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Fatigue in multiple sclerosis – a current perspective

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Fatigue in multiple sclerosis – a current perspective

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Table of contents

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Editorial: Fatigue in multiple sclerosis—A current perspective

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Editorial on the Research Topic
Fatigue in multiple sclerosis—A current perspective

As editors of this Research Topic, we wanted to acknowledge and give scientific space to a symptom that affects so many patients with multiple sclerosis (MS) and which has an enormous impact on the daily lives of those affected, their vocational status, and social participation. It may also affect their adherence to disease-modifying therapies, interfering with expected treatment outcomes (1). Despite recent progress in our understanding of the background of MS, as well as the availability of therapeutic options, understanding the pathophysiology and management of fatigue still remains a challenge (2–4). Thus, there is a need for better recognition of this problem, based on focused research with further clinical implications.

The present Research Topic aims to highlight the current view on risk factors and mechanisms of fatigue in MS, as well as its assessment and management throughout the disease.

The review article by Patejdl and Zettl focuses on the pathophysiology of motor fatigue and fatigability. It gives a comprehensive overview of current concepts, including definitions, assessment approaches, pathophysiology, and training interventions.

Ayache et al. reappraise neurophysiological studies in view of putative mechanisms of fatigue and fatigability in MS. Among the parameters of CNS excitability, evaluated with the use of transcranial magnetic stimulation, those associated with movement preparation and facilitation seem the most consistently related to fatigue. Furthermore, the therapeutic potential of non-invasive brain stimulation is discussed for the short- and long-term amelioration of motor and cognitive fatigability, considering innovative protocols and their combination with pharmacotherapy or exercise.

The first original article by Broscheid, Behrens, Bilgin-Egner, et al. is focused on the meaningfulness of gait parameters in the context of motor performance fatigability (PF) on the one hand and the relevance of minimum toe clearance (MTC) in the quantification of motor PF in people with MS (pwMS) on the other. Importantly, based on the 6-min walk test (6MWT) it was discovered that the second minute of the test delivered more stable gait parameters than the first minute and that MTC in combination with other spatiotemporal gait parameters was not able to detect motor PF, although, there was a decrease in MTC variability observed in some pwMS toward the end of the 6MWT. These results indicate the weakness of reliable data acquisition during the first minute of the 6MWT and also point to the necessity of longer test intervals to discover motor PF.

In the second original article by Broscheid, Behrens, Dettmers, et al., the 6MWT is combined with a cognitive task to create a motor-cognitive dual-task performance to simulate multi-tasking behavior in a real-life setting. PwMS and healthy controls (HCs) had to perform a fast version of the 6MWT, while at the same time performing an arithmetic task. At the same time, the hemodynamic response of their prefrontal cortex was recorded. The results showed an effect on cognitive PF but not on motor PF although participants reported being physically fatigued. The PFC activation remained unchanged. Again, the authors suggest that the 6MWT is, even in the fast version, not long enough to induce objectifiable motor PF.

Tarasiuk et al. in their review on the co-occurrence of fatigue and depression in MS, highlight pathomechanisms potentially shared by these conditions. They include proinflammatory cytokine response and oxidative/nitrosative stress which affect the tryptophane metabolic pathway, impairment of the hypothalamic-pituitary-adrenal axis, and disturbed functionality of cortico-subcortical loop (prefrontal cortex, basal ganglia, and limbic system). Psychosocial aspects of fatigue and depression, their reciprocal relationships, and the need for differentiation are also discussed.

Links between fatigue and mental health in MS are addressed in the cross-sectional study by AlSaeed et al. In the study group of pwMS with mild disability, almost half reported fatigue, and up to 26% presented with symptoms of anxiety or depression. Fatigue level was found to correlate significantly with depression, anxiety, and quality of life, with no relationship between fatigue and demographics or physical activity.

There are two modalities to assess fatigue: asking patients with questionnaires and measuring the impact of fatigue on physical and cognitive functions (fatigability). Block et al., in their review, highlight the value and limitations of the two approaches. In principle, fatigue is a subjective experience, so it has to be explored with self-reported questionnaires, however, this active patient-reported outcome has the problem of recall bias and does not inform about the day-to-day variability of the symptom. On the other hand, the evaluation of physical and cognitive decline with neurophysiological and psychometric tests has the advantage of the objectivity of the measures, however, they may not reflect the subjective perception of fatigue. The authors emphasize the value of remote monitoring with smartphones and wearable devices because they provide a more granular collection of both the patient-reported state and quantify physical and cognitive performances. Block et al. conclude that the combination of fatigue and fatigability measures using remote monitoring may provide a more comprehensive outcome in clinical and research settings.

The problem of the variability of fatigue over time is also addressed by Grothe et al., who examine the month-to-month changes in the perceived level of motor and cognitive fatigue. In a retrospective monocentric cohort study, they find that fatigue was lower during winter and higher during summer, with a nadir in August. However, the oscillations of the fatigue score were modest. Fatigue levels correlated with monthly temperature. The authors underline the importance of taking these seasonal changes in fatigue into consideration in interventional studies on fatigue because they may influence the results.

Many studies have approached the problem of brain magnetic resonance correlates of fatigue (5, 6), and most of them have shown the important role in the involvement of the striato-thalamo-cortical network. The Román et al. study, using an advanced diffusion imaging technique, examines the correlations of white matter and basal ganglia microstructure measures with the rate of cognitive fatigue over time during a fatigue-inducing task. Patients with cognitive fatigability had more severe damage to white matter tracts associated with basal ganglia connectivity, confirming the key role of the fatigue network.

These articles in the Research Topic contribute to shedding light on the most mysterious symptom of the disease - fatigue, which is so difficult to measure because of its multidimensionality and so difficult to treat. In a recent survey of the PROMS initiative, jointly promoted by the International Federation of MS and European Charcot Foundation, pwMS pointed out that fatigue is the first daily problem they have to face and they expressed the importance to improve outcome measures of fatigue with a fundamental patient contribution.

Author contributions

AP-D, I-KP, and GC equally contributed to conception and design of the article, writing particular sections, and revision of the whole text. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
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Co-occurrence of Fatigue and Depression in People With Multiple Sclerosis: A Mini-Review

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Fatigue and depression are common conditions diagnosed in people with multiple sclerosis (MS). Fatigue defined as subjective lack of physical and/or mental energy is present in 35–97% of people with MS, who classify it as one of the most serious symptoms interfering with daily activities and influencing the quality of life. Depression is diagnosed in about 50% of people with MS. Since fatigue and depression frequently coexists, it may be quite hard to differentiate them. Primary fatigue and primary depression in MS are caused by inflammatory, oxidative/nitrosative, and neurodegenerative processes leading to demyelination, axonal damage, and brain atrophy. In people with MS and comorbid fatigue and/or depression there is reported increased serum and cerebrospinal fluid concentration of inflammatory mediators such as tumor necrosis factor, interleukins (IL-1a, IL-1b, IL-6), interferon γ and neopterin. Moreover, the brain atrophy of prefrontal, frontal, parietotemporal regions, thalamus, and basal ganglia was observed in people with MS with fatigue and/or depression. The secondary fatigue and secondary depression in people with MS may be caused by emotional factors, sleep disorders, pain, the coexistence of other diseases, and the use of medications. In some studies, the use of disease-modifying therapies positively influenced fatigue, probably by reducing the inflammatory response, which proves that fatigue and depression are closely related to immunological factors. In this mini-review, the pathogenesis, methods of evaluation and differentiation, and possible therapies for fatigue and depression in MS are discussed.

Keywords: multiple sclerosis, fatigue, depression, anhedonia, fatigue scales

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INTRODUCTION

Fatigue and depression are very common conditions diagnosed in people with multiple sclerosis (MS). Fatigue is present in 35–97% of people with MS (1, 2). It is classified as one of the most serious symptoms interfering with daily activities and influencing the quality of life (QoL) (1–3). Fatigue is defined as a subjective lack of physical and/or mental energy. MS-related fatigue is divided into physical and cognitive (4). Physical fatigue, defined as a decline in motor performance during sustained muscle activity, is caused by physical exhaustion and results from muscle weakness. Cognitive fatigue is defined as a decline in performance during cognitive activity, which results from difficulty with concentration, memory loss, and emotional instability (4–8). Cognitive fatigue starts independently from the physical disability in the early stages of MS and may be present

already in the prediagnostic phase of the disease (9, 10). Cognitive fatigue is one of the key factors resulting in a decreased QoL in all people with MS (8, 11–13). Depression is diagnosed in about 50% of people with MS (14). Depression itself can manifest with fatigue and symptoms of depression may be mistaken for fatigue making these conditions difficult to differentiate. Recent studies have identified a strong correlation between fatigue and depression. These conditions jointly affect more than half of people with MS (15).

The leading and common symptom of cognitive fatigue and depression is anhedonia defined as decreased motivation, a lack of positive affect, and the reduced ability to experience pleasure (14, 16–18). Anhedonia is caused by deficiency of neurotransmitters such as dopamine and serotonin, which leads to impairment in the functioning of mesocorticolimbic pathways projecting from the midbrain to the basal ganglia, the limbic system, and the prefrontal cortex. It results in disrupting the brain's reward and valence system (16, 18). The structural and functional alterations of mesocorticolimbic pathways have been confirmed in neuroimaging studies in people with MS suffering from fatigue and/or depression (18).

The frequent coexistence of fatigue and depression in people with MS suggests a common etiology of both conditions (19–21). Primary fatigue and primary depression in MS are most probably caused by inflammatory, oxidative/nitrosative, and neurodegenerative processes leading to demyelination, axonal damage, and brain atrophy (1). In people with MS and comorbid fatigue and/or depression there is reported increased serum and cerebrospinal fluid (CSF) concentration of proinflammatory cytokines, interleukins, interferon γ (IFNγ), and neopterin (1). Many studies have been also reported the brain atrophy of the prefrontal, frontal, parietotemporal region, thalamus, and basal ganglia (16, 22). The secondary causes of fatigue and depression are emotional stress, sleep disorders, pain, the coexistence of other diseases, and the use of some disease-modifying therapies (DMTs), e.g., interferon-β (22). The treatment of MSrelated fatigue and depression is still challenging. In some studies, the use of natalizumab, fingolimod, and glatiramer acetate positively influenced fatigue, probably by reducing the inflammatory response, which proves that fatigue and depression are related to immunological factors (16).

In the present mini-review, we provide and discuss the latest information on the pathogenesis, methods of evaluation and differentiation, and possible therapies for fatigue and depression in MS.

ETIOPATHOGENESIS OF FATIGUE AND DEPRESSION IN MS

The neuroinflammatory process undergoing the pathogenesis of MS disturbs neural function and may result in fatigue and depression (**Figure 1**) (1–3, 15, 16). In the pathomechanisms of fatigue and depression in MS the crucial role play proinflammatory cytokines including tumor necrosis factor α (TNFα), interleukins (IL-1a, IL-1b, IL-2, IL-6), IFN-γ released by mitogen-stimulated peripheral blood lymphocytes, and neopterin produced by macrophages upon IFN-γ stimulation (23). The proinflammatory mediators lead to the induction of tryptophan catabolism. Tryptophan is a biochemical precursor for serotonin and kynurenine. The low level of these monoamines may lead to fatigue and depression (23). In people with MS with comorbid fatigue and/or depression, there are reported increased serum and CSF concentrations of the pro-inflammatory cytokines, such as interleukins (IL-1a, IL-1b, IL-2, IL-6), TNF-α and IFN-γ. The high concentrations of those pro-inflammatory mediators correlate directly with the level of fatigue and depression (1, 23–25). The proinflammatory cytokines in people with MS induce sickness behavior by disruption of dopamine and serotonin neurotransmission in mesocorticolimbic pathways connecting the midbrain with the basal ganglia, the limbic system, and the prefrontal cortex leading to dysfunctional reward processing and anhedonia (16, 18, 19, 26, 27). Pro-inflammatory cytokines disturb the synthesis of dopamine and serotonin by reducing the synaptic availability of amino acids precursor, disturbing their release, and increasing the reuptake of monoamines (27). The cytokines increase the metabolism of the serotonin precursor tryptophan *via* the alternative kynurenine pathway by inducing indoleamine 2,3 dioxygenase (IDO) (28). In addition, the cytokines decrease the availability of the co-factor tetrahydrobiopterin (BH4) limiting the turnover of the precursor phenylalanine and tyrosine and interfering with the formation of dopamine (29). The synaptic availability of serotonin and dopamine is reduced by decreased presynaptic release and increased activity of pro-inflammatory cytokines acting as reuptake transporters (30).

Recently, it has been shown that the microglia contribute to neurodegeneration by the production of neurotoxic metabolites such as quinolinic acid that maintains inflammation and neurodegeneration through excitotoxicity (16, 28). Increased glutamate levels in the CNS lead to overstimulation of glutamate receptors and neuronal and glial damage (31). Quinolinic acid stimulates release and inhibits the reuptake of glutamate from astrocytes as well as it is direct agonist binding to glutamate N-methyl-D aspartate (NMDA) receptors (32). Stimulation of extrasynaptic NMDA receptors by glutamate was reported to be associated with decreased expression of brain-derived neurotrophic factor (BDNF) and the induction of cell death. The pro-inflammatory cytokines contribute to excitotoxicity in the gray and white matter by hampering glutamate reuptake through astrocytes and oligodendrocytes (16, 31).

The neurodegeneration and decreased neurogenesis are also caused by oxidative and nitrosative stress (O&NS) ongoing in course of MS (1, 23, 33, 34). O&NS induces damage to membrane fatty acids and proteins, which results in the formation of anchorage neo-epitopes, exposed to an autoimmune response. The level of immunoglobulins M (IgM) against these epitopes (ex. palmitic, myristic, S-farnesyl-cysteine) was found to be increased in people with depression and fatigue. O&NS also leads to dysfunction of mitochondria, affects DNA expression, lowers antioxidant and omega-3 polyunsaturated fatty acid levels, and

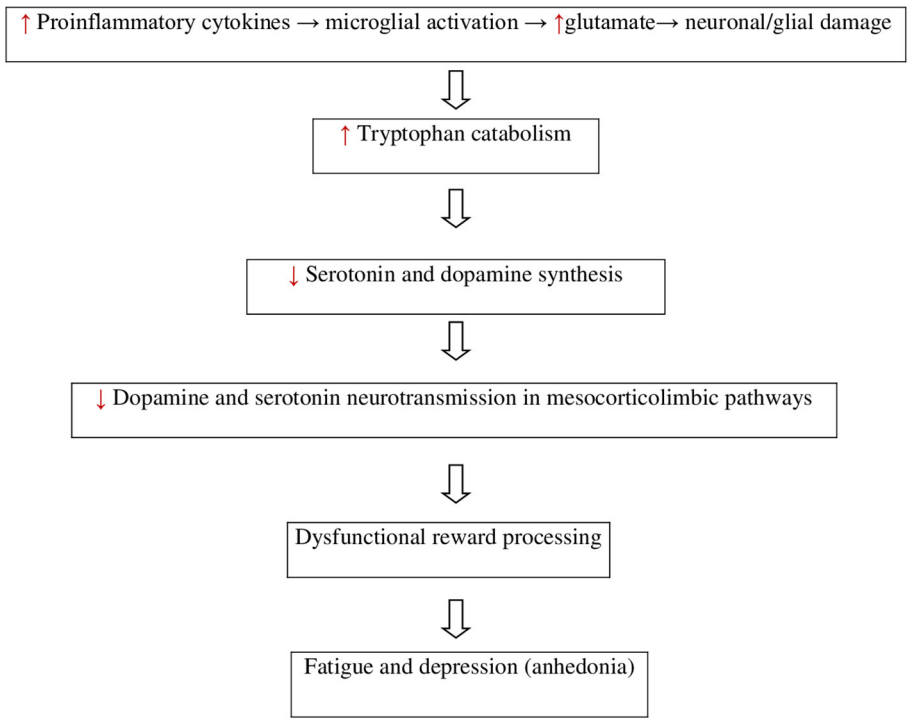

FIGURE 1 | Neuroimmunological finding in MS-related fatigue and depression.

increases translocation of gram-negative bacteria. Evidence of the O&NS pathways shared by depression and fatigue may explain the common co-occurrence of these conditions in the course of MS (35).

In people with MS and comorbid fatigue and/or depression, there was also reported impairment of the hypothalamic-pituitary-adrenal (HPA) axis. The low cortisol and low dehydroepiandrosterone levels have been implicated in chronic fatigue and depression (22, 36, 37). It suggests a possible endocrine contribution to fatigue and depression. People with MS report increased energy after taking corticosteroids as treatment for MS relapse, which supports a possible positive hormonal influence of steroids on fatigue (22).

The etiopathogenesis of MS-related fatigue and depression is also involved serotonergic regulation *via* the brain serotonin transporters (SERT) (38). In people with MS the SERT regulation may be disturbed (38, 39). The SERT inhibitors, such as fluoxetine and sertraline have been reported to have neuroprotective effects in MS (38, 40). Hesse et al. have reported that serotonergic neurotransmission in people with MS is altered in limbic and paralimbic regions, the frontal cortex, which contributes to cognitive fatigue and depression in MS (38). People with MS and comorbid fatigue and/or depression have been reported to have low SERT availability in cortical and subcortical brain areas, limbic and paralimbic regions such as the cingulate cortex, hippocampal/parahippocampal, and insular (38).

ANATOMICAL ABNORMALITIES IN FATIGUE AND DEPRESSION IN MS

Fatigue and depression in people with MS are associated with gray matter atrophy in the prefrontal cortex, the basal ganglia, the striatum, and the limbic system (16, 41–44). Many studies have shown decreased monoaminergic neurotransmission in frontostriatal and frontolimbic pathways in people with MS suffering from fatigue and depression (44–47). Roelcke et al. have shown in positron emission tomography study the decreased glucose metabolism in the basal ganglia and the prefrontal cortex. In turn, Finke et al. and Jaeger et al. have reported in the functional magnetic resonance imaging study the decreased functional connectivity between the ventral striatum, the amygdala, and the prefrontal cortex (48).

SECONDARY CAUSES OF FATIGUE AND/OR DEPRESSION IN MS

Fatigue and/or depression can be a psychological and emotional reaction to the lifestyle changes that occur when people are diagnosed with a chronic disease such as MS (49, 50). Fatigue and depression may be also caused by sleep disorders, pain, and the coexistence of other diseases. Sleep disorders are quite common in people with MS compared to the general population and may result from muscle spasticity and pain, emotional

disturbances, nocturia, taking medications, and restless legs syndrome (RLS) (51). RLSis present in 30–50% of people with MS and deteriorates the sleep quality (52). The frequency of RLS increases with disability progression assessed by the Expanded Disability Status Score (EDSS) (52). In the course of MS dopaminergic diencephalospinal, and reticulospinal pathways projecting to the spinal cord may be damaged, which leads to RLS (53). People with MS presenting medullary lesions affecting respiratory centers may develop sleep breathing disorders such as central sleep apnea (54). The severity of disability assessed with EDSS also proportionally increases the risk of fatigue and depression (15, 55).

The use of some DMTs may also increase the risk of fatigue and depression (56). Fatigue and depression are reported more frequently in people treated with interferon-β, which causes side effects like flu-like symptoms resembling sickness behavior (57, 58). In some articles, depression is listed as a possible side effect of interferon-β (59, 60). On the contrary, there are several studies that have not found any relationship between DMT type and depression (61). There are still no conclusive data regarding DMTs influence on fatigue symptoms. Some publications raise the positive impact of natalizumab, fingolimod, and glatiramer acetate on fatigue and depression (60, 62–67). One of the theories is that antifatigue and antidepressive effectiveness of some DMTs may be related to the suppression of inflammatory pathways leading to depression (68, 69). However, a causal relationship between DMTs, especially T and B-cell depleting therapies, and the risk of depression remains to be shown. It is also important to consider the mode of administration of DMTs. Additional studies evaluating treatment satisfaction and quality of life of people with MS may shed light on the relation between treatment tolerability, mode of DMTs administration, and risk of fatigue and depression (70). There is a higher risk of DMTs discontinuation in people with MS and depression (60).

EVALUATION AND DIFFERENTIAL DIAGNOSIS OF FATIGUE AND DEPRESSION IN PEOPLE WITH MS

Fatigue and depression interfere with patients' daily activity and may lead to DMTs discontinuation. Therefore, there is a need for an early diagnosis and treatment. The assessment of fatigue is difficult and still challenging, as it requires objective measurement tools (5). Fatigue and depression may manifest with the same symptoms, like loss of motivation and anhedonia making these conditions difficult to differentiate. The fatigue in people with MS is classified on the basis of symptoms as physical, cognitive, and emotional. The fatigue symptoms are reduction in physical activity, problems with performing cognitive tasks, decreased concentration, memory disorders, executive difficulties, and a feeling of internal tension, anxiety, sadness (71).

The measurement of fatigue in the dimension of its perception is only subjective, while the objective measurement of fatigue may be assessed by analyzing the way cognitive and motor tasks are performed over time (27). In the subjective assessment of fatigue are used one- or multi-dimensional self-report scales in the form of questionnaires describing fatigue in terms of its occurrence (or not), severity, duration, and dimension (cognitive/physical). The one-dimensional tool is the Visual Analog Scale for Fatigue (VAS-F). The most commonly used multivariate scales are the short seven-point Fatigue Severity Scale (FSS) and the broader 21-point Modified Fatigue Impact Scale (MFIS). MFIS assesses the impact of fatigue on functioning in three dimensions: social, cognitive, and physical (72, 73). Another multidimensional self-report tool is the Fatigue Scale for Motor and Cognitive Function (FSMC), which assesses the occurrence and intensity of physical and cognitive fatigue on two 10-point scales (5). The objective measurement of fatigue in MS is based on quantitative and qualitative data obtained during the performance of the motor and cognitive tasks by patients. Physical fatigue is described in terms of a decrease in strength, energy, accuracy, or speed of performing the activity over time. In the case of cognitive tasks, the indicators of fatigue include the reduction of reaction time and accuracy during task performance (73).

The frequently comorbid depression in MS patients affects the occurrence of cognitive fatigue. The factor connecting both fatigue and depression is attention deficit (74, 75). Brenner and Piehl showed in their studies that depressive patients presented more severe symptoms of fatigue, which suggests that the onset of depression may be a predictor of fatigue and anxiety, and the onset of fatigue and anxiety may be a predictor of depression (76).

According to Penner et al. and Griffith and Zarrouf for depression is a typical depressed mood, hopelessness, loss of self-confidence and self-esteem, causeless self-reproaches or appropriate feelings of guilt, best functionality in the evening, patients usually attribute their illness to psychological factors (35), there is need for excessive sleep (hypersomnia) or early awakening (77). On the other hand for fatigue is typical hopeful and strong wish to recover, best functioning in the morning with a decrease during the day, patients take initiative while searching for treatment (35) and attribute reasons of fatigue for external factors, they may have difficulties to fall asleep and to maintain sleep resulting in decreased sleep quality (77).

In the differential diagnosis of fatigue and depression also should be performed laboratory testing for hematologic and metabolic conditions, such as thyroid studies, iron, 25- hydroxy vitamin D and vitamin B12 deficiency, ferritin, and folate levels (22).

THERAPEUTIC APPROACH TO FATIGUE AND DEPRESSION IN PEOPLE WITH MS

Up to date, there is not enough evidence supporting the use of any medications for the treatment of MS-related fatigue (78). In clinical practice for fatigue treatment in people with MS are used amantadine, modafinil, and amphetamine-like stimulants (methylphenidate) (78). Amantadine is approved by the Food and Drug Administration (FDA) for treatment of influenza and Parkinson's disease and causes an increase in cholinergic and dopaminergic transmission. Modafinil is approved by the FDA for narcolepsy, shift-work sleep disorder, and obstructive

sleep apnea with residual excessive sleepiness. Amantadine and modafinil have been tested in clinical trials for fatigue in people with MS, but their results have been conflicting (79, 80). Recently, Nourbakhsh et al. in a randomized, double-blind trial compared the efficacy, safety, and tolerability of amantadine, modafinil, methylphenidate, and placebo in people with MS-related fatigue. The results of its study have shown no the superiority of these drugs according to placebo in improving MS-related fatigue, which might have been influenced by comorbid depression and other diseases, MS subtype, the severity of the physical disability, or use of DMTs. However, in *post-hoc* analysis modafinil and methylphenidate might have a marginal, but clinically significant effect on fatigue in patients with excessive daytime sleepiness, which suggests that excessive daytime sleepiness may lead to fatigue in some people with MS (78).

In the treatment of fatigue and depression in people with MS are also used drugs enhancing monoamine neurotransmissions, such as selective serotonin and noradrenaline reuptake inhibitors and psychostimulants with dopaminergic effects (2, 19). Tricyclic antidepressants are effective in reducing clinical depression and improving sleep patterns and are reported beneficial for patients with chronic fatigue.

Recent studies show that non-pharmacological interventions, such as physical exercises and psychological therapy may reduce MS-related fatigue or depression more effectively than pharmacological medications (81, 82). Non-pharmacologic treatment of fatigue or depression includes cognitive-behavioral therapy (CBT), relaxation therapy, physical exercises and rehabilitation, resistance training, mindfulness, yoga, and tai chi, optimal diet, and appropriate sleep hygiene (81, 83, 84). CBT changes the dysfunctional and emphasizes more realistic cognitions, behaviors, and emotions that are responsible for fatigue or depression (82). Recent reports show that CBT has a positive effect on MS-related fatigue, however, this effect decreases with cessation of treatment (85).

The very important strategy in MS-related fatigue and/or depression management is self-management education (SME) (8, 86). This is a complex intervention combining the provision of information and behavior change techniques, to influence the way patients experience the disease (8). SME teaches patients how to cope with a disease's symptoms and enables helpful behaviors, habits, and routines. SME in people with MS reduces fatigue and improves QoL (8). According to Lorig and Holman, SME solves medical, emotional, and role management problems, helps make decisions, and taking action, resources utilization, forms a patient/health care provider partnership (86). The medical management of fatigue is based on symptoms reduction and treatment. Emotional management influences thoughts, beliefs, and behaviors related to cognitive fatigue and is approached by CBT and relaxation exercises. The coping with daily tasks and duties is provided by occupational therapy (OT), which teaches conservation and management strategies, e.g., daily activity schedules, occupational balance or workload, and environment adaptation (8).

CONCLUSIONS

The prevalence of fatigue and depression in people with MS is very high. Fatigue and depression in people with MS have multifactorial etiology, such as inflammatory and neurodegenerative processes, oxidative/nitrosative stress, leading to axonal damage, and demyelination, as well as brain atrophy of prefrontal, frontal, parietotemporal regions, thalamus, and basal ganglia. The inflammatory etiology of fatigue and depression in MS was supported by evidence of increased serum and CSF concentration of inflammatory mediators such as TNF, interleukins (IL-1a, IL-1b, IL-6), IFNγ, and neopterin. The secondary fatigue and secondary depression in people with MS may be caused by emotional factors, sleep disorders, pain, the coexistence of other diseases and, the use of some medication. There is not enough evidence supporting the use of any medications for the treatment of MS-related fatigue. In the treatment of depression and fatigue in people with MS are frequently used drugs enhancing monoamine neurotransmission and non-pharmacologic methods, such as CBT, relaxation therapy, OT, and physical rehabilitation. Recently, progress has been made in evaluating CBT or OT, but evaluation of the patient's education, which teaches self-management skills, helps to cope with disease-related fatigue, and leads to improvement of QoL, is lacking. The interventions, such as self-management education are difficult to evaluate, because of many possible outcome dimensions, instruments, and measurement time-points.

Therefore, there is needed for further researches on neuroimmune interactions, inflammatory biomarkers, the HPA-axis, and neurotransmitters in the pathogenesis of fatigue and depression in people with MS. There is also a high need for the development of new assessment tools for fatigue diagnostics and its differentiation with depression, the assessment of pharmacological and non-pharmacological treatment effectiveness, and the influence of DMTs on the development and course of MS-related fatigue and depression.

AUTHOR CONTRIBUTIONS

JT and AK contributed to conception and design of the manuscript and wrote the first draft of the manuscript. JT, AK, KK-T, AC, MC, and JK wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Fatigue, Depression, and Anxiety Among Ambulating Multiple Sclerosis Patients

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Background: Multiple sclerosis (MS) is an inflammatory disease associated with adverse effects: including depression, anxiety, fatigue, which may affect physical activity and the quality of life (QoL) among patients with MS (pwMS).

Objective: This study aims to assess the prevalence of depression, anxiety, and fatigue among pwMS who have no physical disability in Saudi Arabia, and demonstrate any correlation between these factors and physical activity as well as the QoL.

Methods: A cross-sectional study was conducted in the Neuroimmunology outpatient clinics in King Fahad Medical City (KFMC) and King Saud University Medical City (KSUMC) in Riyadh City, KSA. The Arabic version of the Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression levels. The HADS scores were then categorized into three levels according to the total points: normal (0–7 points), borderline (7–10 points), and anxiety/depression (11 – 21 points). The Arabic version of the Fatigue Severity Scale (FSS) was used to measure fatigue (cut-off point ≥5). The physical activity was measured by the Arabic version of the short form of the International Physical Activity Questionnaire (IPAQ), which measure time spent walking, moderate- and vigorous-intensity physical activity of at least 10 minutes duration. The QoL was also measured by the Arabic version of the EuroQOL five-dimensional (EQ-5D-3L) instrument (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Results: A total of 323 pwMS participated in this study, 83 had scores that indicated anxiety (25.7%) and 44 had depression (13.6%). The majority of patients had scores with the normal range of depression and anxiety (70% and 57% respectively). The mean of EuroQol Group visual analogue scale (EQ-VAS) score was 80.43 (SD=19.8). 156 (48.3%) out of 323 pwMS reported fatigue while the remainder had no fatigue (n=167, 51.7%). The results indicate that only 143 patients (44.3%) had participated in vigorous physical activity during the last 70 days, with a median of 3 days per week (IQR= 5–3) and a median of

60 minutes per day 0 (Interquartile range: IQR = 60–30). Only 149 patients (49.2%) had patricpated in moderate physical activities during the previous week with a median of 3 days per week (IQR = 5–3) and a median of 40 minutes per day (IQR = 60–30). 194 patients had participated in walking activities (60.0%) with a median of 5 days per week (IQR = 7–3) and a median of 45 minutes per day (IQR = 60–30). The results revealed that fatigue was positively correlated with depression ($r = 0.407$, p-value < 0.001) and anxiety ($r = 0.289$, p-value < 0.001).

Conclusion: The current study shows depression, anxiety, and fatigue tend to be correlated and clustered together among pwMS in our cohort. However, fatigue is not associated with the intensity of physical activity undertaken. The results of this study are important for the improvement of the clinical management of MS patients.

Keywords: multiple sclerosis, depression, fatigue, physical activity, quality of life, Riyadh, anxiety, Kingdom of Saudi Arabia

INTRODUCTION

One of the most common neurological disorders that can affect young adults is multiple sclerosis (MS) (1). It is a chronic, inflammatory, autoimmune disease that affects the central nervous system. The inflammation leads to demyelination and axonal loss, manifesting as different cognitive, motor, or sensory symptoms depending on the lesions' location (2). The current prevalence of MS in the Kingdom of Saudi Arabia (KSA) is estimated to be around 62 patients per 100,000 Saudi nationals, although unfortunately at present there is no National Regisry of MS (3). In general, MS tends to affects females more than males, with an estimated 3:1 female to male ratio globally (2). In KSA, this ratio was estimated at approximately 2:1 woman to men ratio (3). The majority of MS patients ambulating normally and with no disability according to their median expanded disability status score (EDSS) score 1 (3). The disease's etiology remains unclear (4), but it is thought to be a consequence of a complex interaction between genetic and environmental factors (2, 5).

Depression, anxiety, and fatigue are common among patients with MS (pwMS) and do affect their quality of life (QoL) and physical activity (6–11). In some studies, the prevalence of depressive symptoms and anxiety ranged between 14-54% and 14-41% respectively (6–8, 11). Depression and anxiety have an unpredictable disease nature and are considered to be the most disabling symptoms that affect the QoL and general health in MS patients (11, 12). Associations between depression and disability and non-motor symptoms such as fatigue have been studied but the results are inconsistent (12–15). For example, some studies reported a direct association (12, 14, 16–18) while others did not (19, 20). Furthermore, anxiety was found to be associated with chronic pain while it was moderately associated with disability and fatigue (11, 12, 14). Some studies reported that up to 90% of pwMS had symptoms of fatigue, whereby they defined fatigue as tiredness, low energy, or exhaustion, and that these symptoms might be triggered by activities or increased temperature (11, 12, 14). Factors contributing to fatigue may include the individual presentation of the disease, some treatment side effects, functional status impairment, weakness, pain, and nocturia (21). Moreover, a study by Ayache and Chalah reviewed various causes of fatigue in pwMS which included anemia, vitamin-deficiencies, endocrine disorders, sleep disorders, psychiatric comorbidities, psychological burden, and medication side effects (22). However, there were no clear causes of fatigue in pwMS have been found and the related-literature is inconclusive.

The impact of fatigue, depression and anxiety symptoms on patients QoL should not be ignored. Several studies have investigated the relationship between QoL and depression, anxiety, stress, and fatigue (23–25). The majority of these studies indicated that these factors were significantly correlated with the QoL (23–26). A recent study in KSA found that the majority of Saudi pwMS reported that overthinking about social life problems, mood swings, and sleep disturbance had an impact specifically on disease relapse and its severity (27). Furthermore, the emotional burden, mood swings, and difficulty in making decisions can also have an impact on the disease course, particularly in terms of relapse or its severity as well as in the QoL and psychological wellbeing (27).

Therefore, focusing on improving and alleviating these adverse MS-related symptoms is crucial. However, the prevalence of depression, anxiety, and fatigue in pwMS is not thoroughly studied in Saudi Arabia. Thus, the purpose of this study is to identify the prevalence of depression, anxiety, and fatigue among ambulating pwMS in Saudi Arabia. Furthermore, this study intends to examine the correlations between QoL, physical activity and these symptoms.

Abbreviations: ARFA MS, Saudi MS Association that is approved from Saudi Ministry of Human Resources and social development; EQ-5D-3L, EuroQOL five-dimension questionnaire; EQ-VAS, EQ Visual Analogue Scale; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; IPAQ, International Physical Activity Questionnaire; IQR, Interquartile range; KFMC, King Fahd Medical City; KSA, Kingdom of Saudi Arabia; KSUMC, King Saud University Medical City; MS, Multiple Sclerosis; NMSR, National MS Registry; PwMS, Patient with multiple sclerosis; QoL, Quality of life; SD, Standard Deviation; SPSS, Statistical Package for Social Sciences; VAS, Visual analogue scale.

