S.; Foliart, R.H. Increased depression in multiple sclerosis patients. A meta-analysis. *Psychosomatics* **1993**, *34*, 124–130. [CrossRef] [PubMed]
24. Boeschoten, R.E.; Braamse, A.M.J.; Beekman, A.T.F.; Cuijpers, P.; van Oppen, P.; Dekker, J.; Uitdehaag, B.M.J. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. *J. Neurol. Sci.* **2017**, *372*, 331–341. [CrossRef]
25. Oliva Ramirez, A.; Keenan, A.; Kalau, O.; Worthington, E.; Cohen, L.; Singh, S. Prevalence and burden of multiple sclerosis-related fatigue: A systematic literature review. *BMC Neurol.* **2021**, *21*, 468. [CrossRef]
26. Broch, L.; Flemmen, H.O.; Simonsen, C.S.; Berg-Hansen, P.; Ormstad, H.; Brunborg, C.; Celius, E.G. Fatigue in multiple sclerosis is associated with socioeconomic factors. *Mult. Scler. Relat. Disord.* **2022**, *64*, 103955. [CrossRef]
27. Conradsson, D.; Ytterberg, C.; von Koch, L.; Johansson, S. Changes in disability in people with multiple sclerosis: A 10-year prospective study. *J. Neurol.* **2018**, *265*, 119–126. [CrossRef] [PubMed]
28. Kaya Aygunoglu, S.; Celebi, A.; Vardar, N.; Gursoy, E. Correlation of Fatigue with Depression, Disability Level and Quality of Life in Patients with Multiple Sclerosis. *Noro Psikiyatr Ars.* **2015**, *52*, 247–251. [CrossRef]
29. Opara, J.A.; Jaracz, K.; Brola, W. Quality of life in multiple sclerosis. *J. Med. Life.* **2010**, *3*, 352–358.
30. Schmidt, S.; Jöstingmeyer, P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: Results of a cross-sectional study. *Mult. Scler. Relat. Disord.* **2019**, *35*, 262–269. [CrossRef]
31. Margoni, M.; Preziosa, P.; Rocca, M.A.; Filippi, M. Depressive symptoms, anxiety and cognitive impairment: Emerging evidence in multiple sclerosis. *Transl. Psychiatry* **2023**, *13*, 264. [CrossRef]

