Fatigue in Relapsing Remitting and Secondary Progressive Multiple Sclerosis: Relationship with Information Processing Speed and Executive Functioning

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Abstract

Introduction: Many people with multiple sclerosis (PwMS) experience fatigue as a prominent symptom. Previous studies have examined the relationship between general fatigue and cognitive functioning in multiple sclerosis (MS). However, it remains unclear how mental and physical fatigue relate to impairments in information processing speed (IPS) and executive functioning (EF) in PwMS, and how this manifests in the subtypes relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS). **Method:** A total of 262 PwMS were included, categorized into RRMS (*n* = 164), SPMS (*n* = 59), primary progressive multiple sclerosis (PPMS; *n* = 29) and an unknown subtype (*n* = 10), together with 90 healthy controls (HCs). Assessment included The Dutch Multifactor Fatigue Scale (subscales mental and physical fatigue) for fatigue, IPS tests (The Symbol Digit Modalities Test and Trail Making Test - A) and EF tests (The Dutch version of the Controlled Oral Word Association Test and Trail Making Test - B). **Results:** PwMS had a significantly higher level of both mental and physical fatigue and performed significantly lower on all measures for IPS and EF ($p < .001$) than HCs. When comparing the subtypes, the SPMS group performed significantly lower than the RRMS group on IPS and EF ($p < .001$), whereas no significant differences were found for mental and physical fatigue. Furthermore, a small positive relationship ($r_s = .17$) was found between physical fatigue and the TMT A in the PwMS group, but mental fatigue was not associated with any measure for IPS or EF in all groups. **Conclusion:** Our findings suggest that PwMS exhibit impairments on IPS and EF and experience excessive mental and physical fatigue when compared to controls. Furthermore, the lack of correlation between mental fatigue and IPS or EF performance suggests the need to explore other factors underlying mental fatigue in PwMS.

Keywords: Multiple Sclerosis, Mental fatigue, Physical fatigue, Information Processing Speed, Executive functioning

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Multiple sclerosis (MS) is a chronic neurological disorder known for damage to the central nervous system (CNS) (Dias et al., 2024). Demyelination, a typical process in MS, can occur in several regions of the brain and can cause a wide variety of symptoms (Bellew et al., 2022; Goldenberg, 2012). MS can be divided into different subtypes: relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) (Eshaghi et al., 2021; Locatelli et al., 2024). Each of these subtypes has a different progression of symptoms which can flare or relapse over time (Olek, 2021). MS is the most prevalent degenerative disease of the CNS in younger individuals (Wallin et al., 2019).

Fatigue is a highly prevalent symptom among people with MS (PwMS), with nearly 70% reporting it as one of the most prominent symptoms (Smith & Hale, 2007). Different definitions of fatigue are found in the literature and there are variations for the interpretation of this concept. Fatigue can be described as a state of being in which a person suffers from exhaustion and may experience difficulties with social interactions or performing daily tasks. As a symptom, fatigue is characterized by its multifactorial nature. Mental fatigue occurs when a person has difficulties with processing stimuli due to prolonged focus on a task and maintaining sustained cognitive effort, leading to reduced mental capacity and a decreased drive and motivation to continue with the task. This could possibly lead to a poorer task performance (Bafna & Hansen, 2021). Physical fatigue occurs when a person has difficulties maintaining sustained physical effort and can result in reduced energy and difficulty moving (Skau et al., 2021). Both mental and physical fatigue are commonly reported symptoms by PwMS (Oliva Ramirez et al., 2021).

Prior studies have investigated general fatigue in different subtypes of MS. Fatigue was found to be more prevalent and severe in patients with SPMS than in those with RRMS (Maier et al., 2023; Weiland, 2015), which could possibly be explained by an older age and a higher level of impairment, as these factors are more commonly present in individuals with SPMS (Maier et al., 2023). Overall, fatigue in MS is correlated with a poorer well-being and has a negative impact on daily activities in PwMS, across all subtypes (Andreasen et al., 2019). Although fatigue is a common complaint among PwMS and has a significant negative impact on their lives, the precise underlying mechanisms contributing to fatigue in MS remain unclear.