METHODS

Study Design and Settings

This is a cross-sectional study, conducted in the Neuroimmunology outpatient clinics in King Fahad Medical City (KFMC) and King Saud University Medical City (KSUMC) in Riyadh, KSA. Patients were also recruited from a database provided by the ARFA MS association. ARFA association is a non-profit organization helping pwMS approved by the Saudi Ministry of Human Resources and Social Development. The ARFA MS association accepts MS patients with medical report to confirm the diagnosis.

Study Participants

The study population consisted of patients diagnosed with MS based on the McDonald Criteria (2017) by a neurologist attending KFMC or KSUMC neurology clinics. All patients were aged 18 years and above, with at least a 1-year history of MS with no walking difficulty based on the EQ-5D-3L questionnaire, had no history of relapse in the previous eight weeks, were deemed eligible to participate in this study. Those patients with difficulty in walking and/or those who had a relapse within the previous 8 weeks were excluded from this study since they will probably report high fatigue levels to avoid bais. As well as patients who are illiterate or non-arabic speakers were excluded.

Estimated Sample Size

A total number of 2,313 patients have enrolled in the National MS Registry (NMSR), which is approximately 38% of the estimated number of patients with MS in KSA. More than a half of the patients (80%) have no or minimal disability (3). Hence the expected population of 1700 patients fits the inclusion criteria. While presuming 10% of the expected population are post exclusion of illiterate (N=1530), and assuming the response rate is around 30% based on the clinical experience and as discussed with the research ethics committee; the estimated sample size is N=323, as derived with the help of Cochran's formula outlined below.

Data Collection Methods

The data was collected using a self-reported questionnaire, which was available in the Arabic language. The questionnaire contains five sections. The first section the demographic data (age, gender, marital status, education, area of residence, and current work status) and clinical details (number of years since diagnosis and date of last MS relapse) The remaining sections measure the outcomes of this study. These outcome measures are aim to ascertain many life domains such as physical activity, depression, anxiety, fatigue, disability, and QoL. These outcomes are provided in more detail below.

Hospital Anxiety and Depression Scale (HADS) (28) includes 14 items assessing anxiety (7–item) and depression (7–item), which are rated from 0 to 3. The scores in each subscale are computed by summing the corresponding items, with maximum scores of 21 for each subscale. A score of 0–7 is considered normal, 8–10 as a borderline case, and 11–21 as a case (of anxiety or depression) (28). The Arabic version of HADS is a reliable and valid tool to use with pwMS. A systematic translation process was used to translate the original English HADS into Arabic and validated after a pilot study; reliability was tested by using internal consistency examination (29).

Physical activity was measured by the short version of the International Physical Activity Questionnaire (IPAQ) (30). Which consists of 7 questions that measure the intensity of walking, moderate-intensity activities, and vigorous-intensity through the previous week and the usual occurrence. Computation of the total score for the short form requires the summation of the duration (in minutes) and frequency (days) of walking, moderate-intensity, and vigorous-intensity activities. MET level x minutes of activity x events per week for each of walking, moderate- and vigorous-intensity activities were calculated as follows: walking = (3.3 × walking minutes × number of walking days); moderate activity = (4.0 × moderate activity minutes × moderate activity days); vigorous activity = (8.0 × vigorous activity minutes × vigorous activity days). There are three categories of physical activity used to classify participants (low, moderate, and high) according to the scoring system provided by IPAQ (www.ipaq.ki.se) (31). The Arabic short self-report IPAQ form was validated and the reliability confirmed. It was translated and adapted to the Arabic language and then subjected to back-translation (31).

The EuroQOL five-dimension questionnaire EQ-5D-3L is widely-used globally and has been translated into approximately 150 of languages (32). It is a short patient-reported outcome measure that consists of two sections. The first section measures five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three response levels per dimension – 'no problems', 'some problems', or 'extreme problems'. pwMS in our cohort were asked to provide information regarding their health status by checking the box that indicated the most appropriate statement in every item of each dimension. The result of each dimension is given a 1-score number that exhibits the selected level for that dimension. The scores of all dimensions are then combined and form a 5-scores number that describes the patient's health state. The second section is a visual analogue scale (VAS) rated from 0 (worst health imaginable) to 100 (best health imaginable), which gave an overall impression of the patients' current wellbeing (32). We used previously validated Arabic version of EQ-5D-3L for evaluating health-related QoL in KSA (33).

Fatigue is measured by the Fatigue Severity Scale (FSS), which was found to be sensitive, reliable, and consistent in pwMS with a good response rate of 0 (34). It is a subjective measure of fatigue that is based on the self-reported assessment by pwMS (22). The FSS consists of nine statements describing the severity and impact of fatigue, with possible responses ranging from 1 (strongly disagree) to 7 (strongly agree). Total FSS scores are usually reported as the mean score of the nine items, with higher scores indicating increased severity (34). A cut-off point of ≥ 5 points was considered as the presence of fatigue. The Arabic version of the FSS demonstrated acceptable test-retest reliability, internal consistency, and psychometric properties and was able

to differentiate between pwMS and has been shown capable of differentiating between healthy subjects (35).

The questionnaire of the current study was available online *via* a Google Forms link which was distributed to the patients, the respondents were asked to self-report the questionnaire within 24 hours of receiving the link. The questionnaire link was distributed to the participants through social media platforms such as WhatsApp, Twitter, and Emails.

Statistical Analysis

Demographic and clinical characteristics of the study participants are reported as mean (standard deviation; SD) or median (Interquartile range; IQR) for continuous variables as appropriate. Additionally, categorical variables were reported as counts and percentages or in bar charts as appropriate. Chi-square tests of association were performed to examine the association between two categorical variables. Additionally, the normality of data distribution was examined by the Kolmogorov-Smirnov test. Differences in mean or median scores of each scale were examined using non-parametric tests because the distribution of outcome variables was not normally distributed. Specifically, the Mann-Whitney test was used to assess the differences in outcomes between two independent samples, and the Kruskal Wallis test was used to test for differences in the mean scores of each scale because in involves more than two independent samples. For Kruskal Wallis test with the statistically significant results, the Dunn procedure was used, which accounts for type I error and thus reduces the likelihood of false positive-results (36). The correlation between the continuous scores were assessed by calculating Spearman's correlation coefficient. All statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA) package; two-tailed test and a p-value of less than 0.05 was considered significant.

Ethical considerations

An electronic informed consent was obtained before filling out the questionnaires. All data has been kept confidential and has only been analyzed after the subjects' approval without any personal identifiers.

RESULTS

More than 2000 patients received the questionnaire and 616 patients were answered it. Only 323 pwMS of these met the study inclusion criteria. The majority of participants were females (n=277, 70.3%), Saudis (n=293, 90.3%), and resided in the central region of KSA (n=213, 65.9%). One hundred and forty-five patients (44.9%) belonged to the 18-29 years age group. More than one-half of the respondents were married (n=171, 52.9%) and had university education (n=193, 59.3%). Approximately one-half of the participants were currently employed (n=159, 49.2%). The average length of time senice diagnosis was 5.5 (SD ± 4.7) years, while the average number of years since the last MS relapse was 2.46 (SD ± 2.3) (**Table 1**).

TABLE 1 | Descriptive statistics of the study sample.

	N	%
Age Groups		
18 -29	145	44.9
30 -39	132	40.9
40 – 49	40	12.4
≥50	6	1.9
Gender		
Male	96	29.7
Female	227	70.3
Marital status		
Married	171	52.9
Single	152	47.1
Region		
Central	213	65.9
Eastern	34	10.5
Western	54	16.7
Northern	18	5.6
Southern	4	1.2
Nationality		
Saudi	293	90.3
Non-Saudi	30	9.7
Education		
Secondary or lower	53	16.4
Diploma	35	10.8
University	193	59.8
Postgraduate	42	13.0
Work Status		
Employed	159	49.2
Unemployed	63	19.5
Student	47	14.6
Homemaker	54	16.7
	Mean	**SD**
No. of years after diagnosis	5.5	4.7
Last MS relapse	2.46	2.3

Depression and Anxiety Prevalence

Figure 1 shows the prevalence of anxiety and depression among our cohort as measured by the HADS outcome. The majority of participants had normal depression and anxiety levels. However, more patients had anxiety than depression (25.7% vs. 13.6% respectively).

In this study, the participants exhibited a mean score of depression of 5.63 (SD=4.2) and a mean score for anxiety of 7.34 (SD=4.9), as indicated in **Table 2**. Statistical differences in the mean scores of depression and anxiety by patients' characteristics are also shown in **Table 2**. The mean scores of depression and anxiety did not differ significantly with gender, marital status, nationality, educational level, or work status (P_value >0.05). However, they were statistically significant differences for anxiety by age groups (P_value = 0.011) but not for depression (P-value = 0.608). Specifically, patients aged 18 – 29 years or 50 years and above had a higher mean score of anxiety than those aged 30 – 39 years (P_value = 0.005 and 0.043 respectively). Also, statistically significant differences in mean scores of depression and anxiety were evident among pwMS by region of residence (P_value < 0.05). Patients who lived in the central and western regions had significantly higher depression and anxiety scores than those who lived in the eastern region (P_value < 0.05). The duration in time snice diagnosis of MS and

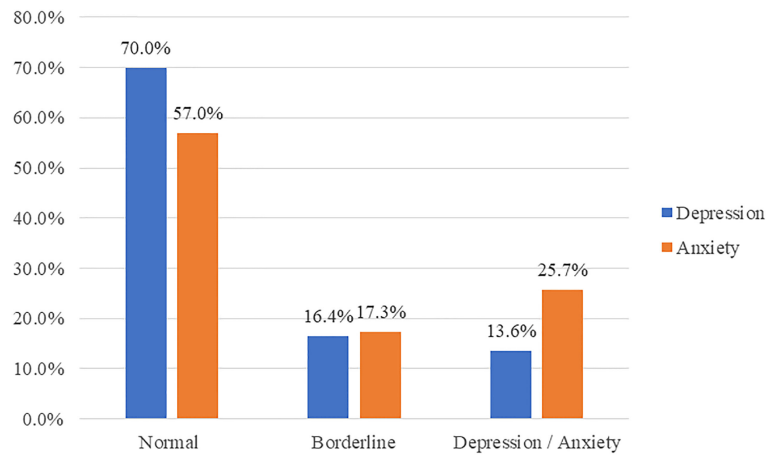

FIGURE 1 | Prevalence of anxiety and depression using HADS.

TABLE 2 | Depression and anxiety total mean scores and by demographic characteristics.

	Depression	*P*_value	Anxiety	*P*-value
Total score	5.63 ± 4.2		7.34 ± 4.9	
Gender				
Male	5.59 ± 4.2	0.988	7.31 ± 4.8	0.925
Female	5.64 ± 4.3		7.42 ± 4.9	
Age Groups				
18 – 29	5.83 ± 4.5	0.608	8.09 ± 4.8	0.011[a]
30 – 39	5.38 ± 3.9		6.57 ± 4.6	
40 – 49	5.45 ± 4.4		7.05 ± 5.6	
≥50	7.50 ± 4.8		10.83 ± 5.0	
Marital Status				
Married	5.66 ± 4.3	0.968	7.67 ± 5.0	0.379
Single	5.59 ± 4.2		7.08 ± 4.8	
Region				
Central	5.93 ± 4.4	0.036[b]	7.44 ± 4.9	0.032[c]
Eastern	3.85 ± 3.6		5.44 ± 4.9	
Western	6.07 ± 4.5		8.5 ± 4.9	
Northern	4.44 ± 2.7		7.22 ± 4.1	
Southern	3.75 ± 2.5		7.25 ± 7.5	
Nationality				
Saudi	5.52 ± 4.2	0.302	7.24 ± 4.9	0.069
Non-Saudi	6.60 ± 4.9		8.87 ± 4.9	
Education				
Secondary or lower	6.81 ± 4.5	0.052	7.49 ± 5.2	0.846
Diploma	4.48 ± 3.2		7.49 ± 4.1	
University	5.39 ± 4.3		7.25 ± 4.9	
Postgraduate	6.17 ± 4.3		7.81 ± 5.1	
Work status		0.072		0.069
Employed	5.28 ± 4.0		7.08 ± 4.8	
Unemployed	5.21 ± 4.0		6.71 ± 5.1	
Student	5.29 ± 4.5		8.00 ± 5.2	
Housewife	5.38 ± 4.4		7.29 ± 4.7	
No. of years since diagnosis	- 0.071[d]	0.206	- 0.112[d]	0.045
Last MS relapse	- 0.058[d]	0.342	- 0.166[d]	0.007

a: P = 0.005 for 18 – 29 versus 30 – 39; 0.113 for 18 -29 versus 40 – 49; 0.140 for 18 – 29 versus ≥ 50; 0.872 for 30 – 39 versus 40 – 49; 0.043 for 30 – 39 versus ≥ 50; 0.160 for 40 – 49 versus ≥ 50.

b: P = 0.004 for central versus eastern; 0.850 for central versus western; 0.273 for central versus northern; 0.341 for central versus southern; 0.010 for eastern versus western; 0.247 for eastern versus northern; 0.801 for eastern versus southern; 0.286 for western versus northern; 0.363 for western versus southern; 0.594 for northern versus southern.

c: P = 0.009 for central versus eastern; 0.155 for central versus west; 0.962 for central versus northern; 0.678 for central versus southern; 0.001 for eastern versus western; 0.073 for eastern versus northern; 0.697 for eastern versus southern; 0.382 for western versus northern; 0.504 for western versus southern; 0.652 for northern versus southern.

d: Correlation coefficient.

the number of years since the last MS relapse were significantly and negatively correlated with anxiety but not with depression.

EQ-5D-3L

According to EQ-5D-3L, a Full Health State was reported in eighty-one participants (25.1%) (i.e., 11111), while no participants exhibited the worst health state (i.e., 33333). No respondents had issues with mobility (n = 323, 100%). the vast majority of the participants had no problems in self-care (n = 313, 96.9%), or usual activities (n = 241, 74.6%). On the other hand, more than one-half had reported having pain or discomfort (n = 171, 52.9%). While half of the patients (n = 163) had no reported problems with anxiety or depression (**Table 3**). Regarding the patients' self-assessment of their health, the mean EuroQol Group visual analogue scale (EQ-VAS) score was 80.43 (SD = 19.8). **Figure 2** shows the frequency distribution of EQ-5D-3L VAS, which indicated that most participants reported a healthy state. About 27.2% (n = 88) of patients had a full score of health status, while only two patients (0.6%) exhibited the worst health status.

Furthermore, the this study the results as shown in **Table 3** indicate that most patients exhibited no problems in mobility, self-care, and usual activities. However, most patients had some problems in pain or discomfort levels. A total of fifty-six men (58.3%) and 107 women (47.1%) had no problems in depression or anxiety. Meanwhile, more than one-half of patients aged 18 – 29 and 50 years and above had problems with depression or anxiety. More than half of married patients, unlike single patients, had problems with anxiety and depression. Most respondents from central (n = 108, 50.7%), eastern (n = 26, 76.5%), and southern (n = 2, 50%) regions had no problems with depression or anxiety while most respondents from western (n = 26, 53.7%) and northern (n = 11, 61.1%) regions had some problems with anxiety or depression.

Fatigue Prevalence

The results indicate that 156 (48.3%) out of 323 pwMS reported fatigue as measured by FSS. This study also stratifies fatigue prevalence by patients' groups as indicated in **Table 4**. Of those patients with fatigue, the majority were women (n = 117, 75.0%), aged 18 – 29 years (n = 69, 44.2%), married (n = 81, 51.9%), Saudis (n = 138, 88.5%), from the central region (n = 106, 67.9%), university educated (n = 89, 57.1%), employed (n = 71, 45.5%), with depression (n = 31, 19.9%), and anxiety (n = 56, 35.9%). The results also indicate that there were no statistically significant associations between FSS and all patients' characteristics except for depression and anxiety (**Table 4**). Furthermore, disease duration in years was not significantly associated with FSS scores (r = - 0.044, p-value > 0.05) (**Table 6**).

Physical Activity Using IPAQ

The descriptive statistics for the five measures of physical activity for the patients with MS are shown in **Table 5**. The results indicate that 143 patients (44.3%) had vigorous physical activities during the previous seven days with median days per week of 3 (IQR = 5 – 3) and median minutes per day of 60 (IQR = 60 – 30). Also, the result found that 159 patients (49.2%) had undertaken moderate physical activities during the previous week with median days per week of 3 (IQR = 5 – 3) and median daily minutes of 40 (IQR = 60 – 30). More than half of participants; 194 patients had undertaken walking activities (60.0%) with median days per week of 5 (IQR = 7 – 3) and median minutes per day of 45 (IQR = 60 – 30). The majority of respondents had answered do not know or not sure about how many minutes they had spent sitting on weekdays (n = 145, 70.7%). However, for those that responded the median minutes per day of sitting on a weekday was reported as 180 (IQR = 360 – 180).

The scores of IPAQ were also calculated to measure the prevalence of the three categories of physical activities as well as the total physical activities for patients. The median vigorous MET-minutes/week score was 960 (IQR = 480 – 2880), median moderate MET-minutes/week was 600 (IQR = 1200 – 240), and median walking MET-minutes/week was 594 (IQR = 1039 – 239). The median total physical activity MET-minutes/week score was 2838 (4802 – 1364). Physical activities from IPAQ were also categorized into high (i.e., total physical activity of at least 1500 MET-minutes/week), moderate (i.e., total physical activity of at least 600 MET-minutes/week), and low (i.e., patients who did not meet high and moderate levels) as indicated in **Figure 3**. It seems that the majority of the participants who performed any level of physical activities were engaged in a high level of physical activity (n = 94, 72.2%). While, 33 patients exhibited a moderate level of physical activity (24.8%), and a very small number of patients had indicated a low level of physical activity (n = 4, 3.0%). There were no statistically significant differences in median total physical activity MET-minutes/week by patients' characteristics (p-value > 0.05). However, time since disease diagnosis was positively and significantly correlated with total physical activity MET-minutes/week (r = 0.203, p-value = 0.019) as shown in **Table 6**.

Correlations Between Depression, Anxiety, EQ-VAS, FSS, and IPAQ

The correlation between the measures used in this study are shown in **Table 6**. The results reveal that FSS and depression were positively and significantly correlated (r = 0.407, *P*-value < 0.001), which indicates that a higher FSS level is associated with a higher level of depression. Similarly, a positive and significant correlation between the FSS and anxiety levels was detected (r = 0.289, *P*-value < 0.001), which suggests that higher FSS scores are associated with higher scores of anxiety. Furthermore, the correlation between depression and anxiety was significant and positive indicating that a higher score of depression is associated with a higher score of anxiety (r = 0.655, *P*-value < 0.001). However, the total IPAQ score was not significantly correlated with depression (r = - 0.087, *P*-value = 0.319), anxiety (r = - 0.069, *P*-value = 0.433), or fatigue (r = - 0.123, *P*-value = 0.158). Moreover, a negative and significant correlation was found between EQ-VAS and depression (r = -0.479, *P*-value < 0.001), anxiety (r = - 0.497, *P*-value < 0.001), and FSS (r = - 0.336, *P*-value < 0.001) but was not significantly associated with IPAQ (r = 0.064, *P*-value = 0.467) and time since disease diagnosis (r = 0.063, *P*-value = 261).

TABLE 3 | Frequency Distribution of EQ-5D 3L of the Total Sample and by patients' Characteristics; N (%).

	Mobility Levels			Self-care Levels			Usual activities Levels			Pain Levels			Depression/Anxiety Levels		
	no problems	some problems	extreme problems	no problems	some problems	extreme problems	no problems	some problems	extreme problems	no problems	some problems	extreme problems	no problems	some problems	extreme problems
Total sample	323 (100)	0 (0.0)	0 (0.0)	313 (96.9)	8 (2.5)	2 (0.6)	241 (74.6)	77 (23.8)	5 (1.5)	132 (40.9)	171 (52.9)	20 (6.2)	163 (50.5)	140 (43.3)	20 (6.2)
Gender															
Male	96 (100)	0 (0.0)	0 (0.0)	89 (92.7)	5 (5.2)	2 (2.1)	76 (79.2)	17 (17.7)	3 (3.1)	39 (40.6)	50 (52.1)	7 (7.3)	56 (58.3)	34 (35.4)	6 (6.3)
Female	257 (100)	0 (0.0)	0 (0.0)	224 (98.7)	3 (1.3)	0 (0.0)	165 (72.7)	60 (26.4)	2 (0.9)	93 (41.0)	121 (53.3)	13 (5.7)	107 (47.1)	106 (46.7)	14 (6.2)
Age Groups															
18 – 29	145 (100)	0 (0.0)	0 (0.0)	142 (97.9)	1 (0.7)	2 (1.4)	107 (73.8)	36 (24.8)	2 (1.4)	55 (37.9)	82 (56.6)	8 (5.5)	62 (42.8)	72 (49.7)	11 (7.6)
30 – 39	132 (100)	0 (0.0)	0 (0.0)	128 (97.0)	4 (3.0)	0 (0.0)	107 (81.1)	24 (18.2)	1 (0.8)	60 (45.5)	65 (49.2)	7 (5.3)	77 (58.3)	49 (37.1)	6 (4.5)
40 – 49	40 (100)	0 (0.0)	0 (0.0)	38 (95.0)	2 (5.0)	0 (0.0)	26 (65.0)	14 (35.0)	0 (0.0)	15 (37.5)	22 (55.0)	3 (7.5)	22 (55.0)	16 (40.0)	2 (5.0)
50	6 (100)	0 (0.0)	0 (0.0)	5 (83.3)	1 (16.7)	0 (0.0)	1 (16.7)	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)	1 (16.7)
Marital status															
Married	171 (100)	0 (0.0)	0 (0.0)	166 (97.1)	3 (1.8)	2 (1.2)	129 (75.4)	39 (22.8)	3 (1.8)	70 (40.9)	90 (52.6)	11 (6.4)	79 (46.2)	77 (45.0)	15 (8.8)
Single	152 (100)	0 (0.0)	0 (0.0)	147 (96.7)	5 (3.3)	0 (0.0)	112 (73.7)	38 (25.0)	2 (1.3)	62 (40.8)	81 (53.3)	9 (5.9)	84 (55.3)	63 (41.4)	5 (3.3)
Region															
Central	213 (100)	0 (0.0)	0 (0.0)	208 (97.7)	3 (1.4)	2 (0.9)	156 (73.2)	54 (25.4)	3 (1.4)	100 (46.9)	107 (50.2)	6 (2.8)	108 (50.7)	92 (43.2)	13 (6.1)
Eastern	34 (100)	0 (0.0)	0 (0.0)	33 (97.1)	1 (2.9)	0 (0.0)	27 (79.4)	7 (20.6)	0 (0.0)	12 (35.3)	20 (58.8)	2 (5.9)	26 (76.5)	7 (20.6)	1 (2.9)
Western	54 (100)	0 (0.0)	0 (0.0)	51 (94.4)	3 (5.6)	0 (0.0)	40 (74.1)	12 (15.6)	2 (3.7)	16 (29.6)	28 (51.9)	10 (18.5)	20 (37.0)	29 (53.7)	5 (9.3)
Northern	18 (100)	0 (0.0)	0 (0.0)	17 (94.4)	1 (5.6)	0 (0.0)	15 (83.3)	3 (16.7)	0 (0.0)	3 (16.7)	14 (77.8)	1 (25.0)	7 (38.9)	11 (61.1)	0 (0.0)
Southern	4 (100)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)
Nationality															
Saudi	293 (100)	0 (0.0)	0 (0.0)	286 (97.6)	5 (1.7)	2 (0.7)	214 (73.0)	75 (25.6)	4 (1.4)	121 (41.3)	155 (52.9)	17 (5.8)	155 (52.9)	119 (40.6)	19 (6.5)
Non-Saudi	30 (100)	0 (0.0)	0 (0.0)	27 (90.0)	3 (10.0)	0 (0.0)	27 (90.0)	2 (6.7)	1 (3.3)	11 (36.7)	16 (53.3)	3 (10.0)	8 (26.7)	21 (70.0)	1 (3.3)
Education															
Secondary or lower	53 (100)	0 (0.0)	0 (0.0)	52 (98.1)	1 (2.9)	0 (0.0)	40 (75.5)	13 (24.5)	0 (0.0)	22 (41.5)	28 (52.8)	3 (5.7)	23 (43.4)	25 (47.2)	5 (9.4)
Diploma	35 (100)	0 (0.0)	0 (0.0)	33 (94.3)	2 (5.7)	0 (0.0)	20 (57.1)	14 (40.0)	1 (2.9)	13 (37.1)	18 (51.4)	4 (11.4)	21 (60.0)	13 (37.1)	1 (2.9)
University	193 (100)	0 (0.0)	0 (0.0)	189 (98.0)	2 (1.0)	2 (1.0)	151 (78.2)	38 (19.7)	4 (2.1)	79 (40.9)	104 (53.9)	10 (5.2)	102 (52.8)	81 (42.0)	10 (5.2)
Postgraduate	42 (100)	0 (0.0)	0 (0.0)	39 (92.9)	3 (7.1)	0 (0.0)	30 (71.4)	12 (28.6)	0 (0.0)	18 (42.9)	21 (50.0)	3 (7.1)	17 (40.5)	21 (50.0)	4 (9.5)
Work Status															
Employed	159 (100)	0 (0.0)	0 (0.0)	154 (96.9)	5 (3.1)	0 (0.0)	126 (79.2)	32 (20.1)	1 (0.6)	69 (43.4)	81 (50.9)	9 (5.7)	88 (55.3)	64 (40.3)	7 (4.4)
Unemployed	63 (100)	0 (0.0)	0 (0.0)	62 (98.4)	1 (1.6)	0 (0.0)	51 (81.0)	12 (19.0)	0 (0.0)	29 (46.0)	31 (49.2)	3 (4.8)	35 (55.6)	24 (38.1)	4 (6.3)
Student	47 (100)	0 (0.0)	0 (0.0)	46 (97.9)	1 (2.1)	0 (0.0)	33 (70.2)	14 (29.8)	0 (0.0)	18 (38.3)	26 (55.3)	3 (6.4)	17 (36.2)	29 (61.7)	1 (2.1)
Homemaker	54 (100)	0 (0.0)	0 (0.0)	51 (94.4)	1 (1.9)	2 (3.7)	31 (57.4)	19 (35.2)	4 (7.4)	16 (29.6)	33 (61.1)	5 (9.3)	23 (42.6)	23 (42.6)	8 (14.8)

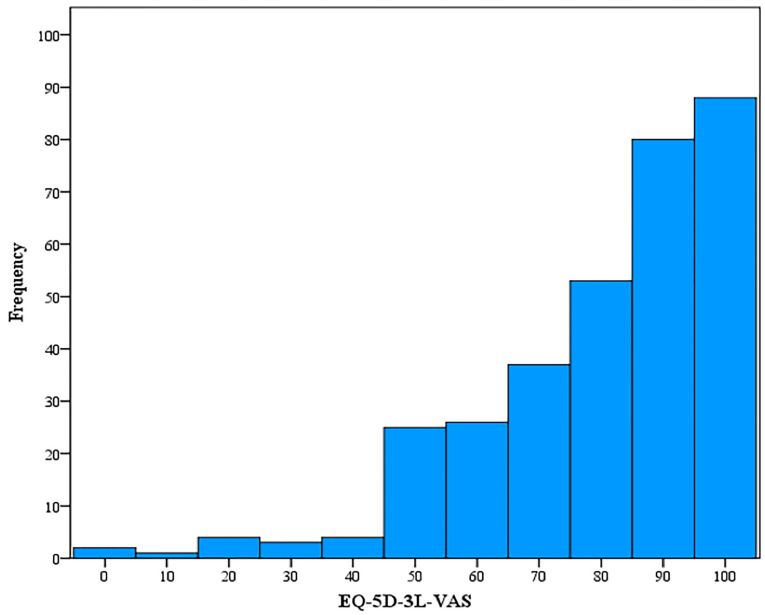

FIGURE 2 | EQ-5D-3L VAS Frequency Distribution.

DISCUSSION

This study shows that patients in our cohort report anxiety or depression as measured by the HADS instrument. Moreover, the average score of depression falls within the normal category. However, the average score of anxiety falls within the symptoms of a borderline case. This suggests that patients in our cohort were more likely to be anxious rather than depressed. The findings of this study are in accordance with previously published research (10, 13, 15, 16, 37) but are contradicted by some others (7, 11, 12, 14). In agreement with this study's findings, for instance, a study conducted in the neighboring United Arab Emirates reported that depression and anxiety were present among 17% and 20% of patients with MS respectively (10). Nevertheless, a systematic review and meta-analysis found that the prevalence of depression was 30.5% among pwMS while the prevalence of anxiety was 22.1% among them, which is not congruent with the current study findings (7).

The results of this study also indicate that depression and anxiety scores did not correlate with gender, marital status, nationality, education, or work status. However, pwMS from central and western regions exhibited higher mean scores of depression and anxiety than those from the eastern region, which might be attributed to the highly urban and increased industrialized lifestyle in the eastern region compared to the western and central region. Patients in the youngest and oldest age groups in our study exhibited higher average anxiety scores than those aged 30 – 39 years but they reported similar depression levels. Furthermore, disease duration was negatively associated with anxiety but not with depression. Łabuz-Roszak et al. found that in pwMS, depression correlated significantly with age, professional status, and educational levels, while anxiety was significantly associated with age and professional status. Nonetheless, they showed that both depression and anxiety were not significantly associated with gender or disease duration (16). However, others have shown that anxiety was more common among women and in those with a history of depression but it did not appear to be associated with age, education, work status, marital status, disease duration, or living status (15). On the other hand, Alsaadi et al. showed that depression and anxiety were not significantly associated with age, gender, education, disease duration, expanded disability status Stage (EDSS), or marital status (10). In two previous studies from Norway, anxiety and depression were more common in pwMS than controls, however, similar to our study, they did not correlate with gender or disease duration (12, 14). A longitudinal study in Southern Tasmania indicated that females were more anxious and depressed than males at cohort entry but this effect was not statistically significant (11). Therefore, the findings of previous studies were not conclusive that could be due to the different study variables; including measurement tool and patient population.

In this study, the QoL was also assessed by the EQ-5D-3L instrument. Most participants exhibited a healthy state as measured by EQ-5D-3L VAS with a mean score of 80.43 (SD = 19.8), which is higher than that reported by Algahtani et al., who estimated it as 73.87 (SD = 23.41) among pwMS in King Abul-Aziz Medical City in Saudi Arabia (38). The findings of this study indicate that decreasing MS relapses is associated with better health outcomes, which is congruent with various

TABLE 4 | Fatigue in multiple sclerosis patients of the total sample and by demographic characteristics, depression, and anxiety.

	Fatigue	No fatigue	*P*-value
Total sample	156 (48.3)	167 (51.7)	
Gender			
Male	39 (25.0)	57 (34.1)	0.073
Female	117 (75.0)	110 (65.9)	
Age Groups			
18 – 29	69 (44.2)	76 (45.5)	0.786
30 – 39	65 (41.7)	67 (40.1)	
40 – 49	18 (11.5)	22 (13.2)	
≥50	4 (2.6)	2 (1.2)	
Marital Status			
Married	81 (51.9)	90 (53.9)	0.724
Single	75 (48.1)	77 (46.1)	
Region			
Central	106 (67.9)	107 (64.1)	0.695
Eastern	9 (5.8)	25 (15.0)	
Western	28 (17.9)	26 (15.6)	
Northern	11 (7.1)	7 (4.2)	
Southern	2 (1.3)	2 (1.2)	
Nationality			
Saudi	138 (88.5)	155 (92.8)	0.179
Non-Saudi	18 (11.5)	12 (7.2)	
Education			
Secondary or lower	26 (16.7)	27 (16.2)	0.637
Diploma	17 (10.9)	18 (10.8)	
University	89 (57.1)	104 (62.3)	
Postgraduate	24 (48.3)	18 (51.7)	
Work Status			
Employed	71 (45.5)	88 (52.7)	0.485
Unemployed	30 (19.2)	33 (19.8)	
Student	25 (16.0)	22 (13.2)	
Homemaker	30 (19.2)	24 (14.4)	
Depression (HADS)			
Normal	89 (57.1)	137 (82.0)	< 0.001
Borderline	36 (23.1)	17 (10.2)	
Depression	31 (19.9)	13 (7.8)	
Anxiety (HADS)			
Normal	73 (46.8)	111 (66.5)	< 0.001
Borderline	27 (17.3)	29 (17.4)	
Anxiety	56 (35.9)	27 (16.2)	

previous research (15, 23, 39, 40). Gupta et al. indicated that the higher rates of MS severity were associated with the worst health outcomes (40).

The present study also shows that the prevalence of fatigue was 48.3% of pwMS, whereby it was more present in women, younger patients, married, Saudis, those living in the central region, university educated, and in patients with normal depression and anxiety. However, fatigue was not significantly associated with age, gender, marital status, nationality, region, education, work status, and disease duration but was significantly associated with anxiety and depression measured by HADS and QoL measured by EQ-VAS. The findings are, to some extent, consistent with other research (6, 12, 14, 16, 17, 23, 41). We find an almost similar prevalence of fatigue to that reported in other studies. For instance, Rzepka et al. detected fatigue in 42% of patients with MS (17). Runia et al. reported the presence of fatigue in 46.5% of patients with MS (41). However, in other research, the prevalence of fatigue is higher, ranged, on average, between 50 – 80% because in patients our cohort was mildly affected and mobile (6, 16, 42). In Poland, for instance, fatigue was prevalent in 61.5% of pwMS and was not significantly associated with age, gender, disease duration, and course, EDSS, education but it was significantly correlated with depression, anxiety, sleep disorder, and professional status (16). Lerdal et al. showed that fatigue was prevalent among 61.1% of pwMS and was negatively correlated with their education but positively correlated with age and disease duration, which contradicted our results (42). A recent study by Rzepka et al. did not find any significant differences in FSS by gender, age, marital status, place of residence, which is consistent with our findings. However, it did find significant differences in FSS by education, EDSS, disease duration, professional status, IPAQ, which contradicted our results (17). Fidao et al. showed that the fatigue prevalence ratio was higher among pwMS with high depression risk, severe disability, obesity, smokers, and unemployed but was lower among pwMS with university education and higher IPAQ (18).

Moreover, the present study also indicates that 96 out of 133 (72.2%) pwMS in Saudi Arabia were engaged with a high level of physical activity. The total IPAQ score was positively and

TABLE 5 | Descriptive statistics of physical activity measured by IPAQ.