32. Bakshi, R.; Shaikh, Z.A.; Miletich, R.S.; Czarnecki, D.; Dmochowski, J.; Henschel, K.; Janardhan, V.; Dubey, N.; Kinkel, P.R. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult. Scler. J.* **2000**, *6*, 181–185. [CrossRef] [PubMed]
33. Amato, M.P.; Ponziani, G.; Rossi, F.; Liedl, C.L.; Stefanile, C.; Rossi, L. Quality of life in multiple sclerosis: The impact of depression, fatigue and disability. *Mult. Scler. J.* **2001**, *7*, 340–344. [CrossRef] [PubMed]
34. Maybury, C.P.; Brewin, C.R. Social relationships, knowledge and adjustment to multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* **1984**, *47*, 372–376. [CrossRef]
35. Matuz, T.; Birbaumer, N.; Hautzinger, M.; Kubler, A. Psychosocial adjustment to ALS: A longitudinal study. *Front. Psychol.* **2015**, *6*, 1197. [CrossRef]
36. Thompson, A.J.; Banwell, B.L.; Barkhof, F.; Carroll, W.M.; Coetzee, T.; Comi, G.; Correale, J.; Fazekas, F.; Filippi, M.; Freedman, M.S.; et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* **2018**, *17*, 162–173. [CrossRef] [PubMed]
37. Ludolph, A.; Drory, V.; Hardiman, O.; Nakano, I.; Ravits, J.; Robberecht, W.; Shefner, J.; for The WFN Research Group On ALS/MND. A revision of the El Escorial criteria–2015. *Amyotroph. Lateral Scler. Front. Degener.* **2015**, *16*, 291–292. [CrossRef]
38. Cao, H.; Peyrodie, L.; Agnani, O.; Cavillon, F.; Hautecoeur, P.; Donzé, C. Evaluation of an Expanded Disability Status Scale (EDSS) modeling strategy in multiple sclerosis. *Med. Biol. Eng. Comput.* **2015**, *53*, 1141–1151. [CrossRef]
39. Cedarbaum, J.M.; Stambler, N.; Malta, E.; Fuller, C.; Hilt, D.; Thurmond, B.; Nakanishi, A., III; Bdnf Als Study Group and 1A Complete Listing of the BDNF Study Group. The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. *J. Neurol. Sci.* **1999**, *169*, 13–21. [CrossRef]
40. Bernheim, J.L.; Theuns, P.; Mazaheri, M.; Hofmans, J.; Fliege, H.; Rose, M. The Potential of Anamnestic Comparative Self-Assessment (ACSA) to Reduce Bias in the Measurement of Subjective Well-Being. *J. Happiness Stud.* **2006**, *7*, 227–250. [CrossRef]
41. Ware, J.E.; Kosinski, M.; Keller, S.D. *SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales*; Health Institute, New England Medical Center: Boston, MA, USA, 1995.
42. Snaith, R.P. The Hospital Anxiety and Depression Scale. *Health Qual. Life Outcomes* **2003**, *1*, 29. [CrossRef]
43. Kübler, A.; Winter, S.; Kaiser, J.; Birbaumer, N.; Hautzinger, M. Das ALS-Depressionsinventar (ADI). *Z. Klin. Psychol. Psychother.* **2005**, *34*, 19–26. [CrossRef]
44. Penner, I.K.; Raselli, C.; Stöcklin, M.; Opwis, K.; Kappos, L.; Calabrese, P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult. Scler. J.* **2009**, *15*, 1509–1517. [CrossRef] [PubMed]
45. Hu, L.T.; Bentler, P.M. Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria versus New Alternatives. *Struct. Equ. Model. Multidiscip. J.* **1999**, *6*, 1–55. [CrossRef]
46. Stone, E.R. *t* Test, Independent Samples. In *Encyclopedia of Research Design*; Salkind, N.J.E., Ed.; SAGE: Los Angeles, CA, USA, 2010; pp. 1551–1556.
47. Lix, L.M.; Keselman, J.C.; Keselman, H.J. Consequences of Assumption Violations Revisited: A Quantitative Review of Alternatives to the One-Way Analysis of Variance F Test. *Rev. Educ. Res.* **1996**, *66*, 579–619. [CrossRef]
48. Mani, V.E.; Thomas, J. A study of the clinical characteristics and severity of amyotrophic lateral sclerosis from North India. *CHRISMED J. Health Res.* **2021**, *8*, 232–238. [CrossRef]
49. Twork, S.; Wiesmeth, S.; Spindler, M.; Wirtz, M.; Schipper, S.; Pohlau, D.; Klewer, J.; Kugler, J. Disability status and quality of life in multiple sclerosis: Non-linearity of the Expanded Disability Status Scale (EDSS). *Health Qual. Life Outcomes* **2010**, *8*, 55. [CrossRef]
50. Ghaem, H.; Haghighi, A.B. The impact of disability, fatigue and sleep quality on the quality of life in multiple sclerosis. *Ann. Indian. Acad. Neurol.* **2008**, *11*, 236–241. [CrossRef]
51. Alshubaili, A.F.; Ohaeri, J.U.; Awadalla, A.W.; Mabrouk, A.A. Quality of life in multiple sclerosis: A Kuwaiti MSQOL-54 experience. *Acta Neurol. Scand.* **2008**, *117*, 384–392. [CrossRef]
52. Miller, A.; Dishon, S. Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. *Qual. Life Res.* **2006**, *15*, 259–271. [CrossRef]
53. Aymerich, M.; Guillamón, I.; Jovell, A.J. Health-related quality of life assessment in people with multiple sclerosis and their family caregivers. A multicenter study in Catalonia (southern Europe). *Patient Prefer. Adherence* **2009**, *3*, 311–321. [CrossRef] [PubMed]
54. Marrie, R.A.; Horwitz, R.; Cutter, G.; Tyry, T. Cumulative impact of comorbidity on quality of life in MS. *Acta Neurol. Scand.* **2012**, *125*, 180–186. [CrossRef] [PubMed]
55. Rainone, N.; Chiodi, A.; Lanzillo, R.; Magri, V.; Napolitano, A.; Brescia Morra, V.; Valerio, P.; Freda, M.F. Affective disorders and Health-Related Quality of Life (HRQoL) in adolescents and young adults with Multiple Sclerosis (MS): The moderating role of resilience. *Qual. Life Res.* **2017**, *26*, 727–736. [CrossRef]
56. Kever, A.; Buyukturkoglu, K.; Riley, C.S.; De Jager, P.L.; Leavitt, V.M. Social support is linked to mental health, quality of life, and motor function in multiple sclerosis. *J. Neurol.* **2021**, *268*, 1827–1836. [CrossRef]