In addition to fatigue, impairments in cognitive functioning are common in MS as well. Prior research shows that up to 65% of PwMS present with cognitive deficits (Patti et al., 2015). Cognitive functions consist of a range of mental capacities, including learning, reasoning, memory, problem-solving, decision-making, processing speed and attention. PwMS show most deficits in information processing speed (IPS), memory, attention, and executive functioning (EF) (Chiaravalloti & DeLuca, 2008). These deficits can contribute to a decline in life satisfaction and can limit the daily functioning of PwMS (Bellew et al., 2022).

Prior studies have investigated the severity of cognitive impairments in different subtypes of MS. It is estimated that approximately a third of patients with RRMS exhibit cognitive impairments, affecting domains such as motor performance, memory and learning, attention, and EF (Prakash et al., 2008; Wu et al., 2024). Many RRMS patients develop SPMS after several years, whereas the duration of this transition sometimes varies by decades (5-30 years) (Tremlett et al., 2008). Therefore, it is suggested that the same impairments are present in SPMS patients, but more severe. Brochet & Ruet (2019) showed that, when comparing SPMS patients with RRMS patients, SPMS patients had increased cognitive dysfunction in several different domains. These domains included memory, IPS and EF.

To provide suitable care for PwMS who experience fatigue, it is relevant to know what processes underlie fatigue in MS. The cognitive coping hypothesis suggests that brain-injured individuals might experience fatigue as a result of the increased demands on cognition which is necessary to meet the requirements of completing daily tasks. It is assumed that these individuals need to compensate for deficits in their information processing abilities (Van Coevorden-van Loon et al., 2022; Zomeren, 1981), which could also be relevant for PwMS, since impairments in IPS are common. Extended use of compensatory strategies requires more cognitive resources, which could be an explanation for the experienced fatigue in PwMS. Prior research has investigated this relationship and suggests an association between impaired IPS and fatigue in MS. While some studies have demonstrated this association, others have failed to find such a relationship. Therefore, further research is needed.

Additionally, in various neurological disorders, including MS, fatigue is suggested to be associated with a dysfunction between the frontal brain areas and the basal ganglia (Chaudhuri & Behan, 2004; Dobryakova et al., 2013). These brain regions are also strongly associated with EF, a domain known to be affected in MS (Herd et al., 2014; Szczepanski & Knight, 2014). Several studies have shown a relationship between reduced executive functioning performance and fatigue in MS; however, previous studies have not been conclusive (Erani et al., 2022; Holtzer & Foley, 2009).

Based on prior studies which investigated the relationship between cognitive functioning and fatigue in other neurological patient groups, it is expected that impairments in IPS and EF are particularly related to mental fatigue, rather than physical fatigue (Van Coevorden-van Loon et al., 2022; Yigit et al., 2021). However, as far as we know, studies specifically investigating the relationship of IPS and EF with both mental and physical fatigue as separate constructs are scarce in MS. It is important to gain a better understanding of the processes underlying mental and physical fatigue across different MS subtypes. This provides us with valuable insights to optimize and personalize care for PwMS experiencing mental and physical fatigue in clinical practice.

The aim of this study therefore is to investigate how mental and physical fatigue in MS relate to impairments in IPS and EF. In addition, it will be investigated how these constructs are related to one another in different subtypes of MS, namely RRMS and SPMS. For the entire PwMS group, as well as within the separate RRMS and SPMS groups, it is hypothesized that higher mental fatigue is related to lower performance on tasks for IPS and EF, whereas physical fatigue is not. Furthermore, it is hypothesized that a stronger relationship between mental fatigue and IPS and EF will be found in the SPMS group compared to the RRMS group, given the prolonged disease course in this former group, generally characterized by more demyelination and neurodegeneration and therefore more cognitive impairments.

Method

Design and Setting

This study contains data from the observational, prospective, MS-CEBA study (Reinhardt et al., 2024). The majority of participants have been recruited from the Neurology department of the University Medical Center Groningen (UMCG), Martini Hospital Groningen (MHG) and the Medical Center Leeuwarden (MCL). In addition, participants could sign up for participation themselves. Furthermore, a dataset from the ICONS study (Khosdelazad et al., 2022) was used for the inclusion of healthy controls (HCs). The data collection followed the ethical protocols of the UMCG, and all patients and HCs signed an informed consent. After informed consent was obtained, the researcher scheduled the neuropsychological assessment.