	N (%)	Median (IQR)
Vigorous physical Activities		
Days per week	143 (44.3)	3 (5-3)
Minutes per day	142 (99.3)	60 (60 – 30)
None	0 (0)	
Don't know/Not sure	1 (0.7)	
Moderate physical Activities		
Days per week	159 (49.2)	3 (5 – 3)
None	164 (50.8)	
minutes per day	159 (100.0)	40 (60 – 30)
Don't know/Not sure	0 (0)	
Walk		
Days per week	194 (60.0)	5 (7 – 3)
None	129 (40.0)	
minutes per week	191 (98.5)	45 (60 – 30)
Don't know/Not sure	3 (2.5)	
Sitting on a weekday	205 (63.5)	
Minutes per day	60 (29.3)	180 (360 – 120)
Don't know/Not sure	145 (70.7)	
Vigorous MET-minutes/week	–	960 (480 – 2880)
Moderate MET-minutes/week	–	600 (1200 – 240)
Walking MET-minutes/week	–	594 (1039 – 239)
Total physical activity MET-minutes/week	133 (41.2)	2838 (4802 – 1364)

Time in hours is converted to minutes.

TABLE 6 | Correlations Between Depression, Anxiety, EQ-VAS, FSS, and IPAQ.

	Depression	Anxiety	FSS	IPAQ	EQ-VAS
Disease duration (in years)	-0.071	-0.112*	-0.044	0.203*	0.063
Depression		0.655*	0.407*	- 0.087	- 0.479*
Anxiety			0.289*	- 0.069	- 0.497*
FSS				- 0.123	- 0.336*
IPAQ					0.064

**Significant at 5% level of significance.*

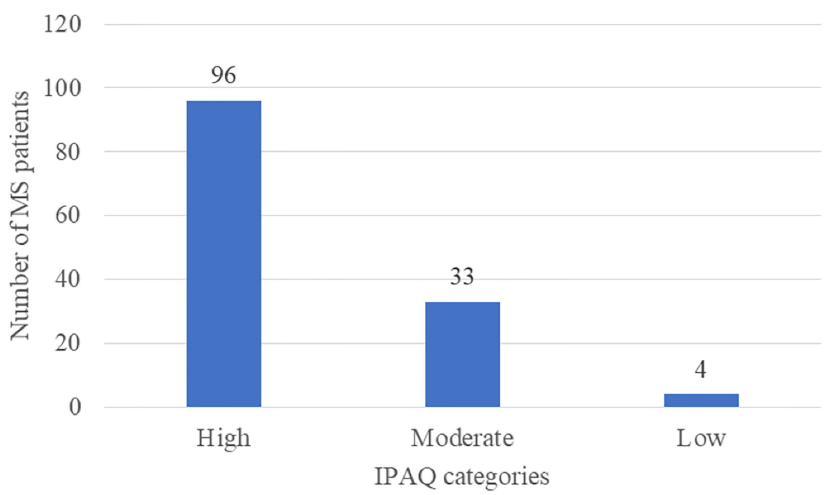

FIGURE 3 | Levels of Physical Activities among pwMS.

significantly correlated with disease duration, but it was not significantly associated with depression, anxiety, FSS, and EQ-VAS, as well as did not significantly differ by age, gender, marital status, nationality, region, education, and work status. This could be due to the low number of respondents on the IPAQ, where only 133 out of 323 patients had answered that part of the questionnaire. A study in Poland indicated that the prevalence of high physical activity among pwMS was 45%, which is lower than our findings. Moreover, a significant correlation between IPAQ and FSS scores was detected, which contradicted our results (17). A study by Fidao et al. showed that the prevalence ratio fatigue among pwMS was significantly lower for patients engaged with high physical activity in comparison to those inactive and minimally active patients, which is not consistent with our findings (18). Marck et al. exhibited that the increased levels of physical activity measured by IPAQ have significantly improved the QoL (43). A recent study by Reguera-García et al. reported that 33.3% and 34.3% of pwMS have vigorous and moderate levels of physical activity during COVID-19 outbreak, respectively measured by IPAQ-short form (44).

The correlations between depression, anxiety, and fatigue were also assessed in our cohort of patients. The results of this study suggested moderate correlations between depression and anxiety as well as depression and fatigue but a weak correlation was found between anxiety and fatigue. Previous studies reported significant inter-correlation between depression, anxiety, and fatigue in terms of symptoms cluster approach (22, 45–51). For instance, a study by Motl and McAuley assessed the symptom cluster of fatigue, pain, and depression as a correlate of decreased QoL in the pwMS cohort. They showed that high QoL was associated with low levels of fatigue, pain, depression, and vice versa (45). Brown et al. conducted a longitudinal study in Australia and found that anxiety and fatigue were substantially predicted by depression, while later depression was considerably predicted by anxiety and fatigue. Other factors including combinations of unhealthy behaviors such as smoking, drug use, no exercise, or relaxation, and psychological factors such as low optimism, avoidance coping were significantly predicted psychological distress (i.e., depression and anxiety). Meanwhile, immunotherapy status was significantly associated with fatigue and state anxiety as well as fatigue was predicted by patients' demographics and life-event stressors (46). Chalah et al. reported that there is a bidirectional relationship between fatigue and neuropsychological factors (i.e., anxiety, depression, and alexithymia) (47).

It is important to note that the MS-related literature has tried to illustrate the associations between these adverse outcomes from different perspectives and mechanisms that underlie them (22). From a psychological perspective, anxiety, depression, and fatigue had a bidirectional relationship that might be explained by patients' cognitions, emotions, and behaviors (22, 46–48, 52). For instance, Schreiber et al. indicated that anxiety, depression, and somatic symptoms were considered as relevant mediators of fatigue (48). From a pathophysiological perspective, however, some studies pointed out that anxiety and depression in pwMS were associated with pathologies including the frontal lobes and/or their connections (22, 50, 53–59). The development of depressive symptoms was also attributed to temporal, parietal, and limbic abnormalities (56). As for anxiety, some studies showed that the development of anxiety symptoms was associated with damage in septo-fornical in this cohort (50). Concerning fatigue, previous research documented that it has been associated with neural substrates involving the cortico-thalamocortical loop as the basis for developing fatigue in pwMS. Such a loop revealed several cortical and subcortical areas, of which the frontoparietal regions and/or their connections are largely involved (22, 58, 59). On the other hand, from a therapeutic perspective, some studies indicated that anxiety, depression, and fatigue treatments and medications may not be feasible and suggested further treatment modalities that should be investigated (22, 60). Considering these mechanisms and the fact that some neural hubs are common for various symptoms, damage that occurred in these hubs would lead to a cluster of complaints and hence might explain the joint incidence of psychological distress and fatigue (22, 54). Therefore, further studies are needed to assess the underlying mechanisms of these symptoms.

The results reveal that about one-half of respondents were not engaged in physical activity. This could be resolved by educational programs for pwMS to improve their coping with the disease. Therefore, further research is needed to identify this problem. Furthermore, it would be useful to conduct longitudinal research with follow-up pwMS and better to include variables like coping strategies, resilience, sense of cohesion, and some more precise physical capacities rehabilitated by the disease. It is important to note that depression, anxiety, and fatigue will be probably higher if pwMS who have a motor disability were included.

The current study has some limitations. First, this study measures only self-reported assessments of fatigue, depression, anxiety, QoL, and physical activity among patients with MS, not actual psychiatric diagnoses. Nevertheless, the instruments exhibited robust psychometric characteristics that have been applied across a wide range of studies (14, 29, 33, 35, 61, 62). Furthermore, the current study assessed the cross-sectional prevalence of the pwMS cohort and lacks some important clinical variables including MS type, immunotherapy, disease-specific treatments or medications, and Expanded Disability Status Scale (EDSS) score as well as it did not control for potential confounders. Therefore, further studies should tackle these variables that might improve the results. Second, the questionnaire used does not specifically identify the type of physical activity which would inform decisions. Third, the current study was based on subjective assessment and self-reporting of fatigue and thus was not able to identify its clear causes whether it was simply due to MS complications such as sleep disorders, endocrine dysfunction, and mood disorders, or rather a primary MS fatigue (22). Finally, this study did not take into account the role of social support on coping strategies for MS patients, which might affect the quality of the results (21).

CONCLUSION

The current study shows that depression, anxiety, and fatigue, are frequent among pwMS in Saudi Arabia. Moreover, fatigue is associated positively with anxiety and depression, negatively with EQ-VAS, but not with physical activity. The results of this study are important for the improvement of the clinical management of MS patients. Furthermore, potential clinicians should have more focus on anxiety and depression symptoms among people with MS disease to develop appropriate treatments for those patients. Finally, support programs should be made available for pwMS to ensure adequate coping with the disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

SAS and NA conceived of the presented idea. AA, TA and SAS planned and carried out the simulations. RA, HA and SAS developed the theory and performed the computations. NA contributed to the interpretation of the results. NA and SAJ verified the analytical methods. RA and SAS investigate and supervised the findings of this work. SAS carried out the experiment. SAS and NA wrote the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors discussed the results and contributed to the final manuscript.

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Effects of a 6-Min Treadmill Walking Test on Dual-Task Gait Performance and Prefrontal Hemodynamics in People With Multiple Sclerosis

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Fatigue is one of the most limiting symptoms in people with multiple sclerosis (pwMS) and can be subdivided into trait and state fatigue. Activity-induced state fatigue describes the temporary decline in motor and/or cognitive performance (motor and cognitive performance fatigability, respectively) and/or the increase in the perception of fatigue (perceived fatigability) in response to motor or cognitive tasks. To the best of our knowledge, the effects of a 6-min walk test (6MWT), which was often used to assess motor performance fatigability in pwMS, on motor-cognitive dual-task performance (i.e., walking + arithmetic task) and prefrontal cortex (PFC) hemodynamics are not well-known. This is of importance, since daily activities are often performed as multitasks and a worse dual-task walking performance is associated with an increased risk of falling. Consequently, we investigated the effect of a fast 6MWT (comfort velocity + 15%) performed on a treadmill on motor-cognitive performance fatigability (spatio-temporal gait parameters/accuracy during the arithmetic task) and perceived fatigability measures (rating of perceived exhaustion; RPE) as well as PFC hemodynamics recorded during dual-task walking in pwMS and healthy controls (HCs). Twenty pwMS (48.3 ± 9.0 years; 13 females/7 males; expanded disability status scale 2.7 ± 1.0, first diagnosis 13.8 ± 8.8 years) and 24 HC with similar age and sex (48.6 ± 7.9 years; 17 females/7 males) were included. Only cognitive performance fatigability (increased error rate) during dual-task walking was found after the fast 6MWT on the treadmill in pwMS. However, the changes in gait parameters did not indicate motor performance fatigability, although both the groups reported perceived fatigability (increased RPE) after the fast 6MWT. Moreover, no change in the PFC activation was detected in both groups. Our results suggest that the intensity and/or duration of the fast 6MWT was not sufficient to induce motor performance fatigability in pwMS. These factors should be addressed by future studies on this topic, which should also consider further parameters, e.g., muscular oxygenation and/or myoelectrical activity, to verify that exercise intensity and/or duration was appropriate to induce motor performance fatigability in pwMS.

Clinical Trial Register: DRKS00021057.

Keywords: fNIRS, functional near-infrared spectroscopy, fatigue, fatigability, 6MWT, MS

INTRODUCTION

Over 75% of people with multiple sclerosis (pwMS) report that fatigue is the most limiting symptom with a high negative impact on daily life (1). In the MS context, fatigue is often defined as a subjective lack of physical and/or mental energy that is perceived by the affected person or caregiver interfering with usual and desired activities (2). However, this definition does not cover the different dimensions of fatigue comprising perceptual and performance aspects that were investigated separately in the past (3–6). To resolve this, Enoka and Duchateau (3) provided a fatigue definition and framework, which were recently adapted to describe the dimensions and mechanisms contributing to fatigue in pwMS (7). Within this framework, a distinction is made between trait and state fatigue. Trait fatigue describes the fatigue perception of pwMS over a longer period of time (e.g., weeks or months) and is associated with primary disease-related and secondary mechanisms (e.g., depression and medication). In contrast, activity-induced state fatigue describes the temporary decline in motor and/or cognitive performance (performance fatigability) and/or the increase in the perception of fatigue (perceived fatigability) in response to a motor or cognitive task. Thereby, motor performance fatigability is determined by the activation characteristics as well as the contractile function of muscles (3) and cognitive performance fatigability by the integrity of the central nervous system (e.g., neural excitability, metabolites, and neurotransmitter) (6, 8). Perceived fatigability strongly depends on the psychophysiological state of the individual (9). Both the performance fatigability and perceived fatigability are interdependent and should be investigated in conjunction (7).

The majority of studies assessing motor performance fatigability in pwMS used single muscle or muscle group performance tests, while only a few studies employed whole-body exercises such as walking (10). The latter is of particular importance for activities of daily life. In this context, the 6-min walk test (6MWT) was mostly applied as a fatigue intervention and/or assessment with discrepant effects on motor performance fatigability indices in pwMS, i.e., some showed a decline in walking velocity (11, 12) and others not (13) depending on the degree of disability (14). However, these studies only investigated performance fatigability while executing a single-task 6MWT. Therefore, to the best of our knowledge, the effects of a 6MWT on motor-cognitive dual-task performance (e.g., walking + arithmetic task) are not well-known. This is of particular importance, since daily activities are often performed as multitasks and a worse dual-task walking performance is associated with an increased risk of falling (15). In general, pwMS display a decreased gait performance during dual-task walking compared to single-task walking, with gait performance being worse than that of healthy controls (HC) in both conditions (16). This motor-cognitive interference during dual-task walking was explained by impaired cognitive functions (17), i.e., especially the attentional capacity [located among others in the prefrontal cortex (PFC)] in pwMS (18). For instance, Hernandez et al. have demonstrated that the PFC activation during single- and dual-task overground walking was higher in pwMS than in HC (19), which may be due to structural and functional changes related to MS (20). Moreover, they have shown that PFC activation was higher during dual-task walking compared to single-task walking in both groups presumably due to higher attentional demands (19).

Nevertheless, it is currently not known if motor performance fatigability induces a reallocation of attentional resources and/or compensatory processes during dual-task walking in pwMS compared to HC. For instance, the findings of Vuillerme et al. point in this direction showing that motor performance fatigability of the calf muscles resulted in a decreased cognitive performance (auditive reaction time task), while conducting a motor task (maintaining static postural control) in healthy young adults (21).

Based on the literature presented above, we investigated the effect of a fast 6MWT performed on a treadmill on performance and perceived fatigability measures as well as PFC hemodynamics recorded during dual-task walking in pwMS and HC. We expected that the fast 6MWT performed on a treadmill induces a deterioration in motor (spatio-temporal gait parameters) and/or cognitive performance (accuracy in calculating backward in steps of 3) associated with a change in PFC activation [relative oxy-/deoxyhemoglobin concentrations (HbO/HbR)] in pwMS, due to their limited attentional and/or cognitive capacity, but not in HC.

METHODS

Participants

In total, 20 pwMS and 24 HC with similar age and sex were enrolled in this cross-sectional study. No sample size calculation was performed because comparable studies were lacking to obtain an effective size. However, our sample size was higher than those of other functional near-infrared spectroscopy (fNIRS) walking studies in pwMS (19, 22, 23). For inclusion, a MS diagnosis according to the revised McDonald criteria (24) had to be confirmed and the last acute episode as well as cortisone intake had to be at least 1 month ago. Furthermore, the expanded disability status scale (EDSS) (25) should not be higher than 4.5. This ensured that the subjects were able to walk at least 300 m at a stretch without aids. HC were excluded if any orthopedic, neurological, or untreated cardiovascular disease were present. The study procedure was approved by the ethics committee of the Medical Faculty of the Otto von Guericke University Magdeburg (Germany) (No.: 116/18).

Study Procedure

This study was conducted at the Otto von Guericke University Magdeburg (Germany) and the Kliniken Schmieder Konstanz (Germany). Patients with MS were recruited at the clinic by medical professionals during their admission to the rehabilitation clinic. The healthy subjects were recruited via a local newspaper article. The participants were informed about the study in a personal conversation and written informed consent was obtained. In total, the participants had three

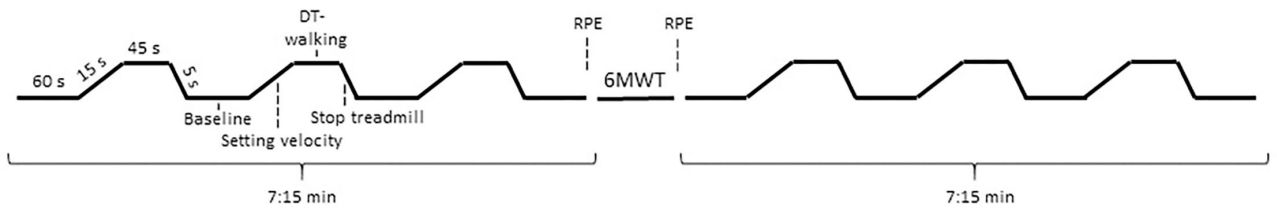

FIGURE 1 | Experimental protocol. DT-walking, dual-task walking; 6MWT, 6-min walk test; RPE, rating of perceived exhaustion.

appointments: (i) pre-assessment of clinically relevant outcomes, (ii) familiarization, and (iii) the main measurement. All the measurements were done in the morning in a rested state with at least 24 h between sessions. During the pre-assessment, questionnaires were filled in [12-Item Multiple Sclerosis Walking Scale (MSWS-12) (26), Fatigue Scale for Motor and Cognitive function (FSMC) (27) and Beck Depression Inventory-II (BDI-II) (28)] and the 6MWT (29) was performed. Before and after the 6MWT, subjects were asked to rate their perceived exhaustion (RPE) using a Borg scale (6 = no exhaustion, 20 = maximal exhaustion). In the familiarization session, the comfort walking velocity on the treadmill was determined, the test protocol was explained in detail, the measurement equipment was applied and the first block of the measurement protocol was carried out (see **Figure 1**). A block design recommended for fNIRS recordings was used (30) during which the subjects had to alternate between standing (baseline) and dual-task walking every 60 s. Throughout the standing phase (baseline, 60 s), the participants should stand as stable as possible with hands on the rails without talking. Afterwards, the treadmill was accelerated to the prior determined individual comfort velocity within 15 s. During the subsequent dual-task walking (45 s), the subject had to calculate backwards by 3 from a randomly chosen number between 300 and 400 as it was used previously by Mofateh et al. (31). The subjects were told beforehand that if they make a mistake they should continue with the calculations and they were not corrected by the instructor. If they continued to calculate correctly backwards by 3 after the error, the answers were considered as correct. Finally, the treadmill was stopped within 5 s and the subjects stood still for further 60 s. This protocol was repeated three times in a row with a total duration of 7:15 min. The start and stop of the treadmill were announced loudly by the instructor.

The main measurements were conducted according to the above described dual-task-walking protocol prior and after the fast 6MWT performed on the same treadmill with comfort velocity plus 15% (see **Figure 1** for more detail). Directly after the last standing phase of the pre-block, the treadmill was started and the subjects should concentrate on walking only for 6 min. Subsequently, the participants started with the first baseline measurement (standing) of the post-block. Before and after the fast 6MWT, RPE was inquired as an index of perceived fatigability. The study was performed on the treadmill to protect the pwMS from falling, due to motor or cognitive exhaustion, by using a harness during walking.

Equipment and Outcome Measures

The gait parameters were derived from the acceleration and gyroscope data acquired with inertial measurement units (IMUs/MTw, Xsens Technologies BV, The Netherlands) fixed dorsally at both feet. Data were recorded during the dual-task assessments and the fast 6MWT on the treadmill with a sampling frequency of 120 Hz. The spatio-temporal gait parameters were calculated based on the algorithms of Hamacher et al. (32). The outcome parameters were stride length, stride time, stance time, swing time, and the minimum toe clearance (MTC) as well as their relative variability expressed by the coefficient of variation [CV (%) = standard deviation/mean × 100]. If these parameters changed significantly, we have interpreted this as motor performance fatigability. Cognitive performance fatigability was evaluated by the change in accuracy rate (number of correct calculations and total errors) during dual-task walking from before to after the fast 6MWT.

Two portable continuous-wave fNIRS systems were utilized (NIRSport, NIRx Medical Technologies, New York, USA) each attached to a standardized cap with 56 and 58 cm circumference, respectively (EasyCap GmbH, Herrsching, Germany). The smaller cap was used for people with a head circumference of <57 cm and the larger one for $\geq$ 57 cm. Each fNIRS system is composed of eight sources and eight detectors as well as eight short-separation channels with an average source-detector distance of 30–40 mm. The wavelengths inherent to the system are 760 and 850 nm and the sampling frequency is fixed at 7.81 Hz. The placement over the PFC was done with the fNIRS Optodes' Location Decider (fOLD) toolbox (33). The sensitivity of the channels was described in Broscheid et al. (34). The cap was positioned with Cz centrally [according to the international 10–20 system for electroencephalography (35)] between the nasion and inion and preauricular points on the left and right side. To reduce the influence of ambient light, an additional darkening cap was placed over the system.

The PFC was subdivided into the right, left and medial dorsolateral PFC Brodmann area 9 and 46 (r/lDLPFC9, r/lDLPFC46, mDLPFC9), the right, left, and medial frontopolar cortex Brodmann area 10 (r/l/mFPC10) and the right and left Broca Brodmann area 45 (r/lBroca45). These subareas were built by the following channels: 17,20 and 22 (lDLPFC9); 1,18 and 21 (rDLPFC9); 13 (lDLPFC46); 6 (rDLPFC46); 19 (mDLPFC9); 10,11,12 and 14 (lFPC10); 4,5,7 and 8 (rFPC10); 9 (mFPC10); 15 and 16 (lBroca45); 2 and 3 (rBroca45). The outcome parameters were the mean HbO and HbR concentrations in the respective

subareas during the dual-task walking protocol performed prior and after the fast 6MWT.

In order to control physiological fNIRS signal confounders, a 3-channel electrocardiography system (SOMNOtouch^{TM} NIBP, SOMNOmedics GmbH, Germany) was applied and heart rate as well as heart rate variability (HRV; specified by the time interval between two R-spikes/RR-interval) were determined.

Functional Near-Infrared Spectroscopy Data Processing

To process and convert the fNIRS data, Homer3 (version 1.32.4) was used (36). First, non-existing values were replaced by spline interpolation (function hmrR_PreprocessIntensity_NAN). Afterwards, channels with a too weak or too strong signal as well as a too high standard deviation were excluded (function hmrR_PruneChannels: data range $= 1 \times 10^{-2}$ to 1×10^{7}; signal-to-noise threshold $= 2$; source detector separation range: 0.0–45.0 mm). The preprocessed raw data were then converted to optical density data (function hmR_Intensity2OD) (36). Using the spline interpolation and a digital Savitzky–Golay filter motion artifacts were removed (function hmR_MotionCorrectSplineSG: $p = 0.99$; frame size $= 15$ s) (37). Furthermore, the 3rd order Butterworth bandpass filter was applied to diminish physiological artifacts (function hmrR_BandpassFilt: Bandpass_Filter_OpticalDensity) (30). Therefore, the high-pass filter was set to 0.01 Hz to minimize the proportion of oscillations associated with vascular endothelial function (30) and the low-pass filter to 0.09 Hz to primarily filter out Mayer waves (38). Subsequently, the optical density data were converted to concentration data by the Beer–Lambert Law adapting the differential path length factor to the age of each participant (39). Finally, the individual hemodynamic response function (HRF) was calculated with the ordinary least squared deconvolution method by utilizing a general linear model approach (function hmrR_GLM) (40). Within this approach, the HRF was based on a consecutive sequence of Gaussian functions (width of the Gaussian 0.5 and temporal spacing between consecutive Gaussians 0.5). The short separation regression was performed with the nearest short separation channel. The 3rd order polynomial drift baseline correction was applied.

Afterwards, the data were post-processed in MATLAB (version R2020b, The MathWorks, Natick, Massachusetts, USA). First, the acceleration phase of the treadmill (15 s) and the early phase of task onset (15 s) were cut out for each subject to avoid transient effects of movement initiation on the hemodynamic response (41, 42). Second, the last 5 s were cut out to minimize the impact of the expected ending of the walking trial (41, 43). Accordingly, data recorded in the time interval 30–55 s from treadmill start to stop were analyzed. The HbO and HbR concentration data of this time interval of each channel were then averaged for each subject. Finally, the channels were merged to the subareas of the PFC described above.

Statistics

Statistical analysis was performed using IBM SPSS software (version 26, Chicago, USA). Normal distribution was checked with the Shapiro–Wilk test indicating that the majority of the data were normally distributed. Repeated measures ANOVA (rmANOVA) were carried out with the factors time (dual-task assessments prior and after the fast 6MWT as well as for each minute of the fast 6MWT) and group (pwMS and HC). It was assumed, as described in Blanca et al. (44), that the rmANOVA is robust to violation of the normal distribution. If the sphericity was not given, the Greenhouse–Geisser correction was applied. The effect size was determined using partial eta-squared (η_p^2) (small > 0.01, medium > 0.06, large > 0.14 effect) (45). In case of significant main or interaction effects, Bonferroni *post-hoc* tests were conducted. For the within-group comparison the effect size Cohen's d was determined (small > 0.2, medium > 0.5, large > 0.8 effect size) (45, 46). For the between-group comparison the bias-corrected Hedges' g was used (small > 0.2, medium > 0.5, and large > 0.8 effect size) (46). Statistical significance was accepted at $p \leq 0.05$. Since patient groups are mostly very heterogeneous and a small p-value does not have to be equivalent to clinical relevance (46, 47), also non-significant results were interpreted, if they showed at least a medium effect size ($\eta_p^2 > 0.06$; $d > 0.5$; $g > 0.5$).

RESULTS

Participants Characteristics and Clinical Outcomes

In total, 20 pwMS (13 females/7 males; 48.3 ± 9.0 years; 173.9 ± 9.1 cm; 75.7 ± 11.1 kg) and 24 HC (17 females/7 males; 48.6 ± 7.9 years; 171.7 ± 8.2 cm; 72.2 ± 12.6 kg) were included in the study. The pwMS were mildly to moderately affected (EDSS of 2.7 ± 1.0) and had an average disease duration of 14.0 ± 8.4 years since the first diagnosis. Sixteen pwMS were classified as the relapsing-remitting MS-type, two pwMS as the secondary, and two as the primary progressive MS-type. The pwMS reported moderate perceived walking limitations (MSWS-12: 53.8 ± 20.3%) and severe perceived trait fatigue ($FSMC_{total}$: 68.1 ± 10.9; $FSMC_{cognitive}$: 33.5 ± 10.1; $FSMC_{physical}$: 34.5 ± 9.3). The BDI-II was higher in pwMS (11.3 ± 8.0) than HC (3.0 ± 3.3), but in both cases not conspicuous with regard to depression.

During the overground 6MWT (clinical pre-assessment), the pwMS covered a distance of 470.3 ± 71.3 m and the HC 639.0 ± 56.2 m. Based on the distance walked index (11, 48), four pwMS displayed motor performance fatigability during the 6MWT. However, if the second minute was taken as the baseline for the calculation of the distance walked index as it was recommended by Broscheid et al., it was only one person (13).

Dual-Task Performance

Gait Performance

Gait data of three HC and one pwMS could not be analyzed due to poor data quality. The comfort velocity on the treadmill was 3.0 ± 0.7 km/h in pwMS and 4.8 ± 0.4 km/h in HC.

Group × time interactions could be proven for MTC ($p = 0.021$; $\eta_p^2 = 0.13$), stride length ($p = 0.019$; $\eta_p^2 = 0.14$) and swing time ($p = 0.033$; $\eta_p^2 = 0.11$). A group × time interaction with medium effect size was shown for the MTC_{CV} ($p = 0.124$; $\eta_p^2 = 0.06$) and the stance $time_{CV}$ ($p = 0.119$; $\eta_p^2 = 0.06$). The mean and individual data

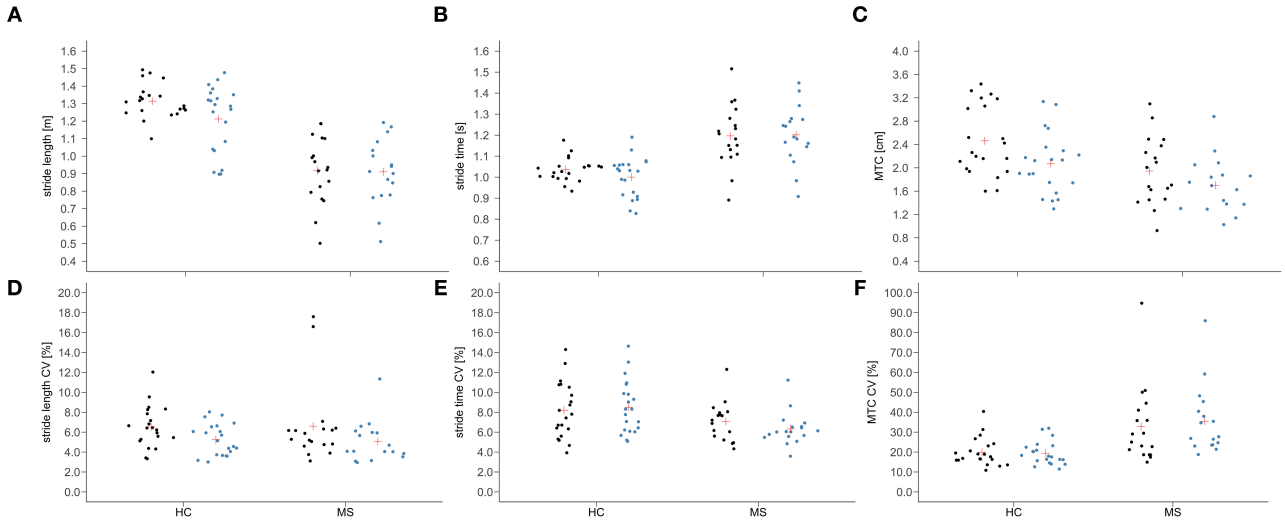

FIGURE 2 | Individual data (dots) and means (red cross) of stride length **(A)**, stride time **(B)**, and minimum toe clearance [MTC; **(C)**] as well as their coefficient of variation [CV; **(D–F)**] before (black) and after (blue) the fast 6-min walk test in people with multiple sclerosis (MS) and healthy controls (HC).

TABLE 1 | Spatio-temporal gait parameters recorded during dual-task walking before and after the fast 6MWT (mean ± standard deviation) and rmANOVA outcomes (*p*-values and effect size partial eta²).

Gait parameter	Group	Dual-task walking performance pre/post 6MWT		*p*-value			Partial eta²		
		Pre	Post	T	G	GxT	T	G	GxT
MTC [cm]	pwMS	1.96 ± 0.57	1.78 ± 0.51	**0.000**	**0.025**	**0.021**	**0.52**	**0.13**	**0.13**
	HC	2.46 ± 0.60	2.07 ± 0.52						
MTC_{CV} [%]	pwMS	32.50 ± 18.73#	35.00 ± 16.21#	0.319	**0.001**	0.124	0.03	**0.25**	0.06
	HC	19.97 ± 7.05#	19.43 ± 5.80						
Stride length [m]	pwMS	0.91 ± 0.19	0.92 ± 0.19	**0.050**	**0.000**	**0.019**	**0.10**	**0.57**	**0.14**
	HC	1.31 ± 0.10	1.21 ± 0.19#						
Stride $length_{CV}$ [%]	pwMS	6.67 ± 3.86#	5.11 ± 1.96#	**0.000**	0.997	0.682	**0.30**	0.00	0.00
	HC	6.53 ± 2.09	5.26 ± 1.59						
Stance time [s]	pwMS	0.61 ± 0.09	0.61 ± 0.09	0.107	**0.013**	0.284	0.07	**0.15**	0.03
	HC	0.56 ± 0.04	0.55 ± 0.06						
Stance $time_{CV}$ [%]	pwMS	16.69 ± 10.73#	17.34 ± 11.77#	0.555	**0.002**	0.119	0.01	**0.22**	0.06
	HC	9.68 ± 3.60#	8.27 ± 1.31						
Swing time [s]	pwMS	0.57 ± 0.19#	0.58 ± 0.18#	0.347	**0.010**	**0.033**	0.02	**0.16**	**0.11**
	HC	0.47 ± 0.02	0.45 ± 0.04						
Swing $time_{CV}$ [%]	pwMS	28.17 ± 27.93#	19.12 ± 8.77	0.453	**0.013**	0.278	0.02	**0.15**	0.03
	HC	15.34 ± 6.68#	16.47 ± 7.87						
Stride time [s]	pwMS	1.18 ± 0.15	1.19 ± 0.14	0.146	**0.000**	0.073	0.06	**0.38**	0.08
	HC	1.04 ± 0.06	1.00 ± 0.10						
Stride $time_{CV}$ [%]	pwMS	12.06 ± 21.72#	6.35 ± 1.57#	0.271	0.724	0.221	0.03	0.00	0.04
	HC	8.20 ± 2.80	8.51 ± 2.67						

MTC, minimum toe clearance; CV, coefficient of variation; pwMS, people with multiple sclerosis; HC, healthy controls; 6MWT, 6-min walk test; T, time effect; G, group effect; GxT, group x time effect; bold, p-value ≤ 0.05; #, non-normally distributed.

of these gait parameters and their CV are illustrated in **Figure 2**. Time effects for the gait parameters MTC ($p < 0.001$; $\eta_p^2 = 0.52$), stride length ($p = 0.050$; $\eta_p^2 = 0.10$) and stride $length_{CV}$ ($p < 0.001$; $\eta_p^2 = 0.30$) were found (**Table 1**). For the stride time ($p = 0.073$; $\eta_p^2 = 0.08$) and the stance time ($p = 0.107$; $\eta_p^2 = 0.07$), the time effect was non-significant but a medium effect size was present. Group effects were shown for all the spatio-temporal gait parameters ($p < 0.05$; $\eta_p^2 = 0.13$–0.57) except stride $length_{CV}$ and stride $time_{CV}$.

The *post-hoc* within group comparisons revealed that the stance time ($p = 0.010$; $d = 0.1$) decreased and the stride time ($p < 0.001$; $d = 0.1$) increased significantly after the fast 6MWT in pwMS (**Supplementary Table 1**). The MTC and stride length$_{CV}$ decreased with a large ($p = 0.087$; $d = 1.0$) and a medium effect size ($p = 0.793$; $d = 0.5$), respectively, in pwMS. For the HC, it was shown that the MTC ($p = 0.010$; $d = 1.1$), stride length ($p = 0.002$; $d = 0.5$), stance time ($p = 0.028$; $d = 0.4$), swing time ($p = 0.028$; $d = 0.5$) and stride time ($p < 0.001$; $d = 0.4$) decreased significantly from pre to post of the fast 6MWT. The stride length$_{CV}$ decreased with a large effect size ($p = 0.883$; $d = 0.9$).