57. Ratajska, A.; Glanz, B.I.; Chitnis, T.; Weiner, H.L.; Healy, B.C. Social support in multiple sclerosis: Associations with quality of life, depression, and anxiety. *J. Psychosom. Res.* **2020**, *138*, 110252. [CrossRef] [PubMed]
58. Gil-González, I.; Martín-Rodríguez, A.; Conrad, R.; Pérez-San-Gregorio, M.Á. Quality of life in adults with multiple sclerosis: A systematic review. *BMJ Open* **2020**, *10*, e041249. [CrossRef]
59. Fidao, A.; De Livera, A.; Nag, N.; Neate, S.; Jelinek, G.A.; Simpson-Yap, S. Depression mediates the relationship between fatigue and mental health-related quality of life in multiple sclerosis. *Mult. Scler. Relat. Disord.* **2021**, *47*, 102620. [CrossRef]
60. Hergesheimer, R.; Lanznaster, D.; Vourc'h, P.; Andres, C.; Bakkouche, S.; Beltran, S.; Blasco, H.; Corcia, P.; Couratier, P. Advances in disease-modifying pharmacotherapies for the treatment of amyotrophic lateral sclerosis. *Expert Opin. Pharmacother.* **2020**, *21*, 1103–1110. [CrossRef]
61. Dorst, J.; Ludolph, A.C.; Huebers, A. Disease-modifying and symptomatic treatment of amyotrophic lateral sclerosis. *Ther. Adv. Neurol. Disord.* **2018**, *11*, 1756285617734734. [CrossRef]
62. Chiaravalloti, N.D.; De Luca, J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* **2008**, *7*, 1139–1151. [CrossRef]
63. Benedict, R.H.B.; Amato, M.P.; DeLuca, J.; Geurts, J.J.G. Cognitive impairment in multiple sclerosis: Clinical management, MRI, and therapeutic avenues. *Lancet Neurol.* **2020**, *19*, 860–871. [CrossRef] [PubMed]
64. Amato, M.P.; Zipoli, V.; Portaccio, E. Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *J. Neurol. Sci.* **2006**, *245*, 41–46. [CrossRef]
65. Sauder, T.; Hansen, S.; Bauswein, C.; Muller, R.; Jaruszowic, S.; Keune, J.; Schenk, T.; Oschmann, P.; Keune, P.M. Mindfulness training during brief periods of hospitalization in multiple sclerosis (MS): Beneficial alterations in fatigue and the mediating role of depression. *BMC Neurol.* **2021**, *21*, 390. [CrossRef] [PubMed]
66. Hardison, M.E.; Roll, S.C. Mindfulness Interventions in Physical Rehabilitation: A Scoping Review. *Am. J. Occup. Ther.* **2016**, *70*, 31–39. [CrossRef] [PubMed]
67. Simpson, R.; Posa, S.; Langer, L.; Bruno, T.; Simpson, S.; Lawrence, M.; Booth, J.; Mercer, S.W.; Feinstein, A.; Bayley, M. A systematic review and meta-analysis exploring the efficacy of mindfulness-based interventions on quality of life in people with multiple sclerosis. *J. Neurol.* **2023**, *270*, 726–745. [CrossRef]
68. Lee, B.; Rumrill, P.; Tansey, T.N. Examining the Role of Resilience and Hope in Grit in Multiple Sclerosis. *Front. Neurol.* **2022**, *13*, 875133. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Acknowledgements

The acknowledgements have been removed for data protection reasons.

Curriculum Vitae

This curriculum vitae has been removed for data protection reasons.