Participants and procedure

Between June 2023 and March 2025, 262 PwMS were included in the study. The 90 HCs from the ICONS study were included between 2019 and 2023. Inclusion criteria were an age between 18 and 70 years, sufficient comprehension of the Dutch language and the absence of other neurological and/or major psychiatric disorders. The data from the participants was collected through a neuropsychological assessment, which was administered by a trained assistant. After signing the informed consent, participants were contacted by the researcher to schedule the neuropsychological assessment. All participants received a questionnaire assessing mental and physical fatigue to complete at home prior to the neuropsychological assessment. The questionnaire was delivered digitally using the secure platform, Research Electronic Data Capture (REDCap) (Harris et al., 2009; Harris et al., 2019). During the neuropsychological assessment, tests for EF and IPS were administered.

Measures

Fatigue questionnaire

The Dutch Multifactor Fatigue Scale (DMFS) is a questionnaire assessing different aspects of fatigue in neurological patient groups. The DMFS includes 38 items on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) and is categorized into 5 subscales (Dornonville de la Cour, 2023). For this study, the subscales for mental fatigue and physical fatigue were used to assess mental and physical fatigue of PwMS, with scores ranging from 7 to 35 for mental fatigue and 6 to 30 for physical fatigue. The DMFS has demonstrated good construct validity and showed acceptable to good reliability for the mental ($\alpha = .86$) and physical subscales ($\alpha = .77$; Visser-Keizer et al., 2015).

Neuropsychological tests for IPS

The Symbol Digit Modalities Test (SDMT) is a test for IPS. Participants are given instructions to match the correct number with the corresponding symbol as fast as possible in 90 seconds (Benedict et al., 2017). The raw score consisted of the number of correct responses within the time limit.

The Trail Making Test (TMT) condition A was used to measure IPS. Participants were instructed to link the numbers from 1 to 25 in order by drawing a line as quickly as possible

(Arbuthnott & Frank, 2000). The raw score was the time in seconds required to complete this task.

Neuropsychological tests for EF

The Trail Making Test (TMT) condition B was used for measuring EF. The duration spent on condition B served as an indicator of cognitive flexibility, an important aspect of EF. For this test, participants must connect circles with both letters and numbers alternately in an ascending order as quickly as possible (Arbuthnott & Frank, 2000). The raw score was the time in seconds required to complete this task.

The Dutch version of the Controlled Oral Word Association Test (COWAT) is a verbal exercise assessing EF. Participants have 60 seconds to come up with as many words as possible, starting with the letters D-A-T (Schmand et al., 2008). The raw score was the number of words produced within the time limit.

Analysis

SPSS Statistics 28 was used to analyse data and to check the assumptions. Descriptive statistics were used to examine the prevalence of mental fatigue and physical fatigue in PwMS and HCs. To examine differences in fatigue, IPS and EF between groups, independent t-tests for parametric data and Mann Whitney U tests for non-parametric data were conducted. Finally, associations between mental fatigue, physical fatigue, IPS and EF were tested with Spearman's rank correlations for nonparametric data. Bonferroni-Holm corrections were applied to correct for multiple comparisons (Holm, 1979). Statistical significance was determined using a p-value of less than 0.05, two-sized.

Research questions

1a: Do PwMS and HCs differ in their levels of mental and physical fatigue?

Comparison between PwMS and HCs on variables mental and physical fatigue with Mann Whitney U tests.

H0: PwMS and HCs do not differ in the level of mental and physical fatigue.

H1: PwMS have a significantly higher level of mental and physical fatigue than HCs.

1b: How do PwMS perform on tasks for IPS and EF compared to HCs?

Comparison between PwMS and HCs on variables performance on IPS and EF tasks with independent t-tests or Mann Whitney U tests.

H0: PwMS and HCs do not differ on tasks for IPS and EF.

H1: PwMS score significantly lower on tasks for IPS and EF than HCs.

2a: Do people with RRMS and SPMS differ in their levels of mental and physical fatigue?

Comparison between the RRMS and SPMS group on variables mental and physical fatigue with Mann Whitney U tests.