The *post-hoc* between group comparisons indicated that both groups differed significantly in MTC (pre: $p = 0.010$; $g = 0.8$; post: $p = 0.087$; $g = 0.5$), stride length (pre: $p < 0.001$; $g = 2.7$; post: $p < 0.001$; $g = 1.5$), swing time (pre: $p = 0.028$; $g = 0.7$), MTC$_{CV}$ (pre: $p = 0.007$; $g = 0.88$; post: $p < 0.001$; $g = 1.3$), and stance time$_{CV}$ (pre: $p = 0.007$; $g = 0.88$; post: $p = 0.001$; $g = 1.1$). However, a medium effect size was proven for swing time (post: $p = 0.087$; $g = 0.5$).

Cognitive Performance

No significant group × time interaction, time or group effects were demonstrated for the total number of errors (pwMS pre: 0.3 ± 0.5/post: 0.7 ± 1.2; HC pre: 0.8 ± 1.0/post: 0.9 ± 0.9) and total number of correct calculations (pwMS pre: 18.0 ± 5.4/post: 18.4 ± 6.7; HC pre: 20.4 ± 8.3/post: 20.9 ± 9.5) during dual-task walking. However, for both, the total number of errors ($p = 0.052$; $\eta_p^2 = 0.09$) and correct calculations ($p = 0.110$; $\eta_p^2 = 0.06$), a time effect with a medium effect size was shown. The within group *post-hoc* tests indicated a significant increase in the error rate after the fast 6MWT in pwMS ($p = 0.028$; $d = 0.6$) but not in HC ($p = 0.596$; $d = 0.1$) (**Supplementary Table 1**).

Prefrontal Cortex Hemodynamics

Due to poor signal quality, the fNIRS data of two pwMS had to be excluded from the statistical analysis. No significant group × time interaction, time, or group effects were found for HbO and HbR for all PFC subareas (**Table 2**). A medium effect size was demonstrated for the group × time interaction for HbR in rFPC10 ($p = 0.124$; $\eta_p^2 = 0.06$). Moreover, a time effect with a medium effect size was observed for HbO in lBroca45 ($p = 0.102$; $\eta_p^2 = 0.07$) and for HbR in mFPC10 ($p = 0.132$; $\eta_p^2 = 0.06$) (**Table 2**).

A significant group effect was detected for HbO in rDLPFC9 ($p = 0.043$; $\eta_p^2 = 0.10$) and in rFPC10 ($p = 0.011$; $\eta_p^2 = 0.15$). Moreover, a medium effect size for the group effect was shown for HbO in mFPC10 ($p = 0.058$; $\eta_p^2 = 0.09$) and for HbR in mDLPFC9 ($p = 0.105$; $\eta_p^2 = 0.06$) as well as in lBroca45 ($p = 0.056$; $\eta_p^2 = 0.09$).

The within group *post-hoc* tests did not reveal any significant differences (**Supplementary Table 1**). In the between groups *post-hoc* test, a higher HbR concentrations with a medium effect size were found for the rFPC10 (pre: $p = 0.100$; $g = 0.5$) in pwMS compared to HC.

The time course of HbO (before and after the fast 6MWT) averaged for pwMS and HC, respectively, is exemplarily displayed for the lDLPFC9 in **Figure 3**. The mean group data show that HbO increased after the start of the treadmill and dropped sharply in both groups, when the target velocity was reached. With a small time delay, after the start of the dual-task walking, the HbO concentration rose steadily above the initial level until the treadmill was stopped. Furthermore, the figure indicates that the standard deviation was particularly large during the acceleration of the treadmill (0–15 s) in both groups.

Heart Rate and Heart Rate Variability

Heart rate (pre 94.36 ± 10.82 bpm/post: 94.10 ± 9.41 bpm) and RR-interval (pre: 647.11 ± 73.88 ms/post: 646.22 ± 64.07 ms) remained stable from before to after the fast 6MWT in pwMS. In HC, the heart rate increased (pre: 94.38 ± 12.17 bpm/post: 98.00 ± 14.51 bpm) and the RR-interval decreased (pre: 660.87 ± 78.60 ms/post: 633.84 ± 87.40 ms). Along with this, group × time interaction and time effects were observed for heart rate (time: $p = 0.028$; $\eta_p^2 = 0.13$; time × group: $p = 0.012$; $\eta_p^2 = 0.16$) as well as the RR-interval (time: $p = 0.004$; $\eta_p^2 = 0.21$; time × group: $p = 0.007$; $\eta_p^2 = 0.19$). The within *post-hoc* tests revealed that the increase in heart rate ($p = 0.001$; $d = 0.9$) and the decrease in RR-interval ($p < 0.001$; $d = 0.2$) were significant in HC (**Supplementary Table 1**). The between-group *post-hoc* tests showed no significant differences nor medium effect sizes for the heart rate and RR-interval.

6-Min Walk Test

Gait Performance

For the gait parameters recorded during the fast 6MWT on the treadmill, group × time interaction and time effects were found for stride length$_{CV}$ (time: $p < 0.001$; $\eta_p^2 = 0.20$; group × time: $p < 0.001$; $\eta_p^2 = 0.24$) and stride time$_{CV}$ (time: $p < 0.001$; $\eta_p^2 = 0.17$; group × time: $p < 0.001$; $\eta_p^2 = 0.22$) (**Table 3**). Significant group effects were proven for all spatio-temporal gait parameters ($p < 0.5$; $\eta_p^2 = 0.15$–0.66) except for the MTC, which, however, exhibited a medium effect size ($p = 0.079$; $\eta_p^2 = 0.08$).

The within-group *post-hoc* tests revealed that stride length$_{CV}$ was lowest in the second minute and differed significantly from the third minute in pwMS ($p = 0.13$; $d = 0.7$) (**Supplementary Table 2**). Additionally, the second minute deviated with a medium effect size from the first ($p = 1.000$; $d = 0.5$) and fifth ($p = 0.105$; $d = 0.5$) minute in pwMS. In the latter, pwMS displayed the highest stride length$_{CV}$. For the stride time$_{CV}$, a non-significant difference but medium effect size was detected between the second and third ($p = 1.000$; $d = 0.5$) and fifth minute ($p = 0.514$; $d = 0.5$), respectively, in pwMS. Again, the stride time$_{CV}$ was lowest in the second minute and highest in the fifth. In the HC, only the stride length$_{CV}$ in the first minute was significantly higher than in the second ($p < 0.001$; $d = 2.4$). Nevertheless, a non-significant large effect size was shown for the difference between the second and the first minute in stride time$_{CV}$ ($p = 0.411$; $d = 1.6$), which decreased from the first to the second minute.

The between-group *post-hoc* tests indicated that the groups differed in the minutes two to six of the fast 6MWT in both gait parameters stride length$_{CV}$ ($p < 0.01$; g range = 1.2–1.4) and stride time$_{CV}$ ($p < 0.05$; g range = 0.7–1.4) significantly. For the

TABLE 2 | Oxy-/deoxyhemoglobin concentrations in the subareas of the prefrontal cortex recorded during dual-task walking before and after the fast 6MWT (mean ± standard deviation) and rmANOVA outcomes (*p*-values and effect size partial eta²).

		Oxyhemoglobin concentration								Deoxyhemoglobin concentration							
				p-values			Partial eta²					*p*-values			Partial eta²		
Parameter	**Group**	**Pre**	**Post**	**T**	**G**	**GxT**	**T**	**G**	**GxT**	**Pre**	**Post**	**T**	**G**	**GxT**	**T**	**G**	**GxT**
lDLPFC9 [µmol/l]	pwMS	0.291 ± 0.614	0.199 ± 0.531	0.216	0.416	0.625	0.04	0.02	0.01	−0.066 ± 0.191	−0.007 ± 0.249#	0.475	0.489	0.441	0.01	0.01	0.02
	HC	0.387 ± 0.515#	0.177 ± 0.695							−0.010 ± 0.178#	−0.012 ± 0.174						
rDLPFC9 [µmol/l]	pwMS	0.071 ± 0.652#	0.251 ± 0.261	0.600	**0.043**	0.261	0.01	**0.10**	0.03	−0.006 ± 0.169#	−0.063 ± 0.198	0.523	0.313	0.292	0.01	0.03	0.03
	HC	0.451 ± 0.499	0.385 ± 0.627#							−0.089 ± 0.203	−0.075 ± 0.224#						
lDLPFC46 [µmol/l]	pwMS	0.191 ± 0.487#	0.134 ± 0.669	0.683	0.781	0.914	0.00	0.00	0.00	−0.131 ± 0.356#	−0.166 ± 0.364	0.548	0.184	0.933	0.01	0.04	0.00
	HC	0.105 ± 0.813	0.007 ± 1.010							−0.019 ± 0.327	−0.065 ± 0.313						
rDLPFC46 [µmol/l]	pwMS	−0.025 ± 0.678	−0.022 ± 0.703	0.218	0.236	0.212	0.04	0.04	0.04	−0.071 ± 0.210	−0.175 ± 0.337	0.144	0.601	0.469	0.05	0.01	0.01
	HC	0.415 ± 0.811	0.020 ± 0.880							−0.126 ± 0.255	−0.162 ± 0.208						
mDLPFC9 [µmol/l]	pwMS	0.241 ± 0.529#	0.177 ± 0.611#	0.923	0.988	0.500	0.00	0.00	0.01	0.024 ± 0.154	0.047 ± 0.142	0.879	0.105	0.675	0.00	0.06	0.00
	HC	0.107 ± 0.587	0.192 ± 0.455							−0.031 ± 0.195#	−0.042 ± 0.244						
lFPC10 [µmol/l]	pwMS	0.327 ± 0.533#	0.041 ± 0.841#	0.443	0.239	0.343	0.02	0.03	0.02	−0.043 ± 0.198#	−0.082 ± 0.305#	0.692	0.584	0.238	0.00	0.01	0.04
	HC	0.119 ± 0.845	0.150 ± 0.486							−0.035 ± 0.283	0.042 ± 0.245						
rFPC10 [µmol/l]	pwMS	−0.170 ± 0.826	−0.070 ± 0.742#	0.777	**0.011**	0.697	0.00	**0.15**	0.00	0.148 ± 0.387#	0.001 ± 0.322	0.541	0.263	0.124	0.01	0.03	0.06
	HC	0.342 ± 0.561	0.326 ± 0.763#							−0.009 ± 0.248	0.056 ± 0.289						
mFPC10 [µmol/l]	pwMS	−0.141 ± 0.444	0.024 ± 0.689	0.486	0.058	0.598	0.01	0.09	0.01	−0.046 ± 0.639#	0.067 ± 0.508#	0.132	0.750	0.984	0.06	0.00	0.00
	HC	0.201 ± 0.641	0.224 ± 0.759							−0.024 ± 0.279	0.087 ± 0.233						
lBroca45 [µmol/l]	pwMS	0.234 ± 0.651#	0.019 ± 0.516	0.102	0.485	0.933	0.07	0.01	0.00	−0.161 ± 0.304	−0.185 ± 0.174	0.256	0.056	0.507	0.03	0.09	0.01
	HC	0.367 ± 0.609	0.130 ± 0.886#							−0.017 ± 0.229	−0.108 ± 0.267#						
rBroca45 [µmol/l]	pwMS	0.059 ± 0.587	0.103 ± 0.434	0.455	0.189	0.306	0.01	0.04	0.03	−0.115 ± 0.291	−0.159 ± 0.316	0.549	0.275	0.785	0.01	0.03	0.00
	HC	0.377 ± 0.692	0.095 ± 0.748							−0.049 ± 0.303	−0.066 ± 0.233#						

l/r/mDLPFC9, left/right/medial dorsolateral prefrontal cortex Brodmann area 9; l/r/mDLPFC46, left/right dorsolateral prefrontal cortex Brodmann area 46; l/r/mFPC10, left/right/medial frontopolar cortex Brodmann area 10; l/rBroca45, left/right broca area Brodmann area 45; T, time effect; G, group effect; GxT, group x time effect; pwMS, people with Multiple Sclerosis; HC, healthy controls; bold, p-value ≤ 0.05; #, non-normally distributed.

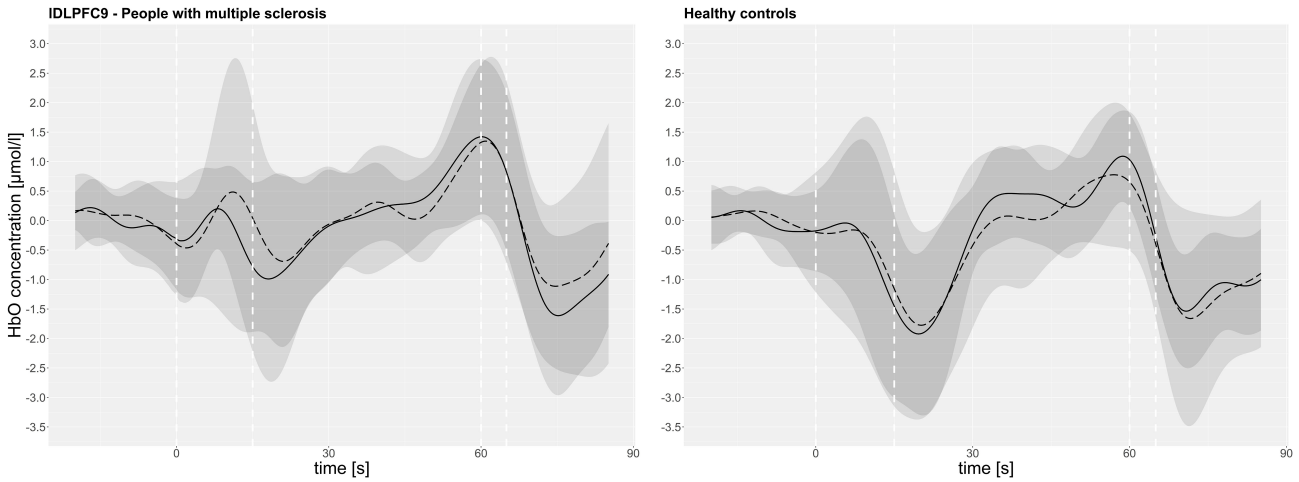

FIGURE 3 | The oxyhemoglobin concentration (HbO) in the left dorsolateral prefrontal cortex Brodmann area 9 (IDLPFC9) of all subjects (mean pre: continuous line, post: dashed line/standard deviation pre: dark gray, post: light gray) over the course of measurement intervals. The dashed white vertical line represents: 0 s = start of the treadmill, 15 s = start of dual-task walking, 60 s = treadmill stopped, 65 s = start of the baseline.

stride time$_{CV}$, the groups differed also in the first minute ($p = 0.027$; $g = 0.7$).

Perceived Fatigability

No group × time interaction effect was observed. A significant time ($p < 0.001$; $\eta_p^2 = 0.56$) and group effect ($p < 0.001$; $\eta_p^2 = 0.36$) was demonstrated for the RPE (pwMS pre: 12.7 ± 2.6/post: 14.2 ± 2.5; HC pre: 9.5 ± 2.3/post: 10.6 ± 2.1).

The within group *post-hoc* tests revealed that the RPE was significantly increased after the fast 6MWT in both groups (pwMS: $p < 0.001$; $d = 1.4$; HC: $p < 0.001$; $d = 0.8$) (**Supplementary Table 1**).

DISCUSSION

This study investigated the effect of a fast 6MWT performed on a treadmill on motor and cognitive performance fatigability, perceived fatigability as well as PFC hemodynamics recorded during dual-task walking in pwMS and HC.

The main findings were that during the motor-cognitive dual-task (i) a distinct change in the spatio-temporal gait parameters toward a decreased MTC and stride length$_{CV}$ and an increased stride time was observed in pwMS following the fast 6MWT. The HC displayed a change toward shorter and faster steps with less variability as well as a smaller MTC. Furthermore, (ii) cognitive performance during dual-task walking only declined in pwMS (increased error rate) and (iii) the PFC hemodynamics did not change in both groups. In addition, (iv) heart rate increased and HRV decreased only in HC after the fast 6MWT.

During the fast 6MWT, (v) stride length$_{CV}$ and stride time$_{CV}$ were lowest in the second minute and highest in the fifth minute in pwMS. In HC, both parameters were significantly higher in the first minute compared to the second. Lastly, (vi) both groups reported a slight but significant increase in perceived fatigue indicated by a higher RPE after the fast 6MWT.

There are only very few comparable studies investigating the impact of different fatiguing motor tasks on spatio-temporal gait parameters and the comparison should be made with caution as the fatigue protocols, the testing protocols (overground vs. treadmill walking), the task conditions (single vs. dual-task condition) and the calculation of the gait parameters (leg sides separated or averaged) were different. For instance, similar to our results, Granacher et al. reported a decreased stride length variability during dual-task overground walking in older adults after maximal isokinetic knee extensions (performed until they reached 50% of their maximal torque value) (49). Moreover, Nagano et al. investigated the influence of a fast 6MWT on spatio-temporal gait parameters [including the minimum foot clearance (MFC)] during 5 min treadmill single-task walking in young and older healthy adults (50). They found that the older adults exhibited a decreased MFC in the dominant leg, an increased MFC in the non-dominant leg and a decreased MFC variability in both legs after the fast 6MWT. In the present study, the MTC (averaged across both the legs) decreased slightly in both groups and the MTC$_{CV}$ remained more or less stable.

In summary, our data imply that both pwMS and HC did not exhibit a clear indication of motor performance fatigability in this study. On the contrary, the observed changes in gait parameters might represent habituation to treadmill walking (51). In this regard, Meyer et al. investigated the change of kinematic gait parameters over 10 min single-task walking on a treadmill. They have found that toe height and step length variability decreased while stride time increased within the first 5 min. Thereafter these gait parameters remained stable (51). The same changes in these spatio-temporal gait parameters were observed in this study during dual-task walking. Thus, the fast 6MWT might have induced habituation to treadmill walking rather than motor performance fatigability. Nevertheless, these results have to be compared also with caution, because we have not observed this habituation effect during the fast 6MWT in both groups,

TABLE 3 | Spatio-temporal gait parameters of every minute of the 6-min walk test (mean ± standard deviation) and rmANOVA outcomes (*p*-values and effect size partial eta²).

Gait parameter	Group	Performance 6-min walk test						*p*-values			Partial eta²		
		1 min	2 min	3 min	4 min	5 min	6 min	T	G	GxT	T	G	GxT
MTC [cm]	pwMS	2.23 ± 0.56	2.23 ± 0.54	2.23 ± 0.59	2.24 ± 0.60	2.28 ± 0.60	2.28 ± 0.62	0.538	0.079	0.222	0.02	0.08	0.04
	HC	2.65 ± 0.61	2.66 ± 0.63	2.59 ± 0.62	2.51 ± 0.59	2.49 ± 0.58	2.47 ± 0.59						
MTC_{CV} [%]	pwMS	30.90 ± 13.85#	30.83 ± 12.17	31.53 ± 16.02#	33.44 ± 14.94	30.45 ± 13.52#	31.83 ± 12.84#	0.496	**0.000**	0.500	0.02	**0.41**	0.02
	HC	17.90 ± 4.70	16.55 ± 4.79	16.61 ± 4.89	16.78 ± 5.56#	17.55 ± 5.35	20.96 ± 15.47#						
Stride length [m]	pwMS	1.06 ± 0.20	1.07 ± 0.20	1.07 ± 0.20	1.07 ± 0.20	1.08 ± 0.21	1.07 ± 0.23	0.511	**0.000**	0.808	0.01	**0.66**	0.00
	HC	1.45 ± 0.10	1.48 ± 0.11	1.48 ± 0.11	1.48 ± 0.11	1.48 ± 0.11	1.48 ± 0.11						
Stride $length_{CV}$ [%]	pwMS	3.64 ± 2.26#	3.39 ± 2.16#	3.73 ± 2.44#	3.98 ± 3.04#	4.23 ± 2.75#	3.78 ± 1.63	**0.000**	**0.001**	**0.000**	**0.20**	**0.26**	**0.24**
	HC	4.56 ± 1.25	1.58 ± 0.43#	1.66 ± 0.40	1.67 ± 0.47	1.67 ± 0.46	1.93 ± 0.95#						
Stance time [s]	pwMS	0.62 ± 0.08	0.63 ± 0.08	0.63 ± 0.07#	0.63 ± 0.07	0.63 ± 0.08	0.63 ± 0.06	0.693	**0.000**	0.629	0.01	**0.51**	0.01
	HC	0.53 ± 0.03	0.52 ± 0.04	0.52 ± 0.04	0.53 ± 0.04	0.53 ± 0.04	0.53 ± 0.04						
Stance $time_{CV}$ [%]	pwMS	8.75 ± 9.50#	9.11 ± 10.45#	9.51 ± 10.70#	9.55 ± 11.44#	9.12 ± 10.27#	9.18 ± 10.55#	0.309	**0.003**	0.174	0.03	**0.22**	0.05
	HC	6.17 ± 2.37	1.94 ± 0.60#	1.92 ± 0.59#	1.90 ± 0.52#	1.93 ± 0.61#	2.84 ± 3.47#						
Swing time [s]	pwMS	0.54 ± 0.18#	0.54 ± 0.18#	0.54 ± 0.17#	0.54 ± 0.17#	0.54 ± 0.17#	0.50 ± 0.11#	0.481	**0.015**	0.458	0.01	**0.15**	0.02
	HC	0.45 ± 0.02	0.45 ± 0.02	0.45 ± 0.02	0.45 ± 0.02	0.45 ± 0.02	0.45 ± 0.02						
Swing $time_{CV}$ [%]	pwMS	9.78 ± 9.38#	9.27 ± 8.44#	10.09 ± 9.66#	10.06 ± 9.85#	10.11 ± 9.83#	11.65 ± 11.89#	0.302	**0.001**	0.528	0.03	**0.28**	0.01
	HC	4.61 ± 3.50#	2.29 ± 0.73	2.24 ± 0.77#	2.27 ± 0.76	2.26 ± 0.75	4.13 ± 7.81#						
Stride time [s]	pwMS	1.16 ± 0.14	1.17 ± 0.14	1.17 ± 0.13	1.17 ± 0.13	1.17 ± 0.13	1.13 ± 0.09	0.273	**0.000**	0.217	0.03	**0.53**	0.04
	HC	0.98 ± 0.05	0.97 ± 0.05	0.97 ± 0.05	0.98 ± 0.05	0.98 ± 0.06#	0.98 ± 0.06#						
Stride $time_{CV}$ [%]	pwMS	2.90 ± 1.91#	2.68 ± 1.48#	3.09 ± 2.10#	3.24 ± 2.51#	3.97 ± 2.95#	3.55 ± 2.04#	**0.000**	**0.001**	**0.000**	**0.17**	**0.24**	**0.22**
	HC	4.37 ± 2.07	1.12 ± 0.33	1.07 ± 0.33	1.10 ± 0.32#	1.11 ± 0.39	1.88 ± 2.85#						

MTC, minimum toe clearance; CV, coefficient of variation; pwMS, people with Multiple Sclerosis; HC, healthy controls; 6MWT, 6-min walk test; T, time effect; G, group effect; GxT, group x time effect; bold, p-value ≤ 0.05; #, non-normally distributed.

but only during the dual-task walking afterward for most of these variables.

Regarding our initial hypothesis, we observed an indication for cognitive performance fatigability (increased error rate during the subtraction task), which might be due to the cognitive impairments (especially in the executive functions and attentional capacity) associated with MS (17).

This cognitive performance decline, without a clear sign of motor performance fatigability, might imply that the pwMS seemed to prioritize the motor over the cognitive task. Holtzer et al. described this with the posture first hypothesis during motor-cognitive dual-tasking (52). Nevertheless, Holtzer et al. also observed that the posture first hypothesis goes along with a higher PFC activation, which was not demonstrated in this study. One reason for these contrasting results could be that they performed overground single- and dual-task walking with a self-controlled walking velocity. In the present study, gait velocity of the participants was externally paced due to the treadmill. Several authors have shown that the PFC is primarily involved in the control of gait velocity and gait initiation (acceleration) (53–55). Thumm et al. compared the PFC activation during single-task overground and treadmill walking. They have demonstrated that the PFC activation was significantly lower during treadmill compared to overground walking in the Parkinson's disease (56). These findings differ from those of Herold et al., who compared, among other areas, the PFC activation during single-task overground and treadmill walking in healthy young adults (57). They demonstrated that the HbO concentrations in the left and right PFC were significantly higher during treadmill compared to overground walking. However, the age structure and health status differed between these as well as our study and are therefore only comparable to a limited extent.

Although the 6MWT was applied several times to investigate motor performance fatigability in pwMS (10), our data indicate that the duration and/or the intensity (comfort speed plus 15%) of the fast 6MWT was not sufficient to induce motor performance fatigability as well as changes in PFC activation at least in our sample of mildly to moderately affected pwMS. The heart rate and HRV data support this notion, which did not change in pwMS, but in HC. Especially the pwMS were rather cautious during the familiarization session when selecting the comfort walking velocity. Therefore, future studies should apply longer and/or more intense walking protocols to investigate motor performance and perceived fatigability in pwMS.

Another reason why motor performance fatigability was not clearly observed after the fast 6MWT might be related to the fNIRS block design. For the fNIRS baseline measurements, the subjects had to rest in a standing position for 60 s after the fast 6MWT and before the first dual-task walking interval was performed. Since the recovery of neural and muscular determinants of performance fatigability is fast after intense exercise, this break could have masked the real extent of the exercise-induced impairments (58, 59).

Finally, one limitation is that no single-task condition was performed to calculate dual-task costs. However, this was intentionally skipped because the exercise-induced impairments

can disappear quickly (58, 59) and a single-task condition would have additionally increased the time delay between the fast 6MWT and the fatigue assessments. Moreover, the fNIRS cap can only be worn for a limited time due to the increasing pressure pain induced by the optodes at the forehead. Therefore, the measurements were kept as short as possible.

Another limitation is that some of the patients received disease modifying and symptomatic treatments, which may have had an impact on walking ability and with it on motor performance fatigability.

CONCLUSION

In summary, cognitive performance fatigability during dual-task walking was demonstrated after the fast 6MWT on the treadmill in pwMS. However, no clear indication of motor performance fatigability was observed. Furthermore, heart rate and HRV remained stable in pwMS and both groups reported only a slight increase in ratings of perceived fatigue. Moreover, no change in the PFC activation was detected in both groups.

Future studies on this topic should increase the intensity and/or duration of the walking fatigue intervention to investigate its impact on performance and perceived fatigability measures in pwMS. Thereby, the level of disability should be considered. Additionally, further parameters such as muscular oxygenation (muscle NIRS) and/or myoelectrical activity (electromyography) should be recorded to detect if exercise intensity and/or duration was sufficient to induce alterations in neuromuscular function as done in studies investigation performance fatigability during single-joint exercise (60). Furthermore, the interactions of cognitive performance fatigability, motor performance fatigability, perceived fatigability as well as their neural correlates should not only be examined on treadmill, but also during overground walking that is closer to everyday walking. Altogether, this might help to detect fatigability in pwMS with the aim to improve therapeutic interventions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Otto von Guericke University Magdeburg/Leipziger Str. 44 / 39120 Magdeburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

K-CB, LS, and CD: conceptualization and methodology. K-CB: formal analysis and investigation. K-CB, MB, LS, and CD: interpretation of data. K-CB and MB: writing—original draft preparation. K-CB, MB, LS, CD, and MJ: writing—review and editing. LS, CD, and MJ: resources and supervision. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.822952/full#supplementary-material

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MINI REVIEW
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Fatigue in Multiple Sclerosis: A Review of the Exploratory and Therapeutic Potential of Non-Invasive Brain Stimulation

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Fatigue is the most commonly reported symptom in patients with multiple sclerosis (MS). It is a worrisome, frequent, and debilitating manifestation that could occur at any time during the course of MS and in all its subtypes. It could engender professional, familial, and socioeconomic consequences and could severely compromise the patients' quality of life. Clinically, the symptom exhibits motor, cognitive, and psychosocial facets. It is also important to differentiate between perceived or subjective self-reported fatigue and fatigability which is an objective measure of decrement in the performance of cognitive or motor tasks. The pathophysiology of MS fatigue is complex, and its management remains a challenge, despite the existing body of literature on this matter. Hence, unraveling its neural mechanisms and developing treatment options that target the latter might constitute a promising field to explore. A PubMed/Medline/Scopus search was conducted to perform this review which aims (a) to reappraise the available electrophysiological studies that explored fatigue in patients with MS with a particular focus on corticospinal excitability measures obtained using transcranial magnetic stimulation and (b) to assess the potential utility of employing neuromodulation (i.e., non-invasive brain stimulation techniques) in this context. A special focus will be put on the role of transcranial direct current stimulation and transcranial magnetic stimulation. We have provided some suggestions that will help overcome the current limitations in upcoming research.

Keywords: multiple sclerosis, fatigue, neuromodulation, corticospinal excitability, tDCS, TMS, tRNS

INTRODUCTION

Multiple sclerosis (MS) is one of the most common neurological diseases and a serious cause of disability in young adults. Its natural course is characterized by recurrent relapses and progressive functional decline (1). With disease evolution, patients could accumulate several neurological dysfunctions, including motor deficit, sensory dysfunction, and sphincter disorders, among others (2). In addition, they could suffer from several "silent" "non-motor" complications, such as fatigue, pain, emotional manifestations, and cognitive dysfunctions (3).

Over the last two decades, MS symptoms have preoccupied the scientific community, and tremendous efforts have been made to understand the reasons behind their development and the modalities of their treatments. Among these symptoms, fatigue constitutes a real enigma and has given rise to collective awareness. Although the last few years have shown a growing literature on the characterization, pathophysiology, and treatment of MS fatigue, this symptom continues to challenge the medical and research societies of its difficult-to-treat nature and its resistance to the available pharmacological solutions. Hence, in this review, we will start with a definition of MS fatigue by highlighting the difference between fatigue and fatiguability. Then, we will give an overview of its underlying pathophysiological mechanisms. There will be particular focus on the application of the neurophysiological techniques in this domain. Afterward, we will address the place of non-invasive brain stimulation (NIBS) interventions in the treatment of this symptom.

FATIGUE IN MS

MS fatigue is very common; it could impact the lives of 75–90% of patients suffering from this disease (2, 4). It deeply affects their professional, social, and familial domains and could result in significant health costs and, therefore, should not be neglected (5, 6). For all these reasons, understanding this symptom and adopting novel therapeutic approaches have become more important than ever before.

To start, the definition of fatigue has been a source of confusion for several years. On the one hand, the terms "tiredness," "malaise," and "motor weakness" have been interchangeably used by patients to describe their fatigue; on the other hand, care providers have sometimes perceived fatigue as a lack of self-motivation. Toward the end of the 90's, a consensus was set by the MS Council for Clinical Practice Guidelines and has ended this debate (7). According to this council, MS fatigue corresponds to "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities." Currently, it is recommended to adopt this definition as has been thoroughly discussed in Mills and Young's study (8). In the same perspective of this definition, the intensity of MS fatigue is temperature-dependent in a way that hot or cold temperatures would worsen or alleviate fatigue, respectively. This aspect differentiates it from the "classical" tiredness encountered in healthy individuals.

In addition to the importance of setting a clear definition of fatigue, it is important to stress the difference between subjective or perceived self-reported fatigue and fatigability. While the former reflects a subjective experience that is classically tested by self-administered questionnaires, the latter reflects a performance decrement during the execution of a task and is usually evaluated with various cognitive or physical exercises.

Fatigue is a multifaceted symptom and consists of three domains: the physical, psychosocial, and cognitive domains. Thus, when patients complain about fatigue, the clinician or researcher should understand whether they feel this fatigue in the three domains or whether it only concerns one domain, for instance, the cognitive one. For this reason, some of the self-rated questionnaires that have been developed to diagnose and follow up on this complaint included questions dedicated to the assessment of several aspects of MS fatigue. For instance, the Modified Fatigue Impact Scale (MFIS), one of the most widely used scales, includes 21 questions that examine the three facets of fatigue (i.e., the physical, psychosocial, and cognitive ones) (7). In a similar manner, the Fatigue Scale for Motor and Cognitive Functions includes 20 questions and assesses two dimensions of MS fatigue as its name implies (9). Other scales assess one dimension of fatigue (e.g., the physical dimension), such as the 9-item Fatigue Severity Scale, which is one of the first tools developed to be used in PwMS (10), while others such as the Visual Analog Scale [VAS, (11)] provide a global assessment of this symptom [For a review refer to (1)].

Moreover, when talking about MS fatigue, it is pertinent to distinguish between primary fatigue, which is related to disease-specific mechanisms, and secondary fatigue, which could rather be attributed to comorbidities (motor symptoms, psychiatric manifestations, other medical conditions, or treatments adverse events) (1).

SELECTION CRITERIA

Research was done following PRISMA guidelines using computerized databases (PubMed/MEDLINE, Scopus) (12). An independent review was conducted by two of the authors (SSA and MAC) in order to identify original research articles published in English and French languages at any time till November 2021. The following key terms were used: ("MS" OR "multiple sclerosis") AND ("fatigue") AND ("non-invasive brain stimulation" OR "NIBS" OR "transcranial magnetic stimulation" OR "TMS" OR "theta burst stimulation" OR "TBS" OR "motor evoked potential" OR "MEP" OR "cortical excitability" OR "corticospinal excitability" OR "intracortical inhibition" OR "intracortical facilitation" OR "silent period" OR "interhemispheric inhibition" OR "transcranial direct current stimulation" OR "tDCS" OR "transcranial random noise stimulation" OR "tRNS"). In order to look for additional sources, the bibliographical references of the retrieved articles were also scanned.

PATHOPHYSIOLOGY OF FATIGUE IN MS

Clinical, neuropsychological, neuroanatomical, neuroimmune, and neurophysiological studies attempted to explore this multidimensional symptom. From a clinical perspective, the relationship between fatigue and physical disability appears to be inconsistent; MS fatigue seems to occur in all disease subtypes (4). From a neuropsychological viewpoint, fatigue could be associated with specific emotions, thoughts, and behaviors according to a cognitive-behavioral model proposed by van Kessel and Moss-Morris (13). In addition, this symptom could be associated with emotional factors, with which it may have bidirectional relationships and may share common biological substrates (14). In terms of neuroanatomy, inconsistencies exist regarding conventional measures (e.g., lesion load, global brain atrophy), but more advanced neuroimaging modalities (e.g., tractography, normal-appearing white matter, regional brain volumes and lesion load, brain activity, and functional connectivity at rest or during task performance) have unraveled a cortico-striato-thalamo-cortical loop related to MS fatigue (15–19). The exploration of neuroimmune and neuroendocrine axes has yielded scarce findings linking MS fatigue to some peripheral proinflammatory cytokines (20–22), while the relationship between this symptom and other outcomes were inconsistent {i.e., cerebrospinal fluid markers, orexin-A system, hypothalamus-pituitary-adrenal axis (20, 21, 23, 24), or absent [peripheral T cell populations or markers of inflammation (25, 26)]} [for reviews see (14)]. Finally, neurophysiology also constitutes a discipline that addresses MS fatigue in terms of pathophysiology and management as will be developed in the following sections.

NIBS TO EXPLORE AND MANAGE FATIGUE IN MS

Modulating the activity of brain regions and circuits continues to be a fascinating scientific field and a source of inspiration for researchers worldwide. The story began in the previous century when scientists first tested the impact of a weak electric current on the functioning of neural networks in animals and discovered that the application of a polarizing current on the scalp results in various effects on cortical activity. Afterward, much research has taken place across the world, and the fruit of this long investment has resulted in the development of the various NIBS techniques that we currently have at our disposal. Among these techniques, two are particularly interesting and have been the subject of many scientific investigations into different pathologies. The first is based on a famous law of biophysics—Faraday's law (the law of electromagnetic induction)—, while the second rather uses a weak electric current. These are, respectively, the transcranial magnetic stimulation (TMS) and the transcranial direct current stimulation (tDCS) techniques (27–30).

Neurophysiology of Fatigue in MS Using NIBS

As stated previously, TMS finds its roots in an ancient law of biophysics—the Faraday law. In fact, this law paved the way for the development of what has now become the rescue solution to some crippling neuropsychiatric manifestations, such as depression and neuropathic pain (29). Briefly, Faraday demonstrated that making an electric current flow in a conductive element would induce a magnetic field; the latter could in its turn induce an electric field in another conductive element placed nearby. Hence, applying a magnetic field on the scalp would diffuse toward the underlying cortical networks and would stimulate the corresponding nervous fibers (29).

The first clinical development of TMS served for the study of pyramidal motor conductions, using the technique known as motor evoked potentials (MEP). Performing MEP remains the most common application of TMS (31). This technique uses unique shocks applied to the skull to stimulate the pyramidal cortical neurons and to the spine to activate the nerve roots. A surface electromyographic recording is made at the level of the muscles of interest and the parameters (i.e., latency and amplitude) of the evoked responses are generally measured. Central motor conduction time (CMCT) is another TMS parameter used in clinical settings and reflects the time the nerve impulses take to travel from the motor cortex to the spinal motor neurons. It could be measured by subtracting the MEP latency obtained from spinal magnetic stimulation (also known as peripheral motor conduction time) from TMS-evoked MEP latency (32). Its lengthening may arise from a degeneration or a demyelination affecting the fastest-conducting cortico-motoneuronal fibers (33). Prolonged MEP latency was found to be a significant predictor of fatigue severity (34) while CMCT seems to be unrelated to this symptom (35).

Apart from obtaining conventional MEP, TMS has other important applications such as studying cortical excitability, which assesses different processes of regulation and execution of motor commands using paradigms of single and double cortical pulses. The parameters measured (i.e., motor thresholds (MT), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), cortical silent period (CSP), interhemispheric inhibition (IHI), cerebello-cortical inhibition, among others) provide information on neuronal modulation circuits using well-characterized GABAergic, glutamatergic, or cholinergic neurotransmission (32, 33). Excitability paradigms have been widely used to examine the pathophysiological processes behind several neurological and psychiatric symptoms, among which stands MS fatigue.

To start, concerning single-pulse parameters, no correlation was found between fatigue severity and resting MT (rMT) (36, 37), a parameter that reflects the excitability of the corticomotor neuronal membrane, including the spinal level. It corresponds to the stimulation intensity, as a percentage of the maximal stimulator output, that yields MEP of at least 50 μV amplitude on a fully relaxed muscle in 5 out of 10 trials (32, 33). The CSP is another single-pulse parameter that reflects

cortical (GABA-B) and spinal inhibitions (e.g., Renshaw cells, IA inhibitory interneurons) (32, 33). It could last up to 300 ms and corresponds to the interruption of voluntary muscular activity in a muscle of interest by applying a TMS pulse over the contralateral motor cortex. Prolonged CSP was found to be associated with fatigue severity in one study (38) but not in another one (37). Such discrepancy could be related to the clinical and methodological differences between both studies, such as the cohorts' disease characteristics (predominantly relapsing–remitting vs. progressive disease, respectively) and the adapted fatigue measures (VAS vs. MFIS, respectively).

Besides single-pulse measures, double-pulse measures could also be used. Some of them consist of applying a first subthreshold conditioning stimulus (whose intensity is below the rMT) that would inhibit or facilitate the response of a second suprathreshold stimulus (whose intensity is above the rMT) delivered to the same cortical site depending on the interstimulus interval (ISI) (32). For instance, applying short ($\leq$6 ms) and long ($\geq$7 ms) ISI could yield SICI and ICF which respectively, reflects GABA-A and glutamatergic transmissions. IHI represents another double-pulse measure that consists of conditioning the response of a suprathreshold stimulus by applying a suprathreshold stimulus over the contralateral motor site, and reflects GABAergic transcallosal activity (32). Three works have explored SICI in the context of MS fatigue and found low (36), high (37), or similar (39) pattern of inhibition in fatigued PwMS compared to non-fatigued PwMS and/or healthy controls (HC). In addition, in these three works, no significant group difference (or correlation) was obtained in terms of fatigue and ICF. Moreover, one of the three works included an IHI assessment and found no correlation between this measure and fatigue severity (37).

Some studies also explored the neurophysiological correlates of MS fatigue during motor task performance and tested the relationship of this symptom with movement preparation or execution phases. Some reported positive findings linking MS fatigue to movement-related TMS outcomes. Premovement MEP facilitation which is a normal finding following a motor task was found to be significantly reduced in fatigued PwMS compared to their non-fatigued counterparts and HC (39–41). This finding was correlated with frontal lesion load (39), motor performance decay [decrease in movement rate, (40)], and fatigue severity (39), suggesting a relationship between MS fatigue and abnormalities involving cerebral networks devoted to movement preparation. In addition, higher MEP amplitude was observed with contralateral hand grip following the fatiguing task in HC and non-fatigued PwMS but not in fatigued PwMS. This finding might suggest an involvement of callosal dysfunction in MS fatigue (42). Moreover, fatigue severity seems to be correlated with the time required for the rMT to reach the pre-exercise level (36). Conversely, no group difference in post-exercise MEP facilitation was found between non-fatigued and fatigued PwMS (43).

The second other major application of TMS is the realization of repetitive TMS (rTMS). Briefly, this method consists of delivering trains of stimulation at various frequencies and requiring specific machines (27, 29). Data on rTMS effects derive from numerous studies performed in healthy individuals, in whom low and high frequency (LF and HF) rTMS, respectively led to reduction and augmentation of MEP size. Hence, LF-rTMS and HF-rTMS have been perceived as inhibitory and facilitatory interventions. However, this viewpoint is simplistic, and it is now known that this dichotomy is no more valid since rTMS effects also depend on the baseline excitatory state of the nervous circuits; a state that would vary between individuals and even in the same subject at different moments of the day, it would also vary between healthy networks and those affected by various pathologies. Even more, several studies have documented that the augmentation/reduction of MEP amplitude after the application of HF/LF rTMS over the precentral cortex [i.e., the primary motor cortex (M1)] may be due to a decrease/increase of the GABA mediated inhibitory control of the corticospinal circuit rather than a direct modulation of the motor cortex excitability. Thus, what is perceived as "facilitatory" protocol (HF rTMS) could be in fact "inhibitory" (decrease in the functioning of the GABA interneurons) and vice versa. Other factors that can impact rTMS effects include age, drugs, and genetic factors, among others [For review, please refer to (27)].

In addition to the "classical" rTMS paradigms, a particular form of rTMS has been recently developed, the so-called theta burst stimulation (TBS). It consists of applying bursts (three pulses per burst at 50 Hz) in a repetitive manner at theta frequency (at 5 Hz) (44). TBS could induce changes in corticospinal excitability and the nature of such changes depends on the way the bursts are applied. Continuous and intermittent TBS (cTBS and iTBS) could lead to long-term depression-like and long-term potentiation-like effects, respectively (44).

Concerning rTMS and MS fatigue pathophysiology, it is worth noting here that some study protocols have tested the effects of 5-Hz rTMS over MEP outcomes in PwMS. In one study, MEP outcomes did not significantly differ between fatigued and non-fatigued PwMS, with both patient groups showing an increase in MEP amplitude following the intervention (39). In another study, the expected increase in MEP size was not obtained in fatigued PwMS, an increment that was found in their non-fatigued counterparts and in HC (45). Methodological differences could partly account for the observed changes as the second study included an attentional task (instructions to focus attention on the hand corresponding to stimulation); in addition, as aforementioned, inter-individual variability in terms of the baseline cortical excitability level could be behind such a discrepancy. One should note that the second study also assessed the impact of paired-associative stimulation (peripheral nerve stimulation followed by 5-Hz rTMS) on MEP amplitude and yielded similar findings (i.e., no change in MEP amplitude in fatigued PwMS) (45).

As for TBS, it is worth mentioning that no single study has applied this technique to explore the underlying mechanisms of MS fatigue. Its future application in this context could unveil additional mechanisms incriminated in the generation of this symptom. **Table 1** summarizes the neurophysiological studies that explored MS fatigue.

Treatment of Fatigue in MS Using NIBS

As stated previously, MS fatigue is perceived as a multidimensional construct, thus its management requires a

TABLE 1 | Summary of studies on neurophysiological parameters in MS fatigue.

	Participants	Neurophysiological parameters	Other parameters	Results
Colombo et al. (46)	30 PwMS (15 non-fatigued and 15 fatigued, FSS) Immunomodulant/immunosuppressive drugs: None	MEP of the four limbs	Disability: EDSS Function: Pyramidal functional system score Depression: MADRS	Higher MEP abnormalities in fatigued (n = 5) vs. non-fatigued (n = 1) PwMS Higher lesion loads (parietal lobe, internal capsule, periventricular trigone) in fatigued vs. non-fatigued PwMS Significant association between fatigue scores and MRI lesions burden
Petajan and White (42)	32 PwMS (Classified according to presence or absence of upper extremities weakness) Immunomodulant/immunosuppressive drugs: not provided 10 HC	Evaluation before and after fatiguing exercise of resting and facilitated MEP using TMS (abductor pollicus brevis and flexor carpi radialis)	Exercise-induced changes in energy metabolism (phosphocreatine) measured using 31P magnetic resonance spectroscopy in flexor carpi radialis	Lower peak force, faster decline in force, and prolonged CMCT in PwMS vs. HC Higher MEP amplitude was observed with contralateral hand grip following the fatiguing task in HC and non-fatigued PwMS but not in fatigued PwMS. No group differences in phosphocreatine outcomes.
Romani et al. (47)	60 PwMS (20 fatigued and 40 fatigued, fatigued having FSS scores above the 75th of a previous sample) Immunomodulant/immunosuppressive drugs: None	Evaluation before and after 8-week treatment with 4-aminopyridine and fluoxetine (no placebo control): Somatosensory evoked potentials, TMS, muscle fatigability	Other fatigue measures: FIS Depression: HDRS, BDI Disability: EDSS	At baseline, fatigue test scores consistently correlated with depression and cognitive test scores but not with the fatigability test. Fatigue scores decreased in both treatment groups in a similar way. Due to the design of the study, this cannot be disjoined from a placebo effect. The changes in fatigue scores could not be predicted in the FLX group, whereas in the 4-AP group, higher basal fatigability test scores were associated with a greater reduction in fatigue scores
Perretti et al. (43)	41 PwMS (9 non-fatigued and 32 fatigued Immunomodulant/immunosuppressive drugs: all receiving interferon beta-1a 13 HC	MEP at rest, post-exercise MEP facilitation (PEF), and post-exercise MEP depression (PED)		Reduction in MEP (depression) following fatigue onset in HC but not in PwMS No group difference in post-exercise MEP findings (facilitation) between non-fatigued and fatigued PwMS
Liepert et al. (36)	16 PwMS (8 fatigued and 8 non-fatigued based on FSS (fatigued had FSS $\geq$4) Immunomodulant/immunosuppressive drugs: not provided 6 HC	rMT SICI ICF Three-time measurements in relation to an exercise (repeating hand grip): pre-exercise, postexercise (when rMT was back to the postexercise level), and 15 min later CMAP of the abductor pollicis brevis (following median nerve stimulation) Before and after exercise		At baseline: SICI was lower in fatigued PwMS compared to the other groups After exercise: SICI remained lower in the fatigued group in comparison with their non-fatigued counterparts and HC Fatigue severity correlated with the time required for the rMT to reach the pre-exercise level

(Continued)

TABLE 1 | Continued

	Participants	Neurophysiological parameters	Other parameters	Results
Santarnecci et al. (48)	10 PwMS (fatigue measured using FSS and FIS but not classified according to fatigue scores was performed) Immunomodulant/immunosuppressive drugs: 5 patients receiving β-interferon 10 HC	CSP recorded at the first dorsal interosseus muscle and at the abductor digiti minimi at baseline and after a fatiguing tapping task CSP and fatigue changes before and after chronic amantadine therapy in PwMS	Sleep: ESS Anxiety: Hamilton scale for anxiety Depression: HDRS and BDI	Prior to amantadine therapy: shorter CSP in PwMS vs. HC at baseline and contrasting pattern of CSP changes following fatiguing task in PwMS (increase) and in HC (decrease) After amantadine therapy: • Significant improvement in FSS and marginal improvement in FIS • Normalization of CSP duration in PwMS • Correlation between CSP changes and fatigue improvement (only with FIS, only in the first dorsal interosseus muscle).
Morgante et al. (39)	33 PwMS (17 non-fatigued and 16 fatigued, fatigued had FSS>4) Immunomodulant/immunosuppressive drugs: 32 patients receiving treatments 12 HC	MRI: lesion load TMS: CMCT, SICI, ICF, pre-movement facilitation, and effect of short trains of 5-Hz repetitive TMS	Depression: HDRS	No significant group differences in depression scores Higher frontal lobe LL in fatigued PwMS No significant group difference in SICI/ICF Absence of MEP size increase following repetitive TMS in PwMS compared to HC Lack of pre-movement facilitation in fatigued PwMS vs. non-fatigued PwMS and HC Correlation between pre-movement facilitation abnormalities, frontal LL, and fatigue severity
Scheidegger et al. (49)	23 PwMS Immunomodulant/immunosuppressive drugs: 14 patients receiving the treatment 13 HC	TMS: CMCT by means of the triple stimulation protocol and obtaining central conduction index (CCI) during a fatiguing exercise of the abductor digiti minimi (2 min) followed by recovery (7 min)		No significant group difference in force decline following exercise Less marked CCI decline in PwMS compared to HC No correlation between fatigue scores and CCI or force drop
Russo et al. (40)	24 PwMS (12 non- fatigued and 12 fatigued; fatigued had FSS > 36) Immunomodulant/immunosuppressive drugs: information not provided 10 HC	Motor cortex excitability and the premovement facilitation (PMF) before and after the finger-tapping task		Reduction of correct sequences and the ability to keep a fixed movement rate in fatigued vs. non-fatigued PwMS as well as HC Reduction of post-exercise PMF among fatigued PwMS Correlation between PMF abnormalities and performance decay
Thickbroom et al. (50)	10 PwMS Immunomodulant/immunosuppressive drugs: 9 patients receiving β-interferon 13 HC	MEP amplitudes before and after each cycle of a foot-tapping task	Five cycles of 15 s-foot tapping task followed by 45 min rest period: maximum voluntary contraction of ankle dorsiflexion (at baseline and immediately after the completion of the task) Number of taps Inter tap interval	Increase in MEP amplitudes following exercise in both groups, but more important in PwMS Maximal voluntary contraction is lower in PwMS vs. HC. Decreased maximal voluntary contraction after exercise in both groups but more important in PwMS. No difference was found in the tapping rate.

(Continued)

TABLE 1 | Continued

	Participants	Neurophysiological parameters	Other parameters	Results
Conte et al. (45)	25 PwMS (13 non-fatigued and 12 fatigued based on MFIS (i.e., details NP) Immunomodulant/immunosuppressive drugs: patients receiving treatment (without further information) 18 HC	Experimental conditions (relaxed vs. attention): 5-Hz repetitive TMS and paired associative stimulation while focusing attention on the hand contralateral to the stimulated motor cortex		Absence of attention-induced MEP increase using both techniques in fatigued PwMS compared to non-fatigued patients Correlation between attention-induced repetitive-TMS related changes and fatigue severity (mostly physical subscale)
Russo et al. (41)	30 PwMS (non-fatigued and fatigued based on FSS (i.e., fatigued patients had FSS $\geq$4) Immunomodulant/immunosuppressive drugs: information not provided	Pre movement facilitation	DTI study	Significant difference in premovement facilitation between fatigued and non-fatigued groups Significant correlation between fatigue scores and mean diffusivity in bilateral fronto-thalamic connections
Chaves et al. (51)	82 PwMS Immunomodulant/immunosuppressive drugs: 47 patients receiving treatment	Bilateral aMT and rMT Then ratios were calculated between weaker and stronger side aMT and rMT (Weaker and stronger sides were defined according to performance on pinch and hand grip)	Disability: EDSS Dexterity: 9HPT Cognition: SDMT Walking speed: instrumented walkway Heat sensitivity: VAS Fatigue: VAS Pain: VAS Subjective impact of MS: MSIS-29	Higher excitability in the hemisphere controlling the weaker side Shifting of this asymmetry (i.e., lower excitability in the hemisphere responsible for the weaker side) predicted more severe MS related symptoms and may hint toward a neurodegenerative process
Chaves et al. (38)	82 PwMS Immunomodulant/immunosuppressive drugs: 48 patients receiving treatment	Bilateral aMT, rMT and CSP	Fatigue: VAS Exercise test inflammatory cytokines: TNF	Poor fitness was found in the majority of patients. A link seems to exist between fitness level and CSP (i.e., low level predicted longer CSP) and between CSP and fatigue.
Mordillo-Mateos et al. (35)	17 PwMS Immunomodulant/immunosuppressive drugs: 11 patients receiving treatment 16 HC	CMAP and F wave of right and left first dorsal interosseous muscles (after ulnar nerve stimulation) rMT, MEP amplitude latency (at 120% rMT) and CMCT of above-mentioned muscles These parameters were measured before, immediately, one and two minutes after the fatiguing task	Fatigue: FSS Fatigue: BRPES Motor performance: maximal hand grip, and motor decay	At baseline: lower CMAP and MEP, higher RMT, longer CMCT and higher fatigue scores in PwMS compared to HC Task performance: lesser handgrip strength in PwMS compared to HC In PwMS, fatigue shown to be independent from handgrip strength; fatigue shown to be independent from CMCT
Chalah et al. (37)	38 PwMS [17 non-fatigued and 21 fatigued based on MFIS (i.e., Fatigued: MFIS $\geq$ 45)] Immunomodulant/immunosuppressive drugs: 19 patients receiving treatment	rMT CSP SICI ICF IHI	Neuropsychological parameters: Anxiety and Depression: HADS Excessive Daytime sleepiness: ESS Cognition: SDMT Alexithymia: TAS Neuroradiological measures (Volume based morphometry)	Higher SICI in fatigued patients compared to their non-fatigued counterparts. Fatigued patients also showed higher HADS and TAS scores, as well as larger caudate nuclei and smaller left parietal cortex.

(Continued)

TABLE 1 | Continued

	Participants	Neurophysiological parameters	Other parameters	Results
Coates et al. (34)	26 PwMS (13 non-fatigued and 13 fatigued based on FSS (i.e., fatigued: FSS $\geq$ 4 and MFIS $\geq$ 34) Immunomodulant/immunosuppressive drugs: some patients receiving treatment (without further information) 13 HC	Central parameters: MEP amplitude and latency, CSP Peripheral parameters: femoral nerve electrical stimulation Measured at baseline and every 3 min throughout cycling during of a step test until reaching volitional exhaustion	Clinical parameters: Depression: CES-D Sleep quality: PSQI Quality of life: MSQoL-54 Perceived activity level: GLTEQ Peripheral pro-inflammatory cytokines Axial panoramic ultrasound for knee extensor cross-sectional area, actigraphy (sleep and rest-activity cycles)	Significant worse depression, sleep and quality of life scores in fatigued PwMS compared to the other groups; no group difference in actigraphy, maximal aerobic capacity and perceived activity level Higher interleukin 8 in fatigued PwMS compared to HC During cycling: No time or interaction effect was observed for MEP amplitude or latency. Reduction in CSP compared to baseline in fatigued PwMS compared to the other groups At volitional exhaustion: • Reduced MEP amplitudes and prolonged MEP latencies in fatigued PwMS; loss of group differences in CSP • Higher decline in maximal voluntary contraction force and potentiated twitch force in fatigued PwMS Regression analysis: Prolonged MEP latency, increased peripheral muscle fatigability and depression scores were significant predictors of fatigue severity

aMT, active Motor Threshold; BDI, Beck Depression Inventory; BRPES, Borg Rating of Perceived Exertion Scale ; CES-D, Center for Epidemiologic Studies Depression Scale; CMAP, compound Motor Action Potential; CMCT, Central Motor Conduction Time; CSP, cortical silent period; DTI, Diffuse Tensor Imaging; EDSS, Expanded Disease Severity Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; GLTEQ, Godin-Leisure-Time- Exercise Questionnaire; HADS, Hospital Anxiety and Depression Scale ; HDRS, Hamilton Depression Rating Scale; 9HPT, Nine Hole Peg Test; HC, Healthy Controls; IHI, Interhemispheric Inhibition; ICF, Intracortical Facilitation; MEP, Motor Evoked Potential; MFIS, Modified Fatigue Impact Scale; MSIS 29, Multiple Sclerosis Impact Scale; MSQoL-54, Multiple Sclerosis Quality of Life-54; MS, Multiple Sclerosis; PSQI, Pittsburgh Sleep Quality Index; PwMS, Patients with Multiple Sclerosis; rMT, resting Motor Threshold; SDMT, Symbol Digit Modalities Test; SICI, Short-Interval intracortical Inhibition; TAS, Toronto Alexithymia Scale; TMS, Transcranial Magnetic Stimulation; TNF, Tumor Necrosis Factor; VAS, Visual Analog Scale.

personalized strategy that should address each of its dimensions. In this setting, various therapeutic interventions have been tried including pharmacological and non-pharmacological approaches. Concerning the pharmacological solutions, there is a vast array of literature on this topic, with numerous molecules being tested over the last years and only few having benefited from an in-depth evaluation. This includes amantadine hydrochloride, modafinil, pemoline, carnitine, and potassium channels blockers. Although all these drugs have demonstrated promising results in some studies, other works have failed to document any amelioration of fatigue and have thus questioned their place in the management of this symptom. Moreover, in a recent randomized, placebo-controlled, double-blind trial that compared the effects of amantadine, modafinil, and methylphenidate on MS fatigue, the studied drugs were not significantly superior to placebo in terms of efficacy and engendered more frequent adverse effects (52). Description of the mechanisms of action of these drugs and results of the corresponding studies falls outside the scope of this review [for more details, please refer to (1)].

In what concerns non-pharmacological alternatives, numerous therapies have been assessed so far and have led to some encouraging results, as has been demonstrated with exercise, whole body cryostimulation (53), cognitive behavioral therapies (CBT) (54), and NIBS (55). As mentioned in the introduction, in this review, we will only focus on the latter techniques (i.e., NIBS), the remaining does not match the main purpose of the current review.

As stated previously, tDCS is a NIBS technique that relies on the administration of a feeble electric current through two saline-soaked sponge electrodes, an anode and a cathode, placed on the scalp and connected to a battery-driven stimulator (28). The choice of the electrodes' place and polarity depends on the intended effects. This approach has been shown to be beneficial in several neurological and psychological problems, such as neuropathic pain, anxiety, and depression, to set a few. Therefore, its application in PwMS, and particularly in the context of fatigue, has been the focus of several research teams. The majority of studies that assessed the effects of tDCS on subjective or perceived self-reported MS fatigue adopted a crossover randomized (or pseudorandomized) design, were double-blinded and sham-controlled, and consisted of applying an anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC), the right posterior parietal cortex, the bilateral sensorimotor cortex, the bilateral motor, or the bilateral primary somatosensory cortex. The current used was of weak intensity, ranging from 1.5 to 2 mA; and the session duration varied between 15 and 20 min. While results from bilateral somatosensory cortex/bilateral motor cortex stimulation were encouraging (56–59); those of left DLPFC were controversial, with two studies showing negative results (60, 61) and two others documenting positive outcomes (62, 63). Such a discrepancy seems to be due to the difference in the current intensity [current intensity: 1.5 mA in (60) vs. 2 mA in (62, 63)] and the number of stimulation sessions [3 in (61) and 5 in (62, 63)] across the abovementioned studies. This point of view could be supported by the data of a recent work where robust anti-fatigue effects were seen after the left DLPFC and left M1 stimulation, with more lasting fatigue reduction observed following the former condition (64).

As for the posterior parietal cortex (62) and the bilateral sensorimotor cortex (of hand area) (57), results should be interpreted with caution since they are based on two studies only, and further investigations are needed before drawing any formal conclusion.

Regarding fatigability, cognitive and motor fatigability have been investigated in three studies, two of them tested the impact of one anodal session [over the right parietal cortex in (65) and over the left DLPFC in (66)] on cognitive performance during a particular task [visual task in (65), and measurement of P300 in (66)] and one work assessed the effects of 5 consecutive anodal sessions over M1 on a cluster of symptoms including pain, subjective fatigue, and motor fatigability (67). It has been shown that delivering anodal stimulation over the left DLPFC or the right parietal cortex could counteract cognitive fatigability and prevent decrement in cognitive performance (reflected by prolonged reaction time). On the other hand, anodal stimulation of M1 would result in a decrease in motor fatigability (of the contralateral leg), as well as an amelioration of subjective fatigue and pain.

All the previously reported studies have addressed the short-lasting effects of tDCS and its feasibility over a short period of time (sessions were performed over 1 or 2 weeks). However, to suggest this innovative technique as a therapeutic solution for PwMS, we need to maintain its effectiveness over time; such maintenance requires repetition of the sessions, and this has been addressed in some case studies where sessions (14–19 sessions) were repeated over 4 weeks and ensured a long-term reduction of fatigue and amelioration of cognitive functions as well as the mood state (68, 69).

Although the results of these trials are interesting, a limitation should be considered. In fact, health providers are dealing with a fragile population, thus suggesting to this population that recurrent traveling to the care facilities is a real challenge. Often, these patients are either disabled and/or have a busy personal or professional schedule, which should be taken into consideration. Hence, the best solution would be by organizing a home-based therapy. The feasibility and efficacy of the latter have been tested by Charvet et al., and it has been documented that remotely supervised tDCS sessions are safe, could be coupled with computer-based cognitive training programs, and would help in alleviating fatigue and improving cognitive performance (70).

Besides tDCS, other neuromodulation approaches have been also tried in the setting of MS fatigue. However, the literature is limited to few studies. Two of them have explored the potential role of transcranial random noise stimulation (tRNS) in the treatment of fatigue and three of them have evaluated the place of rTMS or TBS in this context.

Transcranial random noise stimulation yielded beneficial antifatigue effects in one study (71) but not in the other one (72). Compared to Palm and colleagues, Salemi and colleagues had a different study design (crossover vs. parallel arms, respectively),

TABLE 2 | Summary of NIBS studies in MS fatigue.

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
tDCS studies											
Ferrucci et al. (59)	25 *(22 RR, 3 SP)* Immunomodulant/immunosuppressive drugs: patients receiving treatment continued taking them during the study (without further information)	MFIS > 45 EDSS < 6.5	Crossover double-blind, sham-controlled	Yes	1 month	5 consecutive daily sessions	Bilateral M1	Anode: C3 and C4 Cathode right deltoid	1.5 mA and 20 min	FIS	Significant fatigue reduction up to 3 weeks after the last active stimulation session
Saiote et al. (60)	25 *(RR)* Immunomodulant/immunosuppressive drugs: 10 patients receiving treatment	FSS ≥ 4 EDSS ≤ 6	Crossover, double-blind, sham controlled	Pseudo randomization	2 weeks	5 consecutive daily sessions	Left DLPFC	Anode: F3 Cathode: contralateral forehead	1.5 mA and 20 min	MFIS, FSS, MS-SF	Absence of fatigue improvement
Tecchio et al. (56)	10 *(7 RR, 1 SP, 2 PP)* Immunomodulant/immunosuppressive drugs: Information NP	MFIS > 38 EDSS ≤ 3.5	Crossover, double-blind, sham controlled	Yes	Please refer to #	5 consecutive daily sessions	Bilateral whole body S1	Anode: personalized Cathode: Oz	1.5 mA and 15 min	MFIS	Significant decrease in fatigue scores up to 2 months following active condition. [The effects lasted up to 9.6+/- 3.6 weeks after the active condition (vs. 4.8+/- 1.8 weeks following sham condition)]

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Tecchio et al. (57)	21 *(RR)* Immunomodulant/immunosuppressive drugs: Information NP	Physical subscore of MFIS > 15 EDSS ≤ 3	Crossover, double-blind, sham-controlled	Yes	Please refer to #	5 consecutive daily sessions	Bilateral whole body S1 vs. bilateral hand SM area	Anode: personalized Cathode: Oz (S1 condition) vs. under the chin (SM condition)	1.5 mA and 15 min	MFIS	Significant decrease in fatigue scores following active S1 condition (no changes after SM condition)
Hanken et al. (65)	Study 2: 46 *(18 RR, 28 SP)* Immunomodulant/immunosuppressive drugs: 67% receiving the treatment	NP	Parallel groups, double-blind, sham-controlled	Yes	NA	1 session before the performance of a visual vigilance task	Right parietal cortex	Anode: P4 Cathode: left forehead	1.5 mA and 20 min	RT on a visual vigilance task	Anodal right parietal stimulation counteracts the vigilance decrement. This effect was only observed in the setting of mild to moderate cognitive fatigue (and not in case of severe cognitive fatigue)

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Ayache et al. (68)	16 *(11 RR, 4 SP, 1 PP)* Immunomodulant/immunosuppressive drugs: 13 patients receiving treatments	VAS (pain) > 4	Crossover, double-blind, sham controlled	Yes	3 weeks	3 consecutive daily sessions	Left DLPFC	Anode: F3 Cathode: AF8	2 mA and 20 min	MFIS	No effects on fatigue (It is important to mention that fatigue was assessed as a secondary outcome)
Chalah et al. (62)	10 *(8 RR, 1 SP, 1 PP)* Immunomodulant/immunosuppressive drugs: 10 patients receiving treatments	FSS > 5 EDSS ≤ 6.5	Crossover, double-blind, sham controlled	Yes	3 weeks	5 consecutive daily sessions	Left DLPFC vs. Right PPC	Anode: F3 Cathode: AF8 vs. Anode: P4 Cathode: Cz	2 mA and 20 min	MFIS, FIS and VAS	Significant fatigue reduction was obtained after left prefrontal cortex anodal stimulation but not after right parietal stimulation. Long-term effects were not assessed
Charvet et al. (70)	Study 1: 35 (20% RR in active arm, 75% RR in control arm) Study 2: 27 (40% RR in active arm, 58% RR in sham arm) Immunomodulant/immunosuppressive drugs: information NP	SDMT (z score) ≥ −3 EDSS?6.5	Study 1: open label Study 2: parallel groups, double-blind, sham-controlled	Study 1: no Study 2: yes	NA	Study 1: 10 sessions§ Study 2: 20 sessions§ (Remotely supervised sessions, administered at home daily, 5 days per week)	Left DLPFC	Anode: left prefrontal cortex Cathode: right prefrontal cortex (Exact position not precised)	Study 1: 1.5 mA and 20 min Study 2: 2 mA and 20 min (Intensity was set at 1.5 mA if 2 mA was not tolerated)	PROMIS FSS VAS	Study 1: no effect on fatigue Study 2: significant fatigue reduction which was more evident in patients with higher fatigue scores

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Fiene et al. (66)	15 *(14 RR, 1 SP)* Immunomodulant/immunosuppressive drugs: All patients receiving treatments	WEIMuS ≥ 9	Crossover, single blind, sham controlled	Yes	1 week	1 session	Left DLPFC	Anode: F3 Cathode: right shoulder	1.5 mA and 27–28 min	VAS Simple RT P300 components (latency & amplitude)	Active stimulation session counteracted cognitive fatigue and prevented any decrease in task performance (reflected by an increase in P300 amplitude and a stabilization of the RT)
Cancelli et al. (59)	10 *(types NP)* Immunomodulant/immunosuppressive drugs: information NP	MFIS >35 EDSS ?2	Crossover, double-blind, Sham-controlled, study	Yes	Please refer to #	5 consecutive daily sessions	Bilateral whole body S1	Anode: personalized Cathode: Oz	1.5 mA and 15 min	MFIS	Significant fatigue reduction following active stimulation.