H0: People with RRMS and people with SPMS do not differ in the level of mental and physical fatigue.

H1: People with SPMS have a significantly higher level of mental and physical fatigue than people with RRMS.

2b: How do people with RRMS perform on tasks for IPS and EF compared to people with SPMS?

Comparison between the RRMS and SPMS group on variables performance on IPS and EF tasks with Mann Whitney U tests.

H0: People with RRMS and people with SPMS do not differ on tasks for IPS and EF.

H1: People with SPMS score significantly lower on tasks for IPS and EF than people with RRMS.

3: How is the performance on tasks for IPS and EF related to mental and physical fatigue in PwMS?

Correlation analysis between the variables mental fatigue, physical fatigue, and performance on IPS and EF tasks for the PwMS group using the Spearman's rank correlation.

H_0: There is no relationship between the performance on tasks for IPS, EF and mental and physical fatigue in PwMS.

H_1: Lower performance on tasks for IPS and EF are related to higher mental fatigue and not to physical fatigue in PwMS.

4: How is the performance on tasks for IPS and EF related to mental and physical fatigue in the RRMS and SPMS subgroups?

Correlation analysis between the variables mental fatigue, physical fatigue, and performance on IPS and EF tasks for the RRMS and SPMS group using the Spearman's rank correlation.

H_0: People with RRMS and people with SPMS do not differ in terms of the correlation between the performance on tasks for IPS, EF and mental and physical fatigue.

H_1: Within the SPMS group, performance on tasks for IPS and EF are related to mental fatigue and not to physical fatigue. In people with RRMS, performance on tasks for IPS and EF are also related to mental fatigue, but to a lesser extent than in the SPMS group. Here, we also expect no relationship between IPS and EF with physical fatigue.

Results

Participants

A total of 262 PwMS were included, with 164 (62.6%) people with RRMS, 59 (22.5%) people with SPMS, 29 (11.1%) people with PPMS and 10 (3.8%) people with an unknown subtype. In addition, 90 HCs were included. The PwMS and HC group did not differ on age and gender. A difference between groups was found for educational level. Educational level was slightly lower in the PwMS group compared to the HCs (Table 1).

Table 1

Participant Characteristics, M (+*SD*), *n* (%)

Variable	1. HC (*n* = 90)	2. PwMS (*n* = 262)	Difference 1-2	
			X^2/U	*p*
Age	51.7 (10.5)	50.3 (11.2)	U = 10792	.23
Gender, female (%)	62 (68.9%)	206 (78.6%)	$X^2 = 3.5$	.62
Education	5.7 (.7)	5.5 (.8)	U = 10196	.04
EDSS		2.1 (1.3)		
Duration of diagnosis, years		13 (10.1)		

Note. HC = healthy controls; PwMS = people with MS; Education = 7-point scale spanning from 1 (primary-level schooling) to 7 (university degree); EDSS = Expanded Disability Status Scale.

Prevalence of mental and physical fatigue

In the total PwMS group, 75.2% experienced high to very high levels of mental fatigue, and 57.6% experienced high to very high levels of physical fatigue. In the RRMS group, 72% experienced high to very high levels of mental fatigue, and 52.4% experienced high to very high levels of physical fatigue. In the SPMS group, 79,7% experienced high to very high levels of mental fatigue, and 71.1% experienced high to very high levels of physical fatigue.

Fatigue, IPS and EF measures

Table 2 shows the differences in prevalence of mental and physical fatigue, and performance on measures for IPS and EF between HCs and PwMS. PwMS had a significantly higher level of both mental and physical fatigue than HCs. Additionally, PwMS performed significantly lower than HCs on all measures for IPS and EF.