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Chalah et al. (63)	11 *(10 RR, 1 SP)* Immunomodulant/immunosuppressive drugs: 9 patients receiving treatments	FSS > 5 EDSS < 6.5	Crossover, double blind, sham-controlled study	Yes	3 weeks	5 consecutive daily sessions	Left DLPFC	Anode: F3 Cathode: F4	2 mA and 20 min	FSS and MFIS	Significant fatigue reduction (i.e., a decrease of MFIS scores) that persisted up to 1 week following the last active stimulation session
Mortezanejad et al. (64)	*32 (types NP)* Immunomodulant/immunosuppressive drugs: information NP	FSS > 5 EDSS < 4	Parallel groups, double blind, sham controlled	Pseudo randomized	NA	6 sessions (3 sessions per week over two consecutive weeks, sessions were administered every other day)	Left DLPFC vs. Left M1	For left DLPFC stimulation, anode over F3 and cathode over the contralateral supraorbital area For the left primary cortex, anode over C3 and cathode over C4	1.5 mA and 20 min	FSS	Significant fatigue reduction after active left DLPFC and after left M1 conditions. Only left DLPFC anodal stimulation led to long-lasting effects (up to 4 weeks following the last stimulation session)

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TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Workman et al. (67)	6 (RR) Immunomodulant/immunosuppressive drugs: information NP	NA	Crossover, double blind, sham-controlled study	Yes	NP	5 daily consecutive sessions	Left M1	Anode: M1 representation of the more-affected leg Cathode: contralateral supraorbit	2 mA and 20 min	MFIS Motor task VAS (pain)	Improvement of fatigability, reduction of fatigue, and amelioration of pain
tRNS studies											
Palm et al. (72)	16 *(11 RR, 4 SP, 1 PP)* Immunomodulant/immunosuppressive drugs: 13 patients receiving treatments	VAS (pain) > 4	Crossover, double blind, sham-controlled study	Yes	3 weeks	3 consecutive daily sessions	Left DLPFC	Anode: F3 Cathode: AF8	2 mA, random frequencies range 0–500 Hz and 20 min	MFIS	No effects on fatigue (It is important to mention that fatigue was assessed as a secondary outcome)

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Salemi et al. (71)	17 (RR) Immunomodulant/immunosuppressive drugs: 13 patients receiving treatments	MFIS >20 EDSS ≤4.5	Parallel, single-blind, sham-controlled study	Yes	NA	10 sessions (5 consecutive daily sessions per week over 2 consecutive weeks)	M1 of the dominant side or contralateral to the most affected limb	C3 + FP2 or C4 + FP1	1.5 mA, random frequencies range 100–640 Hz and 15 min	MFIS	Significant fatigue reduction after the last session
rTMS studies											
Gaede et al. (74)	28 (26 RR, 2 SP)	FSS ≥ 4 EDSS between 0 and 6	Parallel, semi-blind, sham-controlled study	Yes	NA	18 sessions (3 sessions per week over 6 weeks)	Left prefrontal cortex or bilateral M1	Left prefrontal cortex: H coil 5 cm anterior to the left motor hot spot parallel to the sagittal suture M1: center of the H coil-over M1	Left prefrontal cortex: 120% rMT, 18 Hz, 50 trains (train duration 2 s, ITI 20 s), 1,800 stimuli, 18 min M1: 90% rMT, 5 Hz, 40 trains, bursts of 20 stimuli, ITI 20 s, 800 stimuli, 16 min	FSS	Significant fatigue reduction mostly following M1 stimulation that lasted over 6 weeks

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Korzhova et al. (75)	34 (SP) Immunomodulant/immunosuppressive drugs: None	Modified Ashworth Scale ≥ 2 at the knee joint	Parallel, double-blind, sham-controlled study Concomitant physical therapy	Yes	NA	10 sessions (5 consecutive daily sessions per week over 2 consecutive weeks)	Bilateral M1	Figure of eight coils positioned using neuronavigation over bilateral M1	rTMS: 80% rMT, 20 Hz, stimulation 2 s and ITI 28 s, 1,600 stimuli, 30 min	MFIS	Significant fatigue reduction
Mori et al. (73)	30 (RR) Immunomodulant/immunosuppressive drugs: information NP (not modified 2 months prior and during the study)	EDSS between 2 and 6 Presence of lower limb spasticity	Parallel, double blind, sham-controlled study: • iTBS alone • iTBS + exercise therapy • Sham stimulation + exercise therapy	Yes	NA	10 sessions (5 consecutive daily sessions per week over 2 consecutive weeks)	M1 leg area contralateral to the affected limb	Figure of 8 coils positioned over the optimal site evoking MEP on the contralateral soleus muscle vs. 1 cm ahead and 1 cm lateral to CZ if no detectable MEP at any leg	80% aMT, 5 Hz, 10 bursts, three stimuli per burst at 50 Hz, repeated at 5 Hz, 600 stimuli, 200 s	FSS	Significant fatigue improvement following iTBS combined with exercise therapy, but not following iTBS alone (It is worth noting that fatigue was a secondary outcome)

(Continued)

TABLE 2 | Continued

	Participants	Inclusion criteria	Design	Randomization	Washout interval	Number of stimulation sessions	Stimulation site	tDCS/tRNS electrodes* or rTMS/iTBS coil position	Stimulation parameters and session duration	Fatigue measures	Results
Korzhova et al. (75)	34 (SP) Immunomodulant/immunosuppressive drugs: None	Modified Ashworth Scale ≥ 2 at the knee joint	Parallel, double-blind, sham-controlled study Concomitant physical therapy	Yes	NA	10 sessions (5 consecutive daily sessions per week over 2 consecutive weeks)	Bilateral M1	Figure of eight coils positioned using neuronavigation over bilateral M1	iTBS: 80% rMT, 5 Hz, 10 bursts, three stimuli per burst at 35 Hz, repeated at 5 Hz, 1,200 stimuli, 10 min	MFIS	No changes in fatigue
Tramontano et al. (76)	16 (9 SP, 7 progressive relapsing) Immunomodulant/immunosuppressive drugs: information NP	EDSS between 4.5 and 6.5 Modified Ashworth scale ≤ 1 at the leg	Parallel, double-blind, sham-controlled study Concomitant exercise-based vestibular rehabilitation	Yes	NA	10 sessions (5 consecutive daily sessions per week over 2 consecutive weeks)	Bilateral cerebellum	Figure of eight coils over the left and right cerebellum	Two runs of iTBS over both the right and left cerebellum separated by a 5 min interval	FSS	Significant fatigue reduction following iTBS (It is worth noting that fatigue was a secondary outcome)

aMT, active Motor Threshold; DLPFC, Dorsolateral Prefrontal Cortex; EDSS, Expanded Disability Status Scale; iTBS, intermittent Theta Burst Stimulation; ITI, Intertrain Interval; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; M1, Primary Motor Cortex; MEP, Motor Evoked Potentials; MFIS, Modified Fatigue Impact Scale; MS-SF, Multiple Sclerosis-Specific Fatigue Scale; NA, Not Applicable; NP, Not Provided; PP, Primary Progressive; PPC, Posterior Parietal Cortex; PROMIS, Patient-Reported Outcomes Measurement Information System; rMT, resting Motor Threshold; RR, Relapsing Remitting; RT, Reaction Time; rTMS, repetitive Transcranial Magnetic Stimulation; S1, Primary Somatosensory Cortex; SM, Sensorimotor; SP, Secondary Progressive; tDCS, transcranial Direct Current Stimulation; VAS, Visual Analog Scale. WElMuS, Würzburger Fatigue Inventory for MS.

**Electrodes position is defined according to 10–20 EEG international system.*

#Washout is considered completed when half of the tDCS effect is lost (i.e., in fact, MFIS was obtained each week following the last session of each block, when the MFIS increment met the criteria of the following formula: $\frac{MFIS\ (washout\ time) - MFIS(before\ fisrt\ session)}{MFIS\ (before\ fisrt\ session)} < 0.5\ (\frac{MFIS\ (after\ the\ last\ session) - MFIS(before\ fisrt\ session)}{MFIS\ (after\ the\ last\ session)})$*; it reflected the end of the washout period, the second block could then be administered).*

§Sessions were combined with a computer-based cognitive training program.

Case reports are not included in this table.

applied a larger number of sessions (3 vs. 10, respectively), and targeted a different cortical site (left DLPFC vs. M1 of the dominant side or contralateral to the most affected limb, respectively).

Transcranial random noise stimulation/theta burst stimulation studies targeted different cortical sites and were applied alone or in combination with exercise or physical therapy. Some of these studies suggested promising findings that are worth replicating in future trials (73–76). Briefly, with regards to rTMS, 10–18 sessions applied at 5–20 Hz over M1 bilaterally, with or without physical therapy, resulted in significant fatigue reduction (74, 75). As for TBS, the existing literature on the matter consisted of iTBS protocols. Ten sessions of such intervention, combined with exercise or physical therapy, did not significantly affect fatigue when applied over the cerebellum or M1 bilaterally (75, 76) but yielded antifatigue effects when applied over M1 contralateral to the most spastic limb (73). The latter protocol applied without concomitant exercise did not significantly reduce fatigue compared to the sham (73). Here, it is worth stating that the considered iTBS studies primarily focused on MS spasticity, fatigue being included as a secondary outcome. Therefore, the effects of iTBS on primary MS fatigue merit to be further addressed. Details of NIBS application in MS fatigue are presented in **Table 2**.

CONCLUSION

This review explored the potential role of neurophysiology in the exploration and modulation of fatigue in PwMS. First, in terms of pathophysiology, the available studies that included intracortical excitability and corticospinal excitability outcomes yielded inconsistent findings. For instance, while fatigue was correlated with SICI/CSP (GABA-mediated outcomes) in some studies, such a correlation was not found in other studies. The included studies were cross-sectional; they assessed fatigue using different scales and included PwMS suffering from different disease subtypes. This highlights the relevance of longitudinally studying the dynamics of these parameters across the disease course and subtypes and their relationships with fatigue. In addition, considering secondary factors to fatigue and taking into consideration the symptom cluster in the covariate analysis would also be of help (3). Besides tackling the previously mentioned differences (subjected or perceived self-reported fatigue vs. fatigability, primary vs. secondary), the temporal dimension of fatigue merits to be considered. In this perspective, Palotai and colleagues longitudinally assessed PwMS and suggested different types of fatigue (sustained fatigue vs. one time-point fatigue vs. reversible fatigue), which seem to differ in brain imaging findings (brain parenchymal fraction, T2 lesion volume) (77), a finding that might also apply to corticospinal excitability parameters.

Second, in terms of tDCS, the data altogether suggest promising tDCS effects obtained on MS fatigue. The current challenge remains to find the best parameters to optimize treatment effects (e.g., applying a higher number of sessions, selecting the best cortical target, selecting the best return electrode location, designing patient-tailored electrodes, increasing the current intensity up to 4 mA) (56, 57, 68, 69, 78). As stated with neurophysiological exploration, it would be helpful to consider the temporal dynamics of fatigue and the symptom cluster when assessing the mediators of response to tDCS. It is noteworthy that, when it comes to either exploring or modulating MS fatigue using NIBS techniques, a confounder that needs to be considered or accounted for is the pharmacological profile of the recruited cohorts. For instance, some medications (e.g., disease-modifying therapies, symptomatic treatments) might modify the corticospinal excitability in PwMS (79). In addition, some treatments (e.g., sodium channel blockers, calcium channel blockers, medications that act on neurotransmitters pathways) may also affect the tDCS effects on corticospinal excitability (80). The relationship between the treatment status and the considered outcomes (e.g., SICI, ICF, IHI, CSP, or fatigue improvement) warrants further investigation since this was rarely or not tackled in previous studies.

Third, studying the effects of tDCS on corticospinal excitability would provide further insights into the neurophysiological mechanisms of fatigue and the antifatigue mechanisms of action of tDCS (57, 68).

Finally, home-based tDCS will provide a solution for physically disabled PwMS. The application of psychotherapies (e.g., CBT-based online interventions) and pharmacotherapy might yield synergistic effects (81). Such an approach constitutes a domain that remains to be explored in this context.

AUTHOR CONTRIBUTIONS

SA and MC: conceptualization and methodology. MC, NS, GA, and SA: data analysis, writing—original draft preparation, and writing—review and editing. SA: supervision. All authors have read and agreed to the published version of the manuscript.

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Instrumented Assessment of Motor Performance Fatigability During the 6-Min Walk Test in Mildly Affected People With Multiple Sclerosis

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There are conflicting results regarding the changes in spatio-temporal gait parameters during the 6-min walk test (6MWT) as indicators of gait-related motor performance fatigability (PF) in people with Multiple Sclerosis (pwMS). To further analyze if gait-related motor PF can be quantified using instrumented gait analysis during the 6MWT, we investigated: (i) whether gait parameters recorded during the first or second minute were more stable and thus the better baseline to assess motor PF and (ii) if the minimum toe clearance (MTC) together with "classical" spatio-temporal gait parameters can be used to quantify motor PF in pwMS. Nineteen mildly affected pwMS [12 women/7 men; 47.8 ± 9.0 years; the Expanded Disability Status Scale (EDSS): 2.7 ± 1.0] and 24 healthy controls (HC; 15 women/9 men; 48.8 ± 7.6 years) completed the 6MWT equipped with inertial measurement units. Data were analyzed using the attractor method to compare the stability of gait parameters and, besides "classical" spatio-temporal gait parameters, the MTC was calculated as a potential new marker for motor PF in pwMS as this was shown in healthy older adults. It was found that (i) gait parameters were more stable in the second than in the first minute and (ii) gait-related motor PF could not be detected based on spatio-temporal gait parameters, including the MTC. Descriptive analysis indicated a decrease in MTC variability, which is assumed to be indicative for motor PF, toward the end of the 6MWT in some pwMS. Future studies should investigate gait parameters for the assessment of motor PF in pwMS recorded during more intense and/or longer walking protocols, taking the level of disability into account. Furthermore, using gait parameters recorded in the first minute of the 6MWT as a baseline for the assessment of motor PF should be avoided.

Keywords: MS, fatigue, attractor method, minimum toe clearance, gait kinematics

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INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune inflammatory neurodegenerative disease with diverse symptoms that depend on the lesion site. The disease is often accompanied by motor deficits (1) and fatigue (2) that limit locomotion and quality of life. Over 75% people suffer from fatigue and 40% of people with MS (pwMS) report that this is the most limiting symptom (2). Based on

the definition of Kluger et al. (3) and Enoka and Duchateau (4), fatigue can be assessed either as a trait or a state characteristic. While trait fatigue describes the fatigue perceived by an individual over a longer period of time, state fatigue refers to the acute and temporary change in motor and/or cognitive performance (performance fatigability/PF) and various perceptions that emerge during a defined sustained motor and/or cognitive task (perceived fatigability).

The extent of motor PF induced by motor tasks is determined by changes in the muscle activation characteristics and the contractile function of the involved muscles. Perceived fatigability during motor tasks depends on the psychological status of an individual and the homeostatic perturbations induced by the motor task (4).

There are a variety of methods to quantify motor PF in pwMS but currently, no gold standard exists. Several exercise models were used to assess motor PF in pwMS, which were recently summarized by Severijns et al. (5) and van Geel et al. (6). They have shown that single-joint exercises and physical activities, such as walking, which are close to activities of daily life, were used to induce motor PF. For the latter approach, the 6-min walk test (6MWT) is frequently used (5, 6). However, studies using this paradigm reported discrepant results regarding the discriminative value for the assessment of motor PF in pwMS. In this regard, some studies have focused on the walking velocity (e.g., distance walked index/DWI (7) or deceleration index) (8). A recently published study by Shema-Shiratzky et al. demonstrated that walking velocity did not change significantly across the 6MWT and is thus of limited relevance as a standalone marker for the quantification of motor PF in pwMS. Moreover, they suggested that other kinematic parameters, such as cadence, stride time variability, and gait complexity (sample entropy of the 3D acceleration and gyroscope data), might be more appropriate for this purpose (9).

Besides these variables, a promising spatial gait parameter to quantify gait-related motor PF has not yet been investigated during the 6MWT in pwMS, i.e., the minimum toe clearance (MTC) and its variability. The MTC describes the minimum vertical toe to ground distance in the mid-swing phase (10) and is related to the risk of falling (11). If it approaches zero, the probability of tripping is very high. The MTC variability is able to differentiate between different populations, e.g., young and elderly and fallers and non-fallers (11, 12). A study by Nagano et al. has demonstrated that the MTC variability becomes smaller during prolonged walking in contrast to the variability of step width in older adults. Therefore, it was assumed that the MTC seems to be prioritized with increasing motor PF to reduce the risk of falling (13). Since the hip flexors are weaker (14) and the toe height is increased during treadmill walking in pwMS when compared to healthy individuals (15), it is conceivable that the MTC is sensitive to motor PF in pwMS as shown for healthy older adults (13).

However, the existing approaches have mostly used the first minute of walking (except the deceleration index) as a baseline to quantify gait-related motor PF. This might not be favorable, since people start from a standing position and gait initiation has a high impact on gait measures during the initial meters walked (16). Furthermore, it is known that dynamic cyclic systems, such as running and walking, need a certain time to become stable (transient effect) (17). To evaluate the gait stability, the attractor method introduced by Vieten et al. can be applied (18). According to Newell et al. "Attractors represent equilibrium regions in the geometric space (called state space) that are formed by the relevant variables describing the movement dynamic [. . .]." (19). The stability of cyclic movements, such as walking, can be described by limit-cycle attractors (18), which are "[. . .] a regular oscillation to which all trajectories converge [. . .]" (19).

In summary, gait parameters for quantifying motor PF during walking in pwMS are controversially discussed and there is no agreement about the most indicative parameter or combination of parameters (6). Moreover, it is not clear whether the second minute is more appropriate as the reference baseline for quantifying gait-related motor PF than the first minute of the 6MWT.

Therefore, the aim of this study was to investigate (i) the gait stability during the first 2 min of the 6MWT using the attractor method and (ii) if the MTC and its variability together with classical spatio-temporal gait parameters can be used to quantify gait-related motor PF over the course of the 6MWT in mildly affected pwMS. We expected that gait parameters are more stable in the second minute than in the first one. Furthermore, we assumed that spatio-temporal gait parameters deteriorate over the course of the 6MWT and that the MTC is prioritized (decreased variability), indicating motor PF in mildly affected pwMS.

MATERIALS AND METHODS

Participants

For this cross-sectional study, 19 pwMS and 25 healthy controls (HC) with similar age and sex were included. All pwMS had a confirmed MS diagnosis according to the revised McDonald criteria (20). For inclusion in the study, subjects should be able to walk 300 m without a walking aid and the Expanded Disability Status Scale (EDSS) (21) should not be > 4.5. Furthermore, the last acute episode and the last dose of cortisone should be taken at least 1 month ago. The exclusion criteria for the HC and pwMS were orthopedic, cardiovascular, and neurological diseases with the exception of MS. The Ethics Committee of the Medical Faculty of the Otto von Guericke University (OvGU) Magdeburg (Germany) approved the study (no.: 116/18).

Study Procedure

The study was conducted at the Kliniken Schmieder Konstanz (Germany) in cooperation with the OvGU Magdeburg (Germany). The pwMS were recruited by health professionals at the beginning of their rehabilitation. The HC were recruited from local citizens. In a first interview, the participants were informed about the study, and written informed consent was obtained. To assess the perceived MS-induced walking disability, the pwMS filled out the German version of the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) (22). Trait fatigue was documented with the Fatigue Scale for Motor and Cognitive function (FSMC) (23). Gait analysis was performed using two inertial

measurement units (sampling frequency 120 Hz) (MTw, Xsens Technologies B.V., Netherlands) placed dorsally at each foot (24). For the attractor-based gait analysis, continuous walking was needed so that the 6MWT was performed on a circular oval quite corridor at the clinic with a fixed circumference of 34 m. The subjects should walk as fast as possible but safely and were accompanied by a physiotherapist. No walking aid was used. Every minute was announced loudly by the test instructor. Ratings of perceived exhaustion (RPE) on a Borg scale (25) (6: no exhaustion, 20: maximal exhaustion) were recorded before and after the 6MWT to quantify perceived fatigability.

Gait Data and Processing

To determine which minute of the 6MWT is more stable, the non-linear limit-cycle attractors were calculated utilizing the 3D acceleration and rotation data of the feet for each minute. The outcome parameters were the relative difference between two limit-cycle attractors [δM (1/s)], the relative difference between the variability of two limit-cycle attractors [δD (m/s^2)], and the absolute variability [D (m/s^2)] of each minute. In this study, the second minute was compared with the other minutes of the 6MWT: $\delta M/\delta D_{2vs1min}$, $\delta M/\delta D_{2vs3min}$, $\delta M/\delta D_{2vs4min}$, $\delta M/\delta D_{2vs5min}$, and $\delta M/\delta D_{2vs6min}$. The equations are described in the study by Vieten et al. (18).

To assess motor PF over the 6MWT, the following spatio-temporal gait parameters were calculated for each minute: stride length, stride, stance and swing time, gait velocity, the MTC, and the respective variability [coefficient of variation/CV (%): standard deviation (SD)/mean × 100]. Gait parameters were calculated according to the algorithm of Hamacher et al. (24) based on 3D rotation and acceleration data of the feet. The first 2.5 m of the 6MWT were not considered to reduce the impact of gait initiation. Derived from the gait velocity, the walking distance per minute was constructed to calculate the DWI [decline in walk distance from the first (here also second) to the last minute of the 6MWT in percent]. A decline of more than 10% is interpreted as an indicator of motor PF (26). All calculations were done in MATLAB (The Mathworks®, Version R2019b, Natick, USA).

Statistical Analysis

The statistical analysis was performed with the IBM SPSS software (Version 26, Chicago, USA). Normal distribution was checked with the Shapiro-Wilk test. Despite partially non-normally distributed data, repeated measures ANOVAs with the factors time (each minute of the 6MWT for the gait parameters and pre and post for RPE) and groups (pwMS and HC) were conducted. According to Blanca et al., the ANOVA is robust against violation of normal distribution (27). The effect size for partial eta-squared η_p^2 was determined (small > 0.01, medium > 0.06, and large > 0.14 effect) (28). Bonferroni *post-hoc* tests were performed if significant main or interaction effects were found. The effect size Cohen's d was calculated for the within-group comparisons (small > 0.2, medium > 0.5, and large > 0.8 effect size) (28, 29). The bias-corrected Hedge's g was chosen for the between-groups comparisons (small > 0.2, medium > 0.5, and large > 0.8 effect size) (29). The level of significance was set at $p \leq 0.05$. A trend was interpreted with $p \leq 0.1$. For all repeated measures ANOVAs, the Greenhouse-Geisser correction was applied since the assumption of sphericity was not given.

RESULTS

Descriptive Data and Clinical Outcome Measures

Data of 19 pwMS (12 women/7 men; 47.8 ± 9.0 years) could be analyzed (**Table 1**). The pwMS included were mildly affected (EDSS of 2.7 ± 1.0) and suffered from MS for 13.8 ± 8.6 years since the first diagnosis. Fifteen pwMS exhibited the relapsing-remitting, two primary and two secondary progressive MS types. The HC group consisted of 24 participants (15 women/9 men; 48.8 ± 7.6 years). One participant had to be excluded because of missing data.

The pwMS reported moderate perceived walking limitations [12-Item MSWS: 54.7 ± 23.2%]. Three pwMS declared that they had no walking restrictions. The FSMC revealed that the pwMS included suffered severely from cognitive as well as physical perceived trait fatigue with an overall score of 67.4 ± 18.2 (scale 20–100; ≥ 43 mild/≥ 53 moderate/≥ 63 severe fatigue). Thirteen pwMS rated their motor fatigue as severe, three as moderate, and only one as mild.

Gait Stability – Attractor Method

For all three parameters, δM, δD, and D, a significant time effect ($\eta_p^2 = 0.15$, $F_{1.215,49.832} = 7.483$, $p = 0.006/\eta_p^2 = 0.10$,

TABLE 1 | Descriptive subject data and clinical measures.

	pwMS (*N* = 19)	HC (*N* = 24)
Age (years)	47.8 ± 9.0	48.8 ± 7.6
Sex (f/m)	12/7	15/9
Height (cm)	173.6 ± 9.3	172.7 ± 8.4
Weight (kg)	75.7 ± 11.1	73.9 ± 13.0
Expanded Disability Status Scale	2.7 ± 1.0	n.a.
MS-type (RR/PP/SP)	15/2/2	n.a.
Disease duration (years)	13.8 ± 8.6	n.a.
6MWT (m)	478.1 ± 60.7	641.4 ± 56.5
DWI_{1-6} (≤- 10%/−10-0%/≥ 0%)	4/10/5	0/15/9
DWI_{2-6} (≤- 10%/−10-0%/≥ 0%)	1/9/9	0/14/10
MSWS-12 (%)	54.7 ± 23.2	n.a.
FSMC-total	67.4 ± 18.2	n.a.
Physical subscale	34.0 ± 9.1	n.a.
Cognitive subscale	33.4 ± 10.3	n.a.
RPE pre	10.5 ± 3.3	8.7 ± 1.8
RPE post	12.3 ± 3.1	9.9 ± 2.5

pwMS, people with Multiple Sclerosis; HC, healthy controls; f, female; m, male; RR, relapsing remitting; PP, primary progressive; SP, secondary progressive; 6MWT, 6-min walk test; DWI_{1-6}, distance walked index from min 1 to 6; DWI_{2-6}, distance walked index from min 2 to 6; MSWS-12, 12-Item Multiple Sclerosis Walking Scale; FSMC, Fatigue Scale for Motor and Cognitive function; RPE, rating of perceived exhaustion; n.a., not applicable.

TABLE 2 | Attractor-based gait parameters (mean ± SD) for each minute of the 6-min walk test and repeated measures ANOVAs (*p*-values and partial eta² effect size).

		Performance per minute						*p*-values			Partial eta²	
Gait parameter	**Group**	**Min 1**	**Min 2**	**Min 3**	**Min 4**	**Min 5**	**Min 6**	**Time**	**Group**	**Time × group**	**Time**	**Group**	**Time × group**
D (m/s²)	pwMS	3.40 ± 1.19	3.05 ± 0.81	3.05 ± 0.87	3.19 ± 1.09	3.21 ± 1.14	3.24 ± 1.05	**0.001**	0.198	0.577	**0.13**	0.40	0.02
	HC	3.02 ± 0.78	2.78 ± 0.72	2.82 ± 0.74	2.80 ± 0.71	2.86 ± 0.69	2.85 ± 0.69						
		Min 2 vs. 1	**Min 2 vs. 3**	**Min 2 vs. 4**	**Min 2 vs. 5**	**Min 2 vs. 6**							
delM (1/s)	pwMS	2.33 ± 1.33	1.12 ± 0.54	1.49 ± 0.72	2.10 ± 2.37	2.49 ± 3.11		**0.006**	**0.003**	0.174	**0.15**	**0.193**	0.04
	HC	1.03 ± 0.38	0.67 ± 0.22	0.84 ± 0.36	1.00 ± 0.50	1.18 ± 0.62							
delD (m/s²)	pwMS	0.90 ± 1.52	0.05 ± 0.95	0.38 ± 1.22	0.75 ± 1.72	0.78 ± 2.03		**0.008**	0.230	0.376	**0.10**	0.035	0.02
	HC	0.68 ± 0.64	0.11 ± 0.73	0.01 ± 0.71	0.30 ± 0.77	0.13 ± 0.83							

pwMS, people with Multiple Sclerosis; HC, healthy controls; SD, standard deviation; delM, difference between two limit-cycle attractors; delD, differences between the variability of two limit-cycle attractors; bold, $p \leq 0.1$.

$F_{2.554,104.713} = 4.517$, $p = 0.008/\eta_p^2 = 0.13$, $F_{2.693,110.394} = 6.326$, $p = 0.001$) was found (**Table 2**). Furthermore, a significant group effect could be demonstrated for δM ($\eta_p^2 = 0.19$, $F_{1.000,41.000} = 9.819$, $p = 0.003$).

Bonferroni *post-hoc* within-group comparisons showed a significant difference between $\delta M_{2vs3min}$ and $\delta M_{2vs4min}$ in both groups and between $\delta M_{2vs3min}$ as a reference and $\delta M_{2vs1min}$, $\delta M_{2vs5min}$, and $\delta M_{2vs6min}$, respectively ($p < 0.05$, d = 0.5–1.2) in pwMS (**Table 3**). Moreover, a significant difference was demonstrated between $\delta D_{2vs3min}$ and $\delta D_{2vs1min}$ ($p = 0.009$, d = 0.7) in pwMS and $\delta D_{2vs3min}$ and $\delta D_{2vs4min}$ in HC ($p = 0.021$, d = 0.8). The groups significantly differed in $\delta M_{2vs1min}$, $\delta M_{2vs3min}$, $\delta M_{2vs4min}$, and $\delta M_{2vs5min}$ with medium to large effect sizes ($p < 0.05$, g = 0.7–1.4; **Table 4**).

In **Figure 1**, the limit-cycle attractors and the respective standard deviation of the min 1–3 of the left leg of one person are illustrated. In this representative example, it becomes visible that the limit-cycle attractor of the first minute is clearly different from those of the second and third minutes.

Motor Performance Fatigability – Spatio-Temporal Gait Parameters

Four pwMS were categorized as having motor PF by the DWI_{1-6} (a decline from min 1–6) and only one person with MS by the DWI_{2-6} (a decline from min 2–6; **Table 1**).

For gait velocity, a significant main effect of time was observed ($\eta_p^2 = 0.07$, $F_{1.859,76.222} = 3.263$, $p = 0.047$; **Table 5**). A trend was also found for stride and stance time ($\eta_p^2 = 0.06$, $F_{1.411,57.845} = 2.692$, $p = 0.093/\eta_p^2 = 0.07$, $F_{1.463,59.994} = 2.938$, $p = 0.076$). A significant time × group interaction was demonstrated for the MTC ($\eta_p^2 = 0.10$, $F_{1.775,72.789} = 4.373$, $p = 0.020$) and a trend toward a time × group interaction for the stride $time_{CV}$ and gait $velocity_{CV}$ ($\eta_p^2 = 0.05$, $F_{2.679,109.854} = 2.319$, $p = 0.086/\eta_p^2 = 0.05$, $F_{2.867,117.531} = 2.271$, $p = 0.087$). Moreover, a main effect group could be observed for all spatio-temporal gait parameters over the 6MWT ($p \leq 0.05$; $\eta_p^2 = 0.12–0.62$).

The Bonferroni *post-hoc* tests (**Table 3**) within each group displayed that the stance time in the first minute differed significantly from the second in HC ($p = 0.016$, d = 0.7). Additionally, a significant difference was found between the second and third and the fourth and fifth min for the MTC in HC ($p \leq 0.003$, d = 0.8–1.1).

The *post-hoc* between-groups comparison revealed that pwMS and HC differed in all spatio-temporal gait parameters (mean and CV) from min 2 to 5 of the 6MWT ($p \leq 0.05$, g = 0.7–2.5) significantly (**Table 4**). In the first minute, the groups differed only in the mean values ($p \leq 0.05$, g = 0.7–2.6) and swing $time_{CV}$ significantly ($p = 0.035$, g = 0.6).

Figure 2 illustrates the MTC and MTC_{CV} for each minute of the 6MWT. It is particularly prominent that in pwMS, the MTC_{CV} was decreased from min 5–6. Ten pwMS exhibited a decrease in the MTC_{CV} of 22.57 ± 21.41% and nine pwMS an increase of 13.46 ± 12.81% from min 5–6 (**Figure 2B**). Statistically, no effect could be found for these subgroups. Of these ten pwMS with decreasing MTC variability, only one

TABLE 3 | *Post-hoc* within-group comparisons of the second minute with the other minutes of the 6-min walk test and of the difference between the limit-cycle attractors ($delM_{2vs3}$) and their variability ($delD_{2vs3}$) of min 2 and 3 with the differences of the other minutes of the 6-min walk test (*p* and Cohen's d effect size) only for the significant repeated measures ANOVAs.

Gait parameter	Group	Min 1		Min 3		Min 4		Min 5		Min 6	
		p	d	*p*	d	*p*	d	*p*	d	*p*	d
MTC	pwMS	1.000	0.4	1.000	0.2	1.000	0.2	1.000	0.2	1.000	0.2
Stance time		1.000	0.2	1.000	0.1	1.000	0.2	1.000	0.1	1.000	0.2
Stride time		1.000	0.2	1.000	0.1	0.716	0.3	1.000	0.2	1.000	0.3
Velocity		1.000	0.1	1.000	0.1	1.000	0.1	1.000	0.1	1.000	0.1
$Velocity_{CV}$		1.000	0.2	1.000	0.1	1.000	0.2	1.000	0.1	1.000	0.1
D		0.115	0.5	1.000	0.0	1.000	0.2	0.996	0.3	0.328	0.4
MTC	HC	1.000	0.3	**0.003**	**0.8**	**0.001**	**1.0**	**0.001**	**1.1**	0.406	1.4
Stance time		**0.016**	**0.7**	1.000	0.2	1.000	0.2	1.000	0.1	1.000	0.0
Stride time		0.137	0.6	1.000	0.2	1.000	0.2	1.000	0.1	1.000	0.0
Velocity		0.776	0.3	1.000	0.3	1.000	0.3	1.000	0.2	1.000	0.1
$Velocity_{CV}$		0.114	0.5	1.000	0.2	1.000	0.1	1.000	0.0	1.000	0.2
D		0.545	0.9	1.000	0.2	1.000	0.1	1.000	0.4	1.000	0.3
		Min 2 vs. 1		**Min 2 vs. 4**		**Min 2 vs. 5**		**Min 2 vs. 6**			
$delM_{2vs3min}$	pwMS	**<0.001**	**1.2**	**<0.001**	**1.2**	**0.044**	**0.5**	**0.036**	**0.5**		
$delD_{2vs3min}$		**0.009**	**0.7**	1.000	0.3	0.102	0.5	0.320	0.4		
$delM_{2vs3min}$	HC	0.122	1.2	**0.021**	0.8	1.000	0.9	1.000	1.1		
$delD_{2vs3min}$		**0.098**	**0.7**	1.000	0.1	1.000	0.2	1.000	0.0		

p, p-value; d, Cohen's d; MTC, minimum toe clearance; HC, healthy controls; pwMS, people with Multiple Sclerosis; CV, coefficient of variation; delM, difference between two limit-cycle attractors; delD, differences between the variability of two limit-cycle attractors; D, absolute variability around one limit-cycle attractor; bold, $p \leq 0.05$.

exhibited motor PF detected by the DWI (−17%). The other nine pwMS had a DWI between −8 and 8%.

Perceived Fatigability

A time effect was displayed for RPE ($\eta_p^2 = 0.264$, $F_{1.000,34.000} = 12.224$, $p = 0.001$) but no time × group interaction was found. The within-group *post-hoc* tests revealed that the RPE was significantly increased in both groups from pre to post (pwMS: $p = 0.036$, d = 0.5/HC: $p = 0.009$, d = 0.6). The RPE of pwMS and HC differed significantly at both measurement time points (pre: $p = 0.039$, g = 0.7/post: $p = 0.022$, g = 0.8).

DISCUSSION

The main findings are that (i) gait cycles were less stable in the first compared to the second minute of the 6MWT and (ii) spatio-temporal gait parameters, including the MTC, did not change significantly over time during the 6MWT indicating no gait-related motor PF in pwMS and HC.

Regarding the first research question, we were able to demonstrate a time effect for the attractor-based gait parameters δM, δD, and D. If a system is stable, it can be expected that neighboring attractors and their variability should differ equally. The *post-hoc* tests revealed that the differences between the limit-cycle attractors ($\delta M_{2vs1min}$) and between their variability ($\delta D_{2vs1min}$) among the first 2 min were significantly greater than among min 2 and 3 ($\delta M_{2vs3min}/\delta D_{2vs3min}$) in pwMS. Additionally, a trend toward a time effect could be detected for the stance time in HC. Here, the *post-hoc* test showed that the first minute differed significantly from the second. Overall, these results indicate that gait performance was less stable and variability was greater in the first when compared to the second minute. This might be due to both the gait initiation process and the initial oscillations of dynamic systems at the onset of cyclic movements (transient effect) (17). Until today, the transient effect has only been proven in the context of human locomotion for running in athletes but not for walking. The transient effect during running lasted on average 5 min until the movement pattern became stable (30). However, further studies with longer walking protocols are needed to determine how long the transient effect lasts in healthy subjects and pwMS.

With regard to the second research question, *post-hoc* comparisons indicated that no deterioration of the spatio-temporal gait parameters and thus no gait-related motor PF could be detected in pwMS and HC during the 6MWT. Considering the gait velocity more closely as a commonly used measure of gait-related motor PF, both groups exhibited a U-shape over the 6MWT with the fastest velocity in the first and a similar velocity in the last minute. This pacing behavior was also found in other studies during the 6MWT in pwMS (31–33). Schwid et al. additionally reported that the pacing behavior of pwMS and HC were comparable during the 6MWT (34). In summary, these findings are in line with the results of Shema-Shiratzky et al. who showed that gait velocity over the 6MWT is not an adequate measure to quantify gait-related motor PF in pwMS (9). This applies in particular for mildly affected pwMS, as Escudero-Uribe et al. and Burschka et al. have demonstrated (35, 36). Additionally, Piérard et al. revealed that gait-related motor PF

TABLE 4 | *Post-hoc* between-group comparisons for each minute of the 6-min walk test (*p* and Hedge's g effect size).

Gait parameter	Min 1		Min 2		Min 3		Min 4		Min 5		Min 6	
	p	g	*p*	g	*p*	g	*p*	g	*p*	g	*p*	g
MTC	**0.025**	**0.7**	**0.004**	**0.9**	**0.017**	**0.8**	**0.018**	**0.7**	**0.025**	**0.7**	0.984	0.0
MTC_{CV}	0.078	**0.5**	**0.011**	**0.8**	**0.004**	**0.9**	**0.034**	**0.7**	**0.014**	**0.8**	0.178	0.4
Stride length	**<0.001**	**1.8**	**<0.001**	**1.7**	**<0.001**	**1.8**	**<0.001**	**1.9**	**<0.001**	**1.9**	**<0.001**	**2.0**
Stride $length_{CV}$	0.403	0.3	**<0.001**	**1.3**	**0.005**	**0.9**	**0.001**	**1.0**	**0.009**	**0.8**	**0.003**	**1.0**
Stance length	**<0.001**	**2.1**	**<0.001**	**2.1**	**<0.001**	**2.0**	**<0.001**	**1.9**	**<0.001**	**1.6**	**<0.001**	**1.7**
Stance $length_{CV}$	0.064	**0.6**	**0.007**	**0.8**	**0.01**	**0.8**	**0.001**	**1.0**	**0.004**	**0.9**	**0.005**	**0.9**
Swing length	**0.005**	**0.9**	**0.004**	**0.9**	**0.005**	**0.9**	**0.002**	**1.0**	**0.01**	**0.8**	**0.011**	**0.8**
Swing $length_{CV}$	**0.035**	**0.6**	**0.02**	**0.7**	0.069	**0.6**	**0.011**	**0.8**	**0.022**	**0.7**	**0.04**	**0.6**
Stride time	**<0.001**	**1.8**	**<0.001**	**1.7**	**<0.001**	**1.6**	**<0.001**	**1.6**	**<0.001**	**1.3**	**<0.001**	**1.3**
Stride $time_{CV}$	0.35	0.3	**0.013**	**0.8**	0.073	**0.5**	**0.009**	**0.8**	**0.017**	**0.7**	**0.048**	**0.6**
Velocity	**<0.001**	**2.6**	**<0.001**	**2.4**	**<0.001**	**2.4**	**<0.001**	**2.5**	**<0.001**	**2.3**	**<0.001**	**2.3**
$Velocity_{CV}$	0.361	0.3	**<0.001**	**1.3**	**0.006**	**0.9**	**<0.001**	**1.2**	**0.003**	**0.9**	**0.002**	**1.0**
D	0.211	0.4	0.250	0.3	0.347	0.3	0.160	0.4	0.227	0.4	0.152	0.4
	Min 2 vs. 1		**Min 2 vs. 3**		**Min 2 vs. 4**		**Min 2 vs. 5**		**Min 2 vs. 6**			
delM	**<0.001**	**1.4**	**<0.001**	**1.1**	**<0.001**	**1.2**	**0.032**	**0.7**	**0.051**	**0.6**		
delD	0.531	0.2	0.805	0.1	0.223	0.4	0.258	0.3	0.161	0.4		

p, p-value; g, Hedge's g; MTC, minimum toe clearance; HC, healthy controls; pwMS, people with Multiple Sclerosis; CV, coefficient of variation; delM, difference between the limit-cycle attractors of 2 min; delD, differences between the variability of two limit-cycle attractors; D, absolute variability; bold, $p \leq 0.05$.

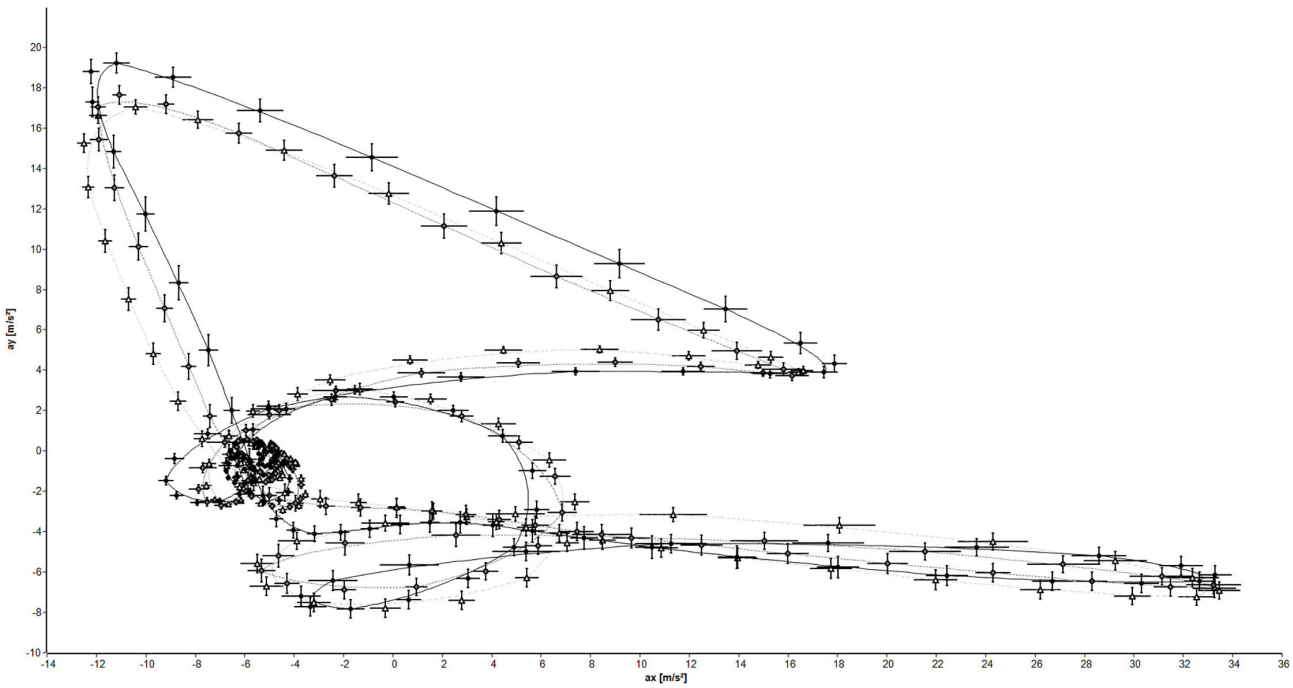

FIGURE 1 | Limit-cycle attractors and standard deviation of the left leg of one person (black circles: 1 min; gray diamonds: 2 min; white triangles: 3 min).

in mildly affected pwMS (EDSS 0–3) manifested an increase of the step width variability and in moderately to severely affected pwMS (EDSS $\geq$ 3.5) as a deterioration in walking velocity over the 500-m walk test (37). On average, the pwMS in our study were mildly affected. This might explain why no decrease in walking velocity over the 6MWT was found in the present study.

However, the results of Shema-Shiratzky et al. suggest that cadence, stride time variability, stride, and step regularity, as well

TABLE 5 | Spatio-temporal gait parameters (mean ± SD) for each minute of the 6-min walk test and repeated measures ANOVAs (*p*-values and partial eta² effect size).

Gait parameter	Group	Performance per minute						*p*-values			Partial eta²		
		Min 1	Min 2	Min 3	Min 4	Min 5	Min 6	Time	Group	Group × time	Time	Group	Group × time
MTC (cm)	pwMS	2.68 ± 0.63	2.58 ± 0.61	2.57 ± 0.62	2.52 ± 0.61	2.50 ± 0.61	2.84 ± 0.68	0.132	**0.021**	**0.020**	0.05	**0.12**	**0.10**
	HC	3.05 ± 0.39	3.15 ± 0.58	3.03 ± 0.58	2.96 ± 0.56	2.90 ± 0.53	2.84 ± 0.53						
MTC_{CV} (%)	pwMS	33.29 ± 14.71	35.80 ± 19.77	39.60 ± 22.68	36.95 ± 23.31	37.04 ± 18.96	30.30 ± 11.13	0.451	**0.006**	0.172	0.02	**0.17**	0.04
	HC	27.07 ± 7.37	24.45 ± 6.33	24.99 ± 5.30	26.15 ± 5.64	26.71 ± 4.99	26.68 ± 5.87						
Stride length (m)	pwMS	1.43 ± 0.16	1.41 ± 0.16	1.41 ± 0.16	1.40 ± 0.15	1.41 ± 0.14	1.40 ± 0.14	0.302	**<0.001**	0.893	0.03	**0.51**	0.00
	HC	1.67 ± 0.11	1.66 ± 0.13	1.66 ± 0.12	1.65 ± 0.12	1.66 ± 0.12	1.66 ± 0.12						
Stride $length_{CV}$ (%)	pwMS	5.58 ± 1.92	5.56 ± 1.54	5.45 ± 2.15	6.47 ± 3.67	5.71 ± 3.06	5.83 ± 2.58	0.360	**0.001**	0.131	0.03	**0.26**	0.05
	HC	4.95 ± 2.77	3.74 ± 1.26	3.84 ± 1.43	3.72 ± 1.33	3.77 ± 1.46	3.81 ± 1.52						
Stance time (s)	pwMS	0.56 ± 0.05	0.57 ± 0.05	0.57 ± 0.05	0.57 ± 0.05	0.56 ± 0.05	0.56 ± 0.05	0.076	**<0.001**	0.263	**0.07**	**0.50**	0.03
	HC	0.48 ± 0.03	0.49 ± 0.03	0.49 ± 0.03	0.49 ± 0.03	0.49 ± 0.03	0.49 ± 0.03						
Stance $time_{CV}$ (%)	pwMS	4.97 ± 3.81	5.49 ± 4.61	5.57 ± 4.46	6.36 ± 5.20	5.36 ± 4.33	6.00 ± 4.80	0.503	**0.003**	0.106	0.02	**0.20**	0.05
	HC	3.42 ± 1.07	2.81 ± 0.55	3.01 ± 1.15	2.68 ± 0.70	2.64 ± 0.64	2.97 ± 1.09						
Swing time (s)	pwMS	0.46 ± 0.03	0.47 ± 0.03	0.47 ± 0.04	0.47 ± 0.04	0.47 ± 0.04	0.47 ± 0.05	0.219	**0.003**	0.452	0.04	**0.20**	0.02
	HC	0.44 ± 0.02	0.44 ± 0.02	0.44 ± 0.02	0.44 ± 0.02	0.44 ± 0.02	0.44 ± 0.02						
Swing $time_{CV}$ (%)	pwMS	5.52 ± 5.11	6.86 ± 8.06	6.99 ± 10.70	10.32 ± 13.71	8.76 ± 12.33	8.76 ± 13.29	0.321	**0.008**	0.225	0.03	**0.16**	0.04
	HC	3.21 ± 0.84	2.89 ± 0.58	2.92 ± 0.64	2.84 ± 0.62	2.78 ± 0.57	3.01 ± 0.89						
Stride time (s)	pwMS	1.02 ± 0.07	1.03 ± 0.07	1.04 ± 0.08	1.04 ± 0.08	1.02 ± 0.08	1.03 ± 0.09	0.093	**<0.001**	0.488	**0.06**	**0.42**	0.02
	HC	0.92 ± 0.04	0.93 ± 0.05	0.93 ± 0.05	0.93 ± 0.05	0.93 ± 0.05	0.93 ± 0.05						
Stride $time_{CV}$ (%)	pwMS	2.59 ± 1.74	3.35 ± 3.05	3.55 ± 4.43	4.87 ± 5.79	4.13 ± 4.95	4.53 ± 6.27	0.340	**0.010**	0.086	0.03	**0.15**	**0.05**
	HC	2.22 ± 0.68	1.73 ± 0.37	1.86 ± 0.86	1.64 ± 0.51	1.61 ± 0.39	1.91 ± 0.82						
Velocity (m/s)	pwMS	1.41 ± 0.19	1.38 ± 0.20	1.36 ± 0.20	1.36 ± 0.19	1.38 ± 0.19	1.37 ± 0.20	**0.047**	**<0.001**	0.796	**0.07**	**0.62**	0.01
	HC	1.82 ± 0.13	1.79 ± 0.15	1.78 ± 0.15	1.78 ± 0.15	1.78 ± 0.16	1.79 ± 0.16						
$Velocity_{CV}$ (%)	pwMS	6.42 ± 1.95	6.66 ± 2.32	6.49 ± 2.75	6.89 ± 2.71	6.43 ± 2.92	6.89 ± 3.02	0.325	**<0.001**	0.087	0.03	**0.26**	**0.05**
	HC	5.69 ± 2.97	4.24 ± 1.41	4.46 ± 1.86	4.14 ± 1.57	4.22 ± 1.64	4.43 ± 1.80						

MTC, minimum toe clearance; HC, healthy controls; pwMS, people with Multiple Sclerosis; CV, coefficient of variation; bold, p ≤ 0.05.

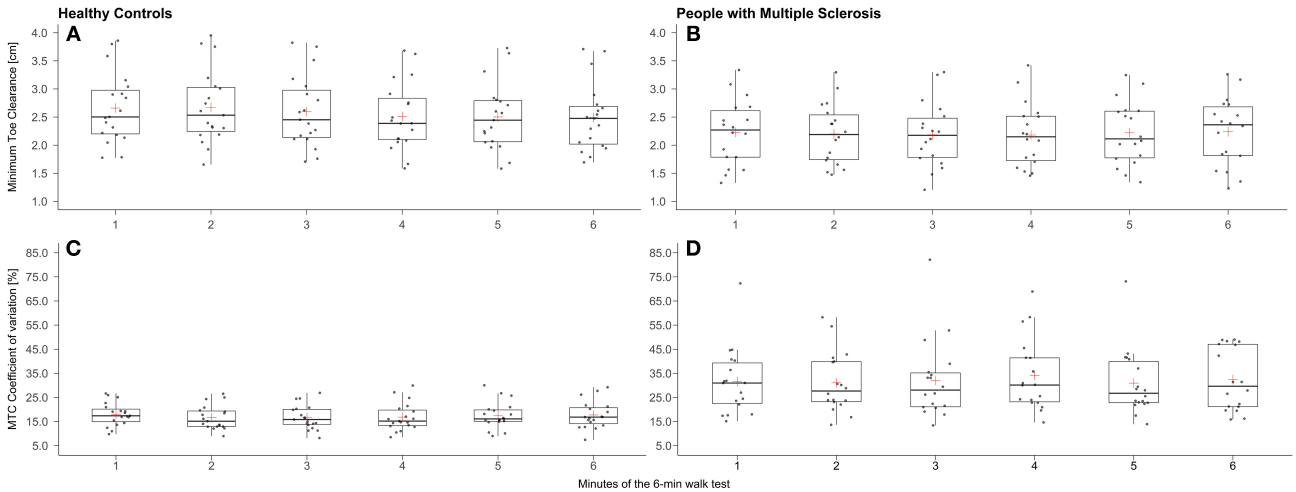

FIGURE 2 | Box plots for minimum toe clearance (MTC) (**A**: healthy controls/**B**: people with Multiple Sclerosis) and its coefficient of variation (**C**: healthy controls/**D**: people with Multiple Sclerosis) of each minute of the 6-min walk test (red cross: mean).

as gait complexity, might be better parameters to quantify gait-related motor PF during the 6MWT. In our study, a time × group interaction could be revealed for the stride time$_{CV}$, but the *post-hoc* tests did not indicate a significant change over time in pwMS and HC. These divergent results could be due to the fact that Shema-Shiratzky et al. compared mildly and moderately affected pwMS without including a control group and that the observed motor PF was mostly present in the moderately affected pwMS during the 6MWT.

Focusing on the MTC, a time × group interaction was found for the mean, but the *post-hoc* test did not reveal significant results regarding motor PF in pwMS. Nevertheless, the MTC$_{CV}$ indicated a noticeable decrease from the fifth to the sixth minute in some of the pwMS. According to Nagano et al. this can be interpreted as an indicator for gait-related motor PF in the elderly (13). A similar result was also revealed by Arpan et al. (38). In this study, the authors examined gait stability over the 6MWT in pwMS and they observed that after the third minute, 60% of pwMS showed an increasingly unstable gait pattern and interpreted this as motor PF. Since no significant differences were found in the present study, it is necessary to investigate the change in MTC variability during longer and/or more intensive walking protocols to further verify this observation.

The slight increase in RPE from pre- to post-6MWT indicates that the walking protocol induced perceived fatigability in both groups with no differences between pwMS and HC. This is in line with the findings of Savci et al. who have also shown that perceived fatigue was increased slightly due to the 6MWT in both groups (39). Therefore, it seems that the walking protocol was not able to induce perceived fatigability differently in pwMS and HC. However, there are only very few studies that have examined this aspect.

Overall, the results of this study indicate that the 6MWT might be insufficient in intensity and/or duration to induce gait-related motor PF in mildly affected pwMS. This might be due to the fact that exercise intensity during the 6MWT was not sufficient to induce motor PF in our subjects. An inherent problem of walking protocols for the assessment of motor PF is that exercise intensity cannot be determined and standardized in relation to the maximal performance. This is in contrast, for example, to fatiguing cycling protocols, which define their exercise intensity as a percentage of the maximal performance achieved during an incremental performance test (e.g., percentage of peak power) (40). This approach ensures that a sufficient exercise intensity can be individually set in a standardized manner to induce motor PF. Furthermore, it enables that outcome data can be compared between individuals or groups. However, the deceleration index takes this partly into account. During this test, the maximal walking velocity over a distance of 25 feet with a dynamic start is determined and compared to the final velocity achieved during a 500-m walk test (8).

Nevertheless, it should be investigated if more intense walking protocols are suitable to induce and monitor gait-related motor PF and perceived fatigability in pwMS. For that purpose, treadmill walking protocols with increasing slope or incremental shuttle walking tests could be used, as it was done in other patient cohorts (41). However, these protocols have not yet been applied to quantify gait-related motor PF and perceived fatigability in pwMS and their feasibility needs to be verified. Besides that, there are other approaches that require longer walking protocols, such as the Fatigue Index Kliniken Schmieder, which is based on the change in gait stability and is executed over maximally 60 min or until a certain degree of perceived exhaustion (Borg RPE scale: 17) (42). However, this approach is too complex and time-consuming for everyday clinical use yet. In addition, considering our data, the calculation of the motor PF index should be revised, because the first minute is taken as a baseline for this approach (42).

Another approach to provoke a higher level of gait-related motor PF could be either to exhaust the participant

cognitively beforehand (43) or to perform an additional cognitive task during walking (44–46). From these studies, it is known that both have an impact on walking performance but to the best of our knowledge, it is not known how much these interventions accelerate gait-related motor PF in pwMS.

Finally, a limitation of this study is that the sample of pwMS was on average mildly affected so that the effect of different degrees of disability on indices of gait-related motor PF and perceived fatigability could not be investigated. In future studies, mildly and moderately affected pwMS should be examined separately, because the degree of disability is an important factor for the extent of motor PF (8, 36, 47).

Another limitation is that the algorithms for the calculation of gait parameters were not validated for pwMS so far. Due to gait abnormalities often observed in pwMS, there might have been some errors in the step detection of the algorithm. Nevertheless, the degree of walking impairment was relatively low in our cohort and has probably not altered the results of the present study.

CONCLUSION

In summary, it could be shown that (i) gait parameters were more stable in the second minute of the 6MWT than in the first minute in pwMS and HC (indicated by the attractor method and spatio-temporal gait parameters, respectively). In addition, (ii) no gait-related motor PF could be detected based on spatio-temporal gait parameters, including the MTC and its variability, during the 6MWT in mildly affected pwMS.

For future studies, the walking protocols should be adapted in intensity and/or duration depending on the level of disability to further investigate the transient effect but also the change in spatio-temporal gait parameters, especially in the MTC and its variability, over time. Additionally, gait parameters recorded during the first minute should be avoided as a baseline for the quantification of gait-related motor PF. Either the effect of a dynamic start has to be investigated or the gait parameters recorded during the second minute should be taken as a baseline for the assessment of gait-related motor PF in pwMS.

DATA AVAILABILITY STATEMENT

The data presented in this article are not readily available due to privacy/ethical restrictions. Requests to access the data should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Otto von Guericke University (OvGU) Magdeburg (Germany). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

K-CB, LS, and CD conceptualized the study and contributed to methodology. K-CB, PB-E, and AP contributed to formal analysis and investigation. K-CB, MB, LS, AP, CD, and MJ contributed to the interpretation of data. K-CB and MB wrote the original draft. K-CB, MB, LS, CD, PB-E, and MJ contributed to writing, reviewing, and editing the manuscript. LS, CD, and MJ contributed to resources and supervision. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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The Seasonal Fluctuation of Fatigue in Multiple Sclerosis

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Background: Fatigue is a common symptom in patients with multiple sclerosis. Several studies suggest that outdoor temperature can impact fatigue severity, but a systematic study of seasonal variations is lacking.

Methods: Fatigue was assessed with the Fatigue Scale for Motor and Cognitive Functions (FSMC) in a temperate climatic zone with an average outdoor temperature of 8.8°C. This study included 258 patients with multiple sclerosis from 572 visits temporally distributed over the year. The data were adjusted for age, sex, cognition, depression, disease severity, and follow-up time. Linear regression models were performed to determine whether the temporal course of fatigue was time-independent, linearly time dependent, or non-linearly time dependent.

Results: Fatigue was lowest during January (mean FSMC: 49.84) and highest during August (mean FSMC: 53.88). The regression analysis showed the best fit with a model that included months + months², which was a non-linear time dependency. Mean FSMC per month correlated significantly with the average monthly temperature ($\rho = 0.972$; $p < 0.001$).

Conclusion: In multiple sclerosis, fatigue showed a natural temporal fluctuation. Fatigue was higher during summer compared to winter, with a significant relationship of fatigue with outdoor temperature. This finding should be carefully taken into account when clinically monitoring patients over time to not interpret higher or lower scores independent of seasonal aspects.

Keywords: multiple sclerosis, seasonal, fatigue, sun, neuropsychological

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by inflammation, degeneration, axonal damage, and demyelination (1, 2). Among the heterogenous symptoms of MS, fatigue is common, with a reported prevalence of about 90% (3–6). Increased fatigue in MS is associated with impaired quality of life (7), reduced vocational status (8), and suicidal ideations (9). The underlying pathophysiology of fatigue in MS remains poorly understood with various studies suggesting immunological, neuroanatomical, and psychological

causes (10, 11). In clinical practice, the evaluation of fatigue is difficult, due to its interactions with overall disability and other neuropsychological impairments (10, 12). Especially the highly prevalent mood disturbances as well as cognitive impairments in MS may confound objective assessment (6, 12). Besides, many patients report a general worsening due to heat exposure, known as Uhthoff's phenomenon (13). In addition to these patient-specific variables, environmental factors, like outdoor temperature, may also influence fatigue severity. Like another common neuropsychological symptom, depression, it seems at least plausible that fatigue might be inversely associated with sun exposure (14, 15). However, a majority of patients have reported that fatigue worsens with heat (4, 16). Nevertheless, a previous serial assessment of 45 patients with MS reported that outdoor temperature had no effect on fatigue (17).

Here, we analyzed real-world data of a cohort of patients with MS to test whether fatigue in MS was time-dependent. We adjusted our analysis for potential interacting variables, including age, sex, cognition, depression, disease severity, and follow-up time. Based on the literature and the presumptions, time dependency can be parameterized in three different ways – a linear course, an increasing during the summer compared to the winter, or the inverse course with increasing during winter and decreasing during summer. Therefore, we constructed several types of regression models and determined which model fit best to our fatigue data.

MATERIALS AND METHODS

Participants

This retrospective cohort study was approved by the local ethics committee of the University of Medicine in Greifswald (BB221/20). Medical reports from the MS outpatient clinic between January 2017 and September 2021 were analyzed. Patients were enrolled when data on all variables of interest were available: date, age, sex, medication, disability score from the Expanded Disability Status Scale (EDSS) (18), depression score from the Beck Depression Inventory (BDI) (19), fatigue score from the Fatigue Scale for Motor and Cognition (FSMC), and information processing speed from the Symbol Digit Modalities Test (SDMT) (20). All data were collected during the clinical visits. All patients are living in Mecklenburg-Vorpommern, in the north-east of Germany next to the Baltic sea. Exclusion criteria were: an acute relapse within the previous 3 months and another central neurological disease. In total, 606 patients with MS with 5117 visits were made between January 2017 and September 2021, out of them 258 patients with MS and 572 visits were enrolled in this study. All patients fulfilled the criteria of MS, according to the 2017 McDonald criteria (21).

Statistical Analysis

We investigated three clinically plausible hypotheses regarding the time-dependency of fatigue over 1 year: (1) no time dependency; (2) a linear trend over time, or (3) a non-linear trend over time. Accordingly, we constructed different regression models that reflected the three hypotheses, as follows:

(1) No Time Dependency:

- NULL model: Fatigue score – BDI + EDSS + SDMT + age + sex

(2) Linear Time Dependency:

- NULL model + months

(3) Non-Linear Time Dependency:

- NULL model + months + months^2
- NULL model + months + months^3
- NULL model + months^2 + months^3
- NULL model + months^2
- NULL model + months^3

To determine which model provided the best description of our data, we applied an information theory-based model-selection approach, based on Akaike's information criterion (AIC) (22). The model with the smallest AIC had the highest support from the data.

We calculated the following parameters:

$$\text{AIC difference: } \Delta\text{AIC}_i = \text{AIC}_i - \text{AIC}_{min} \quad (1)$$

$$\text{Akaike weight: } w_i = \frac{exp\,(-0.5 \cdot \Delta\text{AIC}_i)}{\sum_{r=1}^{R} exp\,(-0.5 \cdot \Delta\text{AIC}_r)} \text{ and} \quad (2)$$

$$\text{Evidence ratio: } ER = \frac{exp\,(-0.5 \cdot \Delta\text{AIC}_{best})}{exp\,(-0.5 \cdot \Delta\text{AIC}_i)} \quad (3)$$

The Akaike weight can be interpreted as the conditional probability that the current model (*i*) is the best model of the set. The evidence ratio provides a measure of how much more likely the best model (*best*) is, compared to the current model (*i*). We used the linear mixed-effects model approach (-xtmixed-) provided in Stata statistical software® (Version 17.1, Stata Corp, College Station, TX, USA) to model the time course over 12 months of a year. Patient-ID and year were considered random factors, because we had repeated visits by patients and several years of follow-up. All models were adjusted for the baseline covariables, age, sex, and possible interacting variables BDI, EDSS and SDMT. *P*-values <0.05 were considered statistically significant.

In a second step, Spearman's rank correlation was performed to asses the relationship between the mean FSMC per month and the average monthly outdoor temperature. Therefore, the mean outdoor temperature in Mecklenburg-Vorpommern during 01/2017 and 09/2021was also added according to the information from the Deutsche Wetterdienst (DWD).

RESULTS

Patient Characteristics

We enrolled 258 patients with MS (176 females, 82 males) and analyzed 572 visits in this study (see **Table 1**). The mean age at the baseline visit was 42.09 years (SD: 12.24), the mean BDI was 9.12 (SD: 8.48), the mean SDMT was 47.38 (SD: 13.59), and the median EDSS was 2.0 (range: 0–8).

TABLE 1 | Patients' characteristics.

		n	Mean	SD
Patients		258		
	Sex (f/m)	176/82		
	Age at baseline (y)		42.09	12.24
	Disease duration at baseline (y)		9.41	7.58
	Disease course at baseline (RRMS/SPMS/PPMS)	198/41/19		
	DMT at baseline			
	Glatiramer acetate	31		
	Interferon beta	28		
	Fingolimod	37		
	Dimethyl fumarate	36		
	Teriflunomide	23		
	Ozanimod	2		
	Siponimod	3		
	Cladribine	5		
	Ocrelizumab	11		
	Natalizumab	25		
	Alemtuzumab	11		
	None	46		
Visits		572	0.130	1.806
	EDSS (median/range)		2	0–8
	BDI		9.12	8.48
	SDMT		47.38	13.59

TABLE 2 | Mean fatigue scores (FSMC), outdoor temperature (°C) and the number of datapoints per month for patients with MS.

Month	N	FSMC mean	95% CI	Mean temperature
January	65	49.84	46.10–53.57	2.0
February	32	50.97	47.46–54.47	2.2
March	39	51.91	48.47–55.35	4.6
April	31	52.67	49.20–56.14	8.4
May	45	53.25	49.73–56.77	12.6
June	65	53.64	50.10–57.18	18.0
July	48	53.85	50.33–57.37	18.3
August	45	53.88	50.42–57.33	18.6
September	58	53.72	50.34–57.11	14.6
October	39	53.38	50.01–56.75	11.1
November	64	52.86	49.36–56.36	6.0
December	41	52.15	48.30–56.01	3.9

Fatigue Scores

The mean number of FSMC scores per patient was 2.2 (range: 1 to 5 scores per patient). The mean number of FSMC scores per month was 47.7 (range: 31 in April to 65 in January and June). The minimum and maximum fatigue scores were documented, respectively, during visits in January (mean FSMC: 49.84) and August (mean FSMC: 53.88, **Table 2**).

Regression Models

Among the hypothetical regression models, the non-linear time dependency model: NULL + months + months^2 fit the data best (**Table 3**). In this model, the parameters, month ($\beta = 1.402$; CI $= 0.229, 2.505$) and month^2 ($\beta = -0.092$; CI $= -0.178, -0.005$), had significant effects ($p = 0.013$, $p = 0.038$, respectively). This model revealed that fatigue increased significantly from June to September (**Figure 1**).

Correlation Between Fatigue Score and Outoor Temperature

Spearman correlation revealed a significant relationship between the mean FSMC per month and the average monthly outdoor temperature ($\rho = 0.972$; $p < 0.001$).

DISCUSSION

This was the first study to demonstrate, in a systematic way, that fatigue had a temporal course in MS. We found that fatigue increased during summer and decreased during winter. Moreover, this fluctuation was not explained by age, sex, disease severity, depression, or cognition.

Previous studies have shown that MS-related fatigue increased with ambient heat, based on different patient questionnaires (4, 16). To our knowledge, only one previous study conducted a longitudinal investigation of seasonal fluctuations in fatigue in relation to outdoor temperature among patients with MS (17). Those authors used a 7-point scale to rate fatigue in a cohort of 45 Greek patients with MS. However, they did not find a significant difference in symptom severity between February, May, August, and November. In contrast, the present study used the validated FSMC to assess fatigue in a large cohort of real-world patients with MS in Germany. With this approach, we identified seasonal fluctuations. The peak fatigue was observed in August (mean FSMC-score: 53.88) and the minimum fatigue was observed in January (mean FSMC-score: 49.84). The discrepancy between our study and the study conducted by Bakalidou et al. (17) might have been due to methodological differences, as our sample was larger ($n = 258$ vs. $n = 45$), we used an international, validated scale for assessing fatigue (FSMC vs. a 7-point Likert scale), and we performed assessments more often (12 vs. 4 time-points per year), compared to the study by Bakalidou et al. Furthermore, the increasing FSMC-score during the summer occurred simultaneously with the rising outdoor temperature, suggesting its causal relationship. In the study conducted in Greece, the mean difference between February and August temperatures was 18.5°C. With this difference, they could not find any seasonal fluctuation in fatigue. In contrast, in the area of Mecklenburg-Vorpommern, where the present study was conducted, the mean seasonal difference in temperature was 15.6 °C (23), and 16.6 °C during the observed period of time, which was less than the seasonal fluctuation observed in the study by Bakalidou et al. (15). Therefore, we detected a seasonal difference in fatigue, despite less fluctuation in outdoor temperature. The temporal association should be validated in different cohorts, especially in areas with different temperature levels.

TABLE 3 | Regression models constructed to investigate the time-dependency of fatigue in MS.

Model name	df	AIC_i	ΔAIC	Aweight	ER
NULL + months + months$^{(2)}$	***11***	***4523.639***	***0.000***	***0.234***	***– –***
NULL + months + months$^{(3)}$	11	4523.960	0.321	0.199	1.174
NULL + months	10	4524.112	0.474	0.185	1.267
NULL + months$^{(2)}$ + months$^{(3)}$	11	4524.821	1.182	0.130	1.806
NULL + months$^{(2)}$	10	4525.290	1.651	0.103	2.283
NULL	9	4525.820	2.181	0.079	2.976
NULL + months$^{(3)}$	10	4526.016	2.377	0.071	3.283

FIGURE 1 | The non-linear time-dependency regression NULL model + months + months^2 provided the best fit to the fatigue data.

Fatigue has both objective and subjective aspects (11). Objective variables, like the MS disease, cannot be changed. However, subjective variables, like mood, cognition, motivation, or activity levels, might be influenced by environmental conditions, like outdoor temperature. We demonstrated that fatigue showed seasonal fluctuations, even after we controlled for the main clinical variables of individual patients, including age, sex, disability, depression, and cognition. That result suggested that outdoor temperature may have an impact on fatigue in patients with MS. Nevertheless, it remains unclear whether this impact is due to a direct effect of the outdoor temperature on body temperature, where an influence on fatigue could be shown (24), or the direct sun exposure (25), or whether it is an indirect effect of homeostatic factors that are also related to fatigue (6, 10, 11). Some authors also define a metacognitive concept of fatigue to explain the subjective experience of fatigue (6), which both might also be influenced by temporal factors like temperature. Alternatively, the association between subjective fatigue and outdoor temperature might also be due other moderating or interacting variables, which have to be considered in future investigations. We here could not determine the underlying causes of fatigue, because we only evaluated seasonal changes. However, we did control for interacting factors like neuropsychological symptoms, cognition, and depression (12). Therefore, we could assume that the variation in fatigue was not caused by simple variations in these variables.