Table 2

Comparisons of fatigue, IPS and EF between HCs and PwMS, M (SD)

Variable	1. HC (n = 90)	2. PwMS (n = 262)	Difference 1-2	
			t/U	p
Fatigue questionnaire				
DMFS-M	17.4 (4.6)	25.3 (5.7)	U = 2772.5	<.001*
DMFS-P	13.1 (4.1)	19.1 (5.1)	U = 3530.5	<.001*
Neuropsychological tests for IPS				
SDMT	60.6 (9.6)	52.1 (13.2)	t = 5.3	<.001*
TMT A	28.4 (8.7)	37.5 (37.2)	U = 9005.5	<.001*
Neuropsychological tests for EF				
TMT B	59 (19)	75.7 (43.8)	U = 8822.5	<.001*
COWAT	40.1 (11.3)	34.2 (10.8)	U = 8236.5	<.001*

Note. HC = healthy controls; PwMS = people with MS; DMFS-M = Mental fatigue subscale of The Dutch Multifactor Fatigue Scale (DMFS); DMFS-P = Physical fatigue subscale of the DMFS; SDMT = The Dutch Multifactor Fatigue Scale; TMT A = Trail Making Test A; TMT B = Trail Making Test B; COWAT = The Dutch version of the Controlled Oral Word Association Test.
*Significant after Bonferroni-Holm corrections for multiple comparisons.

Table 3 shows the differences in prevalence of mental fatigue, physical fatigue, and performance on measures for IPS and EF between the RRMS group and SPMS group. No significant differences were found for mental and physical fatigue between the groups. Additionally, the SPMS group performed significantly lower than the RRMS group on both measures for IPS and on one test for EF.

Table 3

Comparisons of fatigue, IPS and EF between RRMS and SPMS, M (SD)

			Difference 1-2	
Variable	1. RRMS (*n* = 164)	2. SPMS (*n* = 59)	U	*p*
Fatigue questionnaire				
DMFS-M	25.1 (5.8)	25.6 (5.9)	U = 4636.5	.635
DMFS-P	18.7 (5)	20.3 (4.3)	U = 3912	.029
Neuropsychological tests for IPS				
SDMT	55.7 (11.1)	44.6 (13.5)	U = 2533.5	<.001*
TMT A	31.2 (13.2)	49.4 (64.7)	U = 3235.5	<.001*
Neuropsychological tests for EF				
TMT B	65.6 (31)	92.8 (53.9)	U = 2840	<.001*
COWAT	35.8 (10.7)	32.1 (9.3)	U = 3840.5	.019

Note. RRMS = RRMS group; SPMS = SPMS group; DMFS-M = Mental fatigue subscale of The Dutch Multifactor Fatigue Scale (DMFS); DMFS-P = Physical fatigue subscale of the DMFS; SDMT = The Dutch Multifactor Fatigue Scale; TMT A = Trail Making Test A; TMT B = Trail Making Test B; COWAT = The Dutch version of the Controlled Oral Word Association Test.
*Significant after Bonferroni-Holm corrections for multiple comparisons.

Correlations between fatigue, IPS and EF

Table 4 presents the correlation coefficients between mental fatigue, physical fatigue and performance on tasks for IPS and EF, in both the overall group of PwMS as well as separately for both subtypes. When looking into the entire PwMS group, a weak positive correlation was found between physical fatigue and performance on the TMT A. This suggests that greater physical fatigue is associated with reduced IPS. Furthermore, no significant correlations were found between mental fatigue and performance on all tasks for IPS and EF in the entire PwMS group. When examining the RRMS and SPMS groups separately, no significant correlations were found between both mental and physical fatigue and performance on all tasks for IPS and EF.

Table 4

Correlations between fatigue, IPS and EF

	1. PwMS (*n* =262)		2. RRMS (*n* = 164)		3. SPMS (*n* = 59)	
	DMFS		DMFS		DMFS	
Variable	M	P	M	P	M	P
Neuropsychological tests for IPS						
SDMT	-.074	-.066	-.073	-.007	-.099	-.020
TMT A	.126	.170*	.141	.118	.016	.116
Neuropsychological tests for EF						
TMT B	.134	.118	.127	.030	.131	.127
COWAT	-.128	-.085	-.106	-.038	-.124	-.035

Note. PwMS = people with MS; RRMS = RRMS group; SPMS = SPMS group; DMFS-M = Mental fatigue subscale of The Dutch Multifactor Fatigue Scale (DMFS); DMFS-P = Physical fatigue subscale of the DMFS; SDMT = The Dutch Multifactor Fatigue Scale; TMT A = Trail Making Test A; TMT B = Trail Making Test B; COWAT = The Dutch version of the Controlled Oral Word Association Test.
*Significant after Bonferroni-Holm corrections for multiple comparisons.

Discussion

The aim of this study was to investigate how mental and physical fatigue that PwMS experience relate to cognitive functioning in the domains of IPS and EF. Additionally, it was investigated how these constructs are related to one another in different subtypes of MS, namely RRMS and SPMS. First, this study showed that the PwMS group experienced significantly higher levels of mental and physical fatigue and performed significantly worse on all tasks assessing IPS and EF compared to HCs. Furthermore, the results showed that only in the overall PwMS group, a small association was found between physical fatigue and IPS. No associations were found between mental fatigue and the performance on tests for IPS and EF, and neither when looking into the overall group of PwMS nor within the separate subtypes.

In this study, PwMS reported significantly higher levels of mental and physical fatigue than the HC group. These results are consistent with previous findings (Oliva Ramirez et al., 2021; Smith & Hale, 2007). Although the RRMS and SPMS groups did not differ significantly in levels of mental and physical fatigue at the group level, prevalence data indicate a higher level of 7.7% for mental fatigue and a higher level of 18.7% for physical fatigue in the proportion of individuals within the SPMS group compared to the RRMS group. These results are consistent with previous findings, which stated that fatigue was more prevalent in people with SPMS (Maier et al., 2023; Weiland, 2015). In addition, the prevalence data revealed a clear increase in physical fatigue when comparing individuals with RRMS and SPMS, whereas mental fatigue showed a less pronounced difference. Mental fatigue was consistently high across groups and exceeded levels of physical fatigue, regardless of disease subtype. The consistent high level of mental fatigue could be attributed to the already disrupted brain tissue and early neurodegenerative and microstructural disruptions during the early disease course, as such changes have been associated with cognitive fatigue in other studies (Guillemin et al., 2024). Furthermore, research demonstrates that cognitive and physical fatigue develop independently, with physical fatigue being more likely to emerge in the presence of motor function decline, which typically occurs in the later stages of the disease (Ellison et al., 2021; Tarasiuk et al., 2021). It is therefore important to pay attention to mental fatigue in both groups, as this symptom tends to appear early and is often pronounced.

Results from the neuropsychological tests for IPS and EF showed that the PwMS group consistently scored lower than the HC group. This outcome supports previous results and can be explained by structural brain damage, particularly in relation to the interaction between multiple brain regions, which is relevant for IPS (Meijer et al., 2018). In addition, a decline in EF may be attributable to structural decline in thalamic volume and reduced brain parenchymal fraction (Mirmosayyeb et al., 2024). When comparing the RRMS and SPMS group, the SPMS group showed lower performance on all tests for IPS compared to the RRMS group. These findings suggest a decline in IPS in more progressive subtypes of MS, and these results are consistent with previous studies (Lynch et al., 2005). When comparing the two groups on tests for EF, the SPMS group showed lower performance one test (TMT-B), which is in line with previous studies (Brochet & Ruet, 2019). No significant difference was observed on the verbal fluency test (COWAT) between the RRMS and SPMS groups. Previous research has found inconsistent results when examining differences between these groups on verbal fluency. Some studies reported significant differences, whereas others found no such effects (Delgado-Álvarez et al., 2020; Huijbregts et al., 2004; Messinis et al., 2013). A possible explanation could be that the sensitivity of the COWAT is sufficient to detect cognitive decline in the overall group of PwMS when compared to HCs, but may be limited in its ability to identify more subtle differences between disease subtypes.

When examining the relationship between performance on IPS and EF with physical fatigue in the PwMS group, the RRMS group and SPMS group, only a weak association was observed between physical fatigue and IPS in the PwMS group. Similar findings have been reported in other studies, which also demonstrated a comparable relationship between physical fatigue and IPS (Andreasen et al., 2019; Bellew et al., 2022). It is important to consider that the correlation found for the IPS measure reflects a construct that also involves a visuomotor search component. An explanation from a neurobiological perspective could be the presence of brain atrophy and dysfunction in cortico-subcortical pathways (Andreasen et al., 2010). More severe disease progression generally leads to greater brain damage, which may contribute to both physical symptoms/fatigue and cognitive impairments.

Finally, no relationship was found between mental fatigue and the performance on tasks for IPS and EF, both for the entire group of PwMS as well as when looking into the different subtypes. Previous studies have shown mixed results. Some studies found no significant link between subjective fatigue and neuropsychological performance (Morrow et al., 2009; Parmenter et al., 2003), whereas others reported associations between cognitive fatigue and IPS and EF (verbal learning) (Andreasen et al., 2010; Bellew et al., 2022; Diamond et al., 2008). This study contributes to the existing literature suggesting that mental fatigue cannot be explained by impairments in IPS and EF. These results indicate that additional factors are likely involved in the experience of mental fatigue, highlighting the need for further research to clarify these underlying mechanisms.

There are several limitations that should be acknowledged. First, the possibility of healthy participant bias should be considered, as this is a phenomenon in general research and has also been observed in studies involving PwMS (Duquin et al., 2008). The healthy participant bias refers to the systematic tendency for individuals who participate in scientific studies to be healthier than those who decline participation (Leening et al., 2014). This bias may lead to an underestimation of symptoms, reducing the representativeness of the results and limiting their generalizability. Although a small number of participants with the PPMS subtype were included in the study, this number was insufficient to conduct meaningful analyses. Therefore, people with PPMS were not part of the study. Furthermore, the DMFS questionnaire was used to assess mental and physical fatigue. However, this questionnaire had only been validated on patients with a brain injury (Visser et al., 2015). Therefore, the validity of the questionnaire within the context of this study needs to be considered when generalizing the results to PwMS. In addition, the PwMS and HC groups differed in educational level which could have influenced the results between the groups; however, these differences were small. Finally, we did not control for the potential effects of mood and its interaction with cognitive performance and fatigue. It remains unclear whether controlling for this variable could have impacted our findings. This issue has also been highlighted in prior studies (Diamond et al., 2008; Golan et al., 2017; Sadigh-Eteghad et al., 2021). Although the presence of a major psychiatric disorder was an exclusion criterion in this study, we cannot rule out the potential influence of milder forms of depression and its symptoms that may not have been fully accounted for. Several participants reported using psychiatric medication and experiencing mood-related symptoms in our study.

The results of this study highlight the presence of experienced mental and physical fatigue and impairments in IPS and EF in PwMS, processes that play a critical role in everyday life. It is important to take these deficits into account and focus on therapeutic interventions aimed at enhancing coping skills and psychoeducation. Furthermore, our study showed that mental fatigue is consistently high among the entire group of PwMS and across the different subtypes. For this reason, it is recommended that additional attention is given to this aspect during treatment and psychoeducation, because fatigue is often treated as a general concept in clinical practice, rather than being addressed as separate domains such as mental and physical fatigue. Intergrading these implications can help patients, as well as their caregivers, gain a better understanding of their illness, promote greater awareness, acceptance of their limitations and improve their quality of life (Oz & Oz, 2020).

Future research is needed for exploring the underlying mechanisms of mental fatigue to gain a better understanding of the increased brain activity, because the search for a reliable relationship between subjective and objective measures remains inconclusive. This could be done through functional magnetic resonance imaging (fMRI), because it shows promising results (Leavitt & DeLuca, 2010). Furthermore, mental fatigue should be assessed through self-reports simultaneously to give insights into the level of reported fatigue. In addition, as stated in the limitations, it is recommended that future research should include the subtype PPMS in their studies, so that fatigue and possible relationships can be investigated in this group as well. Also, validating the DMFS questionnaire in different patient populations is needed, including PwMS, to ensure the generalizability of the results. Finally, future research should take the variable mood into account and integrate it in their analyses to gain a better understanding of the potential influence on the relationship between fatigue and IPS and EF in PwMS.

In conclusion, our study showed that high levels of both mental and physical fatigue were reported by PwMS. However, mental fatigue was consistently the most pronounced across both MS subtypes and was not related to cognitive performance. Based on these findings, there is insufficient evidence to suggest that the origin of mental fatigue lies in cognitive functioning, specifically in the domains of IPS and EF, and should therefore be further explored. Continued research into the underlying mechanisms is essential to provide appropriate support to patients for this burdensome symptom.

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