This study had several limitations. First, the design of the study was retrospective. However, the data represent real-world data from the outpatient clinics, where all variables were collected during routine consultations. However, all the applied measures were well-known, validated screening tools with high sensitivity, for example, the information processing speed (26). Second, we may not have included confounders like sleep quality. Thus, future prospective studies should include more detailed information. Third, in this cohort study, we only measured 1 to 5 time-points per patient. Future studies should be designed longitudinally, with more time-points, to confirm the associations described in our study. Finally, we did not include a control group. Therefore, we could not exclude the possibility that the seasonal fluctuation in fatigue might have been detectable, independent of the MS disease. Future prospective studies should include a control group to provide a comparison of the fluctuations in fatigue between healthy participants, MS patients and patients with various disease conditions, which also increases the knowledge about the MS specific Uhthoff's phenomenon (13).

In conclusion, we demonstrated that fatigue was modulated temporally throughout the year. This seasonal fluctuation, with an increase in fatigue during the summer, should be taken into account in the assessment for fatigue in patients with multiple sclerosis. In addition, in therapeutic research, this seasonal fluctuation and its association to outdoor temperature should be considered a potential confounding factor when evaluating therapeutic effects in patients with MS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Universitätsmedizin Greifswald. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG, SG, and IP contributed to the conception and design of the study and analyzed the data. MG and IP wrote the manuscript. SG, MS, and SS provided feedback and edited the manuscript. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Role of Remote Monitoring in Evaluating Fatigue in Multiple Sclerosis: A Review

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Fatigue is one of the most common multiple sclerosis (MS) symptoms. Despite this, monitoring and measuring fatigue (subjective lack of energy)– and fatigability (objectively measurable and quantifiable performance decline)– in people with MS have remained challenging. Traditionally, administration of self-report questionnaires during in-person visits has been used to measure fatigue. However, remote measurement and monitoring of fatigue and fatigability have become feasible in the past decade. Traditional questionnaires can be administered through the web in any setting. The ubiquitous availability of smartphones allows for momentary and frequent measurement of MS fatigue in the ecological home-setting. This approach reduces the recall bias inherent in many traditional questionnaires and demonstrates the fluctuation of fatigue that cannot be captured by standard measures. Wearable devices can assess patients' fatigability and activity levels, often influenced by the severity of subjective fatigue. Remote monitoring of fatigue, fatigability, and activity in real-world situations can facilitate quantifying symptom-severity in clinical and research settings. Combining remote measures of fatigue as well as objective fatigability in a single construct, composite score, may provide a more comprehensive outcome. The more granular data obtained through remote monitoring techniques may also help with the development of interventions aimed at improving fatigue and lowering the burden of this disabling symptom.

Keywords: remote monitor, accelerometry, sensors, fatigue, fatigability, remote evaluation, multiple sclerosis

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INTRODUCTION

Evaluating Fatigue or Fatigability?

One of the more challenging aspects of research in multiple sclerosis (MS) fatigue is a lack of consensus on how to define, and therefore measure, this heterogeneous symptom.

Fatigue has variably been described as "an overwhelming sense of tiredness that is out of proportion to the performed activity" (1), "a feeling of difficulty initiating, or sustaining voluntary effort" (2), or "a feeling related to a lack of motivation to deploy resources" (3). A panel of experts (the MS Council for Clinical Practice Guidelines) defined MS **fatigue** as "a ***subjective*** lack of physical and/or mental energy that the individual or caregiver perceives to interfere with usual activities" (4). This definition not only points to the multidimensionality of MS fatigue and its negative impact on patient's life, but also emphasizes the subjective nature of this symptom.

However, this expert definition is still vague and does not answer many important and practical questions about the severity, temporality, or triggers of fatigue. For example, one patient may feel they do not have enough energy for going on a hike, and another may feel they do not have the energy to go from the living room to the mailbox. The severity, and perhaps, the "quality" of fatigue is very different between these two patients, yet the definition does not distinguish between the two, nor does it clarify if the subjective lack of energy happens before or after an effortful activity.

In contrast to the subjective feeling of lack of energy (fatigue), **fatigability** has been defined as a more ***objectively*** measurable and quantifiable performance decline in physical or cognitive tasks. Unfortunately, even the association between subjective fatigue and objective fatigability in MS is not straightforward, as noted in people with advanced MS where change in subjective fatigue did not correlate with cognitive fatigability (5). More encouragingly, subjective fatigue (measured with a validated questionnaire) was associated with an objective measure of physical activity (step count from an accelerometer, as a proxy for physical fatigability) in a cohort of MS with a wide range of disability scores (6). After exertion, a 6-min walk test, gait and motor parameters (postural sway, arm-swing and hand grip strength) demonstrated potential associations with fatigue ratings and fatigability scores (7). These emphasize the need for objective, validated measures that are able to capture real-time fatigability in people with MS (PwMS), during all moments of the day (i.e., during and after going for a hike, going to the mailbox, or sitting watching TV) and over many days at a time.

CURRENT METHODS OF EVALUATION FOR FATIGUE AND FATIGABILITY AND THEIR LIMITATIONS

Fatigue

Clinical methods to characterize patients' feeling of fatigue use self-reported questionnaires (8). Data derived from self-report scales depend on the scale developer's conceptualization of fatigue and the respondent's interpretation of the questions (9). Some scales, developed to quantify fatigue in other medical conditions, are not specific to MS. Most fatigue questionnaires ask patients to retrospectively evaluate previous fatigue, and many have a look-back period of seven to 28 days (hence, calling these measurements **"trait" fatigue**) (10). However, the scores usually do not portray the average fatigue severity in the look-back period and are mainly influenced by the most recent and most severe fatigue states (11). These scales do not provide any information about either diurnal or day-to-day variations in fatigue severity, phenomena that are well-known to patients with MS and their clinicians (i.e. "having good days and bad days") (10). The lack of granularity and placebo-responsiveness of fatigue measures from self-report questionnaires could represent significant limitations to identifying or developing effective fatigue treatments in MS (12).

To address the problem with recall bias, there has been an attempt to use self-report questions or questionnaires to assess the **fatigue "state"** (fatigue severity at the moment) (13). These include visual analog scales and/or asking patients to rate how severe their fatigue is at the moment of assessment. However, because of the diurnal and day-to-day variations of fatigue severity, "state" fatigue needs to be measured several times a day and over a longer epoch to provide a more comprehensive picture of a patient's fatigue severity. This in turn may increase the sense of fatigue in the patient.

Fatigability

Considering the inherent limitations of self-report measures, efforts to measure fatigue more objectively have involved several physical and cognitive performance-based measures. In these tests, compared to healthy controls, patients with MS demonstrate a decline in physical (e.g., sustained muscle contraction) and cognitive function (e.g., visual and verbal memory) after an effortful continuous performance task (14). These declines can happen even if baseline muscle strength and cognitive performance are normal. To date, such objective declines in performance (which we defined as **fatigability**) may not correlate with self-reported fatigue (15, 16). This lack of correlation might be because self-reported fatigue has a look-back period and is supposed to measure "the average fatigue severity" over the look-back period, while the performance-based test measures the fatigability "at the moment." This issue could be overcome by more frequent (or continuous) assessments of the performance.

The lack of correlation between subjective fatigue and objective fatigability may also be due to the multidimensionality of MS-related fatigue. In this case, it is important to incorporate both self-reported and performance-based measures when assessing fatigue in the research setting. Thus far, most clinical trials evaluating the efficacy of medication and interventions for MS-related fatigue have relied solely on self-reported questionnaires.

REMOTE EVALUATION OF FATIGUE AND FATIGABILITY

Subjective Assessments: Fatigue

Almost all validated fatigue questionnaires can be administered and answered remotely by PwMS. These surveys can be accessed via a web page on patients' computers, smartphones or tables, from their homes or workplace. Remote evaluation of fatigue using patient surveys can obviate the need for a clinic visit and facilitates participation in fatigue research by reducing barriers (i.e., eliminating commutes to testing centers). Such a strategy was used in a clinical trial assessing the efficacy of pharmacotherapy for MS fatigue (12). The readability and acceptability of an electronic version of a recently-developed MS-specific fatigue questionnaire were formally demonstrated during the initial evaluation of the instrument (17). The advantage of computerized questionnaires also includes adaptive features, where the list of questions offered to a patient can change based on their answers to previous questions [e.g., Neuro-QOL fatigue survey (18)].

The ubiquitous availability and versatility of portable electronic devices and smartphones provide a unique opportunity to continuously obtain self-reported (fatigue; state and trait) and performance-based (fatigability) measures in patients' real-life settings. This methodology, referred to as ecological momentary assessment (EMA), involves the repeated sampling of subjects' experiences and behavior in the subjects' natural environment and in real-time (19). Applying the EMA to smartphones and electronic devices can create a set of observable behaviors from the interaction between human disease and the person's use of the technology, collectively referred to as digital phenotypes (20). In a study that used a handheld portable electronic device, a self-report of fatigue severity (by asking a single question) was prompted by auditory alarms multiple times a day. Fluctuation in fatigue in both PwMS and healthy individuals was demonstrated in this study (21). In another study, PwMS used a wrist-worn device to record Real-Time Digital Fatigue Scores (RDFS) several times a day, over 3 weeks. Mean RDFS correlated with traditional validated fatigue scores, and captured circadian variation in fatigue severity (22). In a similar way, smartphones can be used for gathering real-time, patient-reported fatigue severity several times a day and in various social situations. This eliminates the recall bias inherent to the currently used questionnaires. Smartphones can also be used to present patients with tasks (such as a reaction time task) to assess performance-based fatigue.

Objective Assessments: Fatigability

In a disease as fluctuating as MS, where symptoms can change hourly, one-time clinic-based measures do not provide us with a complete picture of the persons' performance or deficits. Wearable technology has greatly enhanced the ability to monitor patients' function outside of the clinic; smaller and more discreet wearable monitors can be worn on various parts of the body to provide data from everyday life.

Changes in accelerometer or sensor-based gait and muscle activation metrics can be used to infer the users **fatigability** over minutes, hours or days (23, 24). Physical activity in PwMS is influenced by multiple factors, one of which is the patients current subjective energy levels (**state fatigue**) (25, 26). As noted, physical activity outcomes from accelerometry have been associated with conventional measures of perceived fatigue in MS (27–32). Self-reported fatigue (**state and trait**) has also been associated with sensor-based gait parameters, providing a more objective correlate to an otherwise subjective measure (7, 33–36).

Smartphones

Because texting and web browsing are among smartphones' most used features, keystroke dynamics (KD) data can be studied as a possible measure of fatigue in MS. KD is one of the behavioral biometric characteristics and is based on the assumption that different people have different typing manners. KD has constant and variable components. The constant component is dependent on the person's physical data and does not change over time. The variable component, however, is dependent on the person's psychological state. By associating changes in parameters such as typing speed, the number of mistakes, and usage of specific keys, changes in physical and mental behavior could be determined. For example, in a study of healthy subjects using specific key press and release timing information from text input tasks, average daytime fatigue recognition accuracy of 98% could be reached (37). Also, specific changes in smartphone usage and KD metadata were correlated with mood states in patients with bipolar affective disorder (38). Keystroke features differentiated between PwMS and healthy controls and were correlated with measures of disability, such as the Expanded Disability Status Scale (EDSS). However, KD data were not associated with traditional trait fatigue questionnaires, such as Fatigue Severity Scale (FSS) (39). This lack of correlation could be due to recall bias associated with traditional questionnaires. There is a possibility that KD data better reflect fatigability (as opposed to subjective fatigue). Future longitudinal studies with concurrent measurements of fatigue and fatigability can answer these questions.

Activity Monitors

Types of Activity Monitors

Many gait and activity assessment wearables exist, chiefly divided into *Activity* monitors: measuring the quantity of activity, and *Movement* monitors: for gait quality or movement. The pedometer is the simplest activity monitor - traditionally used to record step counts only (40). The most commonly used research devices in MS are triaxial waist-worn accelerometers (e.g., ActiGraphs) (41). However, these devices tend to express output in activity counts rather than step counts, which are potentially harder to interpret for the lay person. Some devices are designed to wear on lower limbs (i.e., ankle or thigh) (42). Despite variable correlation accuracy with manual step counts, they may not be practical for longer-term use as they look less like 'trendy wearables' and more research or monitoring devices (43, 44). Other devices used in research adhere to the skin, for example, the ActivPAL or the BioStamp (45). A study in MS found that the BioStamp had high accuracy for detecting gait patterns and step number and perceived differences in gait characteristics by disability level (45). Inertial Measurement Unit (IMU) devices are also used for evaluation and monitoring. These small devices are comprised of accelerometers, gyroscopes, and magnetometers which measure linear acceleration, angular velocity, and magnetic field strength, respectively. They can be embedded in shoes or clothing, providing spatio-temporal data. Multisensors, using biaxial accelerometers with heat flux sensors, skin temperature sensors, near-body ambient sensors, galvanic skin response sensors are worn on an armband around the upper arm. These provide a comprehensive picture of activity as well as the environment and physiological state of the user at the time of data capture (46), and by measuring multiple elements are likely to be advantageous for the study of a heterogeneous, multidimensional symptom like fatigue.

Types of Monitoring Outcomes

Remote monitors generate an array of outcomes, including activity counts or step counts (using different levels of granularity and aggregated data summaries; daily or minute-by-minute, intensity, duration), gait kinematics (such as walking speed,

stride length, width and cadence), energy expenditure, heart rate, breathing rate, burnt calories, sleep quality and duration, estimation of activity type, range of movement, distance traveled - and more. Due to the many factors and symptoms that can affect fatigue (state or trait) and fatigability, the use of remote wearable devices that can measure various outcomes concurrently in everyday life would be ideal. Supposedly due to restrictions in size and weight of the devices, none to date evaluate all outcomes in the home setting.

Real-World Examples

A significant benefit of wearable devices is their potential for *ecological and continuous* use. Therefore, commercially available devices made for 'ease of use' and with fashion-conscious designs have made their way into clinical research to improve adherence in longitudinal studies. The Apple iWatch and Fitbit specifically have gained wide publicity (47–73).

In MS, studies evaluating physical activity using commercial wearables have shown (1) strong-moderate correlations between clinical and patient-reported disability measures (6, 74–80), (2) continuous observation provides less biased assessment vs. sporadic cross-sectional measures (6, 74, 81, 82), (3) fatigue is not the only factor affecting sedentary behavior and physical activity in MS (83, 84) and (4) that average daily step count (STEPS) is responsive to change over 1-year, even when conventional measures remain stable (74).

Associations With Fatigability (Performance) and Trait Fatigue (Patient Rating)

In the FITriMS study (a year-long observational study of continuous, remote ambulatory activity in PwMS) participants wore a Fitbit Flex for up to 2 years on their non-dominant wrist and were asked to complete online surveys every 6 months, including a subjective, validated measure of fatigue: the 5-item Modified Fatigue Impact Scale (MFIS-5) (6, 74, 85). Results indicated that STEPS strongly correlate not only with ambulatory function (6) but also with *worse MFIS-5 scores* ($r = -0.44$, $p < 0.05$).

Remote Monitoring Captures Fatiguability and State Fatigue

Initial research using bilateral foot-worn sensors (small IMUs) demonstrated the ability of spatio-temporal gait parameters to predict fatigue level (using the BORG scale for perceived exertion as a proxy for **state fatigue**) (86). Results from the foot-worn sensors demonstrate a significant change in gait parameters pre and post a 6-min walk test – providing information about the subjects' performance/fatigability. These data highlight the promising use of remote monitors as objective measures to evaluate fatigue as well as fatigability in PwMS both inside and out of the clinic setting.

Trait and state fatigue has been correlated to poor sleep quality and quantity (87). Increased physical activity (moderate-to-vigorous physical activity) has been correlated with improved sleep quality and reductions in subjective fatigue (88–90). Given the heterogeneity of symptoms associated with fatigue and the lack of insight into sleep quality and quantity in the home setting, remote devices monitoring sleep and physical activity are beneficial for evaluating personalized correlations on a patient-by-patient basis. Similarly, restless leg syndrome (RLS) is common in PwMS and has been correlated with higher fatigue (trait) and worse sleep quality and quantity (91)– using wearables to evaluate night-time lower extremity movement (from RLS) and sleep metrics can provide tailored information about factors exacerbating or involved in MS fatigue and potentially also fatiguability.

General Limitations and Possible Solutions (i.e., Future Work)

Fatigue, by definition, remains a subjective symptom, and similar to pain, the measurement and monitoring tools will rely on patients' reports. Although subjective fatigue contributes to reduced physical, cognitive, and psychosocial activities among patients, many other factors result in decreased activity and fatigability. The pathophysiology of MS fatigue is also multifactorial and is different among patients and even for a given patient over the disease course. So, finding a single serological, cerebrospinal fluid, structural, or functional imaging biomarker for MS fatigue may not be attainable.

In this situation, we recommend combining ecological momentary fatigue assessment (i.e., for state and trait fatigue, using repeated questionnaires via smartphone applications) and remote real-world measurement of physical and cognitive function (fatigability) as a solution to this complex problem. Perhaps, it is possible to design a combined 'composite score' that incorporates both subjective fatigue and objective fatigability into a single construct. Isolating the concept of fatigue from similar concepts, such as depression and excessive daytime sleepiness, and understanding how they affect and interact with each other may lead to more specific and targeted treatments for patients.

Looking forward, remote monitors can be used for therapeutic intervention. Exercise, as well as energy conservation methods, are known to be beneficial for treating MS fatigue (89, 92, 93). Using monitors can help personalize when, how and how much activity a person can perform before getting exhausted. A real-world example, from the FITriMS study, was the use of the Fitbit step count as a "dose-meter" – allowing the participant to know when they needed to slow down to ensure sufficient energy for the rest of the day, and even subsequent days.

CONCLUSION

Subjective fatigue is one of the most common MS symptoms. Validated questionnaires are the most common tools for monitoring and measuring this disabling symptom. Most fatigue questionnaires can be administered remotely and can therefore be used for remote evaluation of fatigue in patients. Through deployment via smartphones and other mobile technologies, ecological momentary assessment may enable clinicians and researchers to better understand the patients' fatigue level, and its fluctuation and response to treatment in real-life settings. Objective decline of patients' function with exertion: what has been defined as fatigability, can be evaluated using wearable devices assessing level of physical activity - that can be influenced

by fatigue severity. Wearables can also quantify the objective decline. By combining validated questionnaires, momentary and frequent subjective assessments, and objective measures of function and its decline with exertion, remote monitoring techniques will provide a more comprehensive picture of a patient's burden of symptoms and treatment response.

AUTHOR CONTRIBUTIONS

VB and BN contributed to conception and design as well as drafting and revision of the manuscript. RB contributed to concept and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Associations of White Matter and Basal Ganglia Microstructure to Cognitive Fatigue Rate in Multiple Sclerosis

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Fatigue, including cognitive fatigue, is one of the most debilitating symptoms reported by persons with multiple sclerosis (pwMS). Cognitive fatigue has been associated with disruptions in striato-thalamo-cortical and frontal networks, but what remains unknown is how the *rate* at which pwMS become fatigued over time relates to microstructural properties within the brain. The current study aims to fill this gap in knowledge by investigating how cognitive fatigue rate relates to white matter and basal ganglia microstructure in a sample of 62 persons with relapsing-remitting MS. Participants rated their level of cognitive fatigue at baseline and after each block (x7) of a within-scanner cognitive fatigue inducing task. The slope of the regression line of all eight fatigue ratings was designated as "cognitive fatigue rate." Diffusional kurtosis imaging maps were processed using tract-based spatial statistics and regional analyses (i.e., basal ganglia) and associated with cognitive fatigue rate. Results showed cognitive fatigue rate to be related to several white matter tracts, with many having been associated with basal ganglia connectivity or the previously proposed "fatigue network." In addition, cognitive fatigue rate was associated with the microstructure within the putamen, though this did not survive multiple comparisons correction. Our approach of using cognitive fatigue rate, rather than trait fatigue, brings us closer to understanding how brain pathology may be impacting the experience of fatigue in the moment, which is crucial for developing interventions. These results hold promise for continuing to unpack the complex construct that is cognitive fatigue.

Keywords: multiple sclerosis (MS), cognitive fatigue, diffusional kurtosis imaging (DKI), white matter, basal ganglia, microstructure

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INTRODUCTION

Fatigue, including cognitive fatigue (i.e., lack of mental energy), is one of the most widely reported symptoms in multiple sclerosis (MS), impacting more than 70–90% of individuals with the disease (1, 2). The presence and severity of fatigue negatively impacts employment, quality of life, psychological status, and ability to complete basic and complex activities of daily living (3–5). What

we know about cognitive fatigue to date, however, has largely stemmed from subjective self-report inventories, which rely on retrospective ratings and carry several limitations. There is evidence that measuring fatigue in the moment (i.e., state fatigue) may provide a more accurate measure, as it is less contaminated by outside factors such as bias, memory, and mood state (6).

Adding to the complexity and nuance of measuring cognitive fatigue is the absence of a metric that tracks change over time, or how quickly a person with MS becomes fatigued during a cognitively demanding task (i.e., *rate* of cognitive fatigue). Studies examining cognitive fatigue rate in MS are limited, but we can deduce the importance of considering rate through the *temporal fatigue hypothesis*. The *temporal fatigue hypothesis* posits that there is a positive relationship between mental effort and subjective cognitive fatigue, regardless of cognitive load, such that as length of time engaged in a mentally demanding task increases, so does level of reported subjective cognitive fatigue (7–9). Several studies have found increases in subjective cognitive fatigue in relation to time spent engaging in a cognitively demanding task, with little or no association found between subjective cognitive fatigue and performance (10–12). No studies have directly investigated the *rate* at which persons with MS fatigue while engaging in a fatigue inducing task. The current study aims to fill this gap by examining the rate of cognitive fatigue over time during a fatigue inducing task.

Investigations of cognitive fatigue and white matter microstructure using diffusion weighted imaging (DWI) have produced potential white matter correlates of cognitive fatigue that appear to be consistent with the striato-thalamo-cortical network proposed by multiple investigators [see (13–16)]. In separate studies examining persons with MS, fibers connecting the posterior hypothalamus and mesencephalon, external capsule, internal capsule, frontal and occipital juxtacortical fibers, uncinate fasciculus, forceps minor, superior longitudinal fasciculus, and cingulum have all been associated with trait fatigue (17–19). Reduced striato-thalamo-cortical and frontal network integrity have also been associated with cognitive fatigue in veterans with a history of mild to moderate traumatic brain injury and older adults (20, 21).

In addition to the contribution of white matter damage to cognitive fatigue in neurological (i.e., MS) and non-neurological populations, brain structures, particularly the basal ganglia, have also shown associations. Chaudhuri and Behan (13) were among the first to propose that the basal ganglia are implicated in cognitive fatigue due to interruptions of basal ganglia circuitry (i.e., striato-thalamo-cortical loop). Subsequent work using neuroimaging has supported this hypothesis by linking the structure and function of the basal ganglia to both cognitive and general fatigue in MS [e.g., (22, 23)]. Additional studies in MS (14, 24–28) and non-MS populations (29–32) further support the basal ganglia as a primary pathophysiological contributor to fatigue.

Previous studies have linked cognitive fatigue and changes to white matter and/or basal ganglia structure, but limitations exist. First, most studies have relied on trait fatigue as the primary independent/dependent variable, which has limited accuracy due to retrospective self-report biases. Second, no previous studies have taken *rate* of fatigue into account, thereby missing a crucial aspect of cognitive fatigue. Lastly, while basal ganglia activation/connectivity and overall volume have been examined, no previous studies have utilized advanced DWI to examine the microstructure of the basal ganglia. The current study aims to fill these gaps in the current literature by examining the relationship between cognitive fatigue rate (i.e., how quickly or slowly an individual becomes cognitively fatigued during a fatigue inducing task) and white matter and basal ganglia microstructure using advanced DWI.

METHODS

Participants

The current study represents secondary analyses on a previously collected prospective dataset. Seventy-three participants with clinically definite relapsing-remitting MS (RRMS) according to McDonald criteria (33) were recruited for the study. Eleven participants were not included due to incomplete study sessions or substantially missing behavioral data (i.e., did not come in for scheduled session, etc.), leaving 62 participants enrolled in the study. Of the 62 participants, six were missing or had unusable neuroimaging data and were thus excluded from the neuroimaging portion of the study. There were no demographic or neuropsychological differences between the participants included and excluded from neuroimaging analyses, aside from years of education completed. The participants included in neuroimaging analyses had more years of education ($M = 16.13$, $SD = 1.71$) than those who were excluded ($M = 14.50$, $SD = 2.51$, $p = 0.038$). **Table 1** provides demographic characteristics for the study sample.

RRMS participants were recruited from local universities and MS clinics, flyers posted throughout the community and on MS-related websites, ads placed within local MS chapter newsletters, and from a database of over 500 MS participants who have participated in research at our institution in the past. Inclusion criteria for the MS group were as follows: between 30–65 years of age; RRMS subtype (verified by each participant's neurologist); free of exacerbations for at least 1 month prior to the screening; and able to ambulate without an assistive device. Exclusion criteria were as follows: history of head injury, stroke, seizures, or any other neurological history outside of MS; current treatment/use of steroids, benzodiazepines, antipsychotics, and/or neuroleptics (i.e., at the time of the phone screen or study session); unable or unwilling to consent; and contraindications for MRI. All prospective participants underwent a telephone screen to determine eligibility, and eligible participants were scheduled for an in-person study session which included consenting, completion of questionnaires, neurocognitive testing, and MRI. All participants were compensated for their time ($100 USD). All study procedures were conducted in English and were approved by the Kessler Foundation Institutional Review Board. Each participant received the same battery and administration was standardized such that the order of the battery was kept consistent across participants.

TABLE 1 | Descriptive characteristics of demographic and behavioral data.

	Sample ($N = 62$) *n* (%)
Age	52.2 ± 8.5, 54 (30–66)
Female	50 (80.6%)
Race/ethnicity	
Latinx/hispanic	7 (11.3%)
Afro-Latinx	1 (1.6%)
Non-Latinx Black	4 (6.5%)
White	39 (62.9%)
Asian	1 (1.6%)
Other	9 (14.5%)
Not reported	1 (1.6%)
Years of education	16.0 ± 1.8, 16.0 (12–20)
Disease Duration*	19.1 ± 10.8, 17.5 (2–43)
Lesion Volume (mL)	6.4 ± 7.6, 3.1 (0–40.1)
MFIS Cognitive	18.8 ± 8.9, 17.0 (0–39)
MFIS Psychological	3.39 ± 2.16, 3.0 (0–8)
MFIS Physical	17.73 ± 8.0, 19.0 (0–35)
MFIS Total	37.9 ± 16.1, 38.0 (4–75)
CMDI Mood	8.08 ± 3.68, 6.0 (6–25)
CMDI Evaluative	14.02 ± 6.10, 13.0 (1–42)
CMDI Vegetative	25.53 ± 6.64, 24.50 (11–40)
CMDI Total	77.2 ± 23.8, 70.1 (45–181)
STAI State	31.8 ± 10.5, 28.0 (20–63)
STAI Tait	36.2 ± 11.6, 34.0 (21–61)
SDMT Raw	50.9 ± 12.8, 52.0 (17–74)

**Missing data for four participants; MFIS, Modified Fatigue Impact Scale; CMDI, Chicago Multiscale Depression Inventory; STAI, State Trait Anxiety Inventory; SDMT, Symbol Digit Modalities Test.*

Behavioral Measures

Each participant completed a set of questionnaires measuring depression, state and trait anxiety, and trait fatigue. These variables were examined to better understand the variance of cognitive fatigue rate.

Chicago Multiscale Depression Inventory

The Chicago Multiscale Depression inventory [CMDI; (34)] is a 50-item inventory consisting of four subscales: mood (14 items), evaluative (14 items), vegetative (14 items), and positive affect (eight items). These subscales can be used separately or in combination with one another. Participants rate themselves on a 5-point Likert scale (1- "Not at all" to 5-"Extremely") the extent to which each word/phrase (e.g., sad, joyful, unworthy, gloomy) describes them "during the past week, including today." The CMDI was designed specifically for use in medical populations, including MS. Raw scores for the mood, evaluative, and vegetative subscales and the total score were used in statistical analyses.

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory [STAI; (35)] is a 40-item measure divided into two, 20-item scales to assess current ("state"; e.g., "I am tense," "I am worried") and longstanding ("trait"; e.g., "I am content," "I am a steady person") anxiety. Participants rate themselves on a 4-point Likert scale (state: 1- "Not at all" to 4- "Very much so"; trait: 1- "Almost never" to 4- "Almost always") based on how they feel in the moment ("state") and how they generally feel in their lives ("trait"). Raw scores for state and trait anxiety were used in statistical analyses.

Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS) is a 21-item self-report questionnaire based on Fisk et al.'s (36) Fatigue Impact Scale. Items makeup three subscales that measure the effects of fatigue on cognitive (10 items; e.g., "I have been less alert"), physical (9 items; e.g., "I have had to pace myself in my physical activities"), and psychosocial (2 items; e.g., "I have been less motivated to participate in social activities") functioning. Participants rate themselves on a 5-point Likert scale (0- "Never" to 4- "Almost always") the extent to which fatigue has impacted them in the stated way during the previous 4 weeks. Raw scores for cognitive, physical, and psychosocial subscales were used in statistical analyses.

Fatigue Induction Task

We used the same fatigue induction task that we have used in previous research (18, 37). On every trial, subjects were presented with a rotating, colored rectangle. The rectangle was rotating either quickly or slowly and was colored either red or blue. The stimulus on each trial therefore afforded two tasks: a color categorization task in which subjects pressed one button on an MR-compatible button box if the rectangle was colored red and another if it was colored blue; and a speed categorization task in which subjects pressed one button if the stimulus was rotating quickly and another if it was rotating slowly. The color and speed trials were optimized for deconvolution and were pseudo-randomly mixed such that on some trials subjects switched from one task to the other while on others they repeatedly performed each task. E-Prime software was used to present the stimuli and to record responses. Subjects worked through seven blocks of the task-switching paradigm to induce fatigue.

Visual Analog Scale-Fatigue

Participants' cognitive fatigue was assessed with a visual analog scale (VAS) at baseline and after each block of the fatigue induction task for a total of eight ratings. Participants were asked: "How tired are you right now?" and were asked to indicate their level of fatigue on a scale from 0 to 100, with 0 being minimally fatigued and 100 being maximally fatigued. To mask the purpose of the study, three additional VAS ratings were also administered (in randomized order) before and after each task block: happiness, sadness, and frustration. The slope of the regression line for each participant's eight VAS-F ratings was operationalized as "cognitive fatigue rate."

Neuroimaging Acquisition

Neuroimaging data collection was completed on a 3-Tesla Siemens Skyra scanner. Data were collected using 20- and 32-channel head coils. Diffusion weighted imaging (DWI) data were collected A>>P using two separate sequences which were

optimized to produce comparable data (sequence 1: b = 1,000, 2,000 s/mm,^{2} TR = 5,600 ms, TE = 97 ms, FOV = 220 mm, voxel size = 2.3 × 2.3 × 3.0 mm^3, multi-band acceleration factor = none, TA= 6 min 50 s; sequence 2: b = 1,000, 2,000 s/mm,^{2} TR = 3,000 ms, TE = 95 ms, FOV = 220 mm, voxel size = 2.3 × 2.3 × 3.0 mm^3, multi-band acceleration factor = 2, TA = 3 min 46 s). In addition, high-resolution magnetization prepared rapid gradient echo (MPRAGE) and T2 fluid attenuated inversion recovery (T2 FLAIR) images were acquired for each participant to quantify lesion volume (MPRAGE: TE = 3.43 ms; TR = 2,100 ms, FOV = 256 mm; flip angle = 9°; slice thickness = 1 mm, voxel = 1 × 1 ×1 mm^3, matrix = 256 × 256, in-plane resolution = 1 mm^3 isoptropic; T2 FLAIR: TE = 91 ms; TR = 9,000 ms, FOV = 256 mm; flip angle = 150°; slice thickness = 3 mm, voxel = 1 × 1 × 3 mm^3, matrix = 256 × 216, in-plane resolution = 1 × 1 × 3 mm^3).

Lesion Quantification

White matter lesions were quantified using the Lesion Segmentation Toolbox v3.0.0 (LST) in Statistical Parametric Mapping 12 (SPM12), developed by Schmidt et al. (38). Prior to implementing the Lesion Segmentation Toolbox, each participant's T1-weighted and T2 FLAIR-weighted scans were visually inspected for artifacts and distortions. Six participants' data were poor quality and unusable. Missing data for these participants was imputed using Multiple Imputation by Chained Equations (MICE), which uses an iterative series of predictive models to 'fill in' missing data (39).

The lesion growth algorithm (LGA) option within the LST was used to quantify lesions. In brief, T1-weighted images were segmented into three different tissue classification maps: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The T2 FLAIR-weighted images were bias-corrected and coregistered to the T1-weighted image. Next, the FLAIR intensity distribution for each tissue classification map was obtained and FLAIR-hyperintense outliers, representing sclerotic lesions, were added together to create a combined conservative lesion belief map. The conservative lesion belief map of each participant underwent an iterative process using a lesion growth model. During this process, each voxel within the neighborhood of a conservatively identified lesion was labeled as "lesion" or "other" depending on whether voxels share a common border or not; the lesion growth algorithm assumes that voxels that are completely surrounded by lesion voxels are more likely to represent lesions. The program then moves from conservative assumptions about the lesion map to more liberal assumptions by weighting the likelihood of a voxel belonging to gray or white matter vs. lesions. This process is enhanced by a hidden MRF segmentation model and a priori knowledge of the location of white matter (38). The final outputted lesion maps were used to quantify whole brain lesion volume in milliliters (mL) for each participant.

Diffusion Weighted Imaging

All diffusion weighted imaging data was visually inspected for gross artifacts. As noted above, six participants were missing or had unusable imaging data and were thus excluded from the diffusion weighted imaging portion of the study. Diffusion data was preprocessed using PyDesigner's standard pipeline which integrates packages from FMRIB Software Library (FSL), MRtrix3, and Python (40–49). Preprocessing steps included denoising, Gibb's ringing correction, EPI distortion correction, eddy current correction, co-registration, brain mask computation (0.20 threshold), smoothing (FWHM = 1.25), and Rician bias correction. A Diffusional Kurtosis Imaging (DKI) model was applied to the data to produce DKI maps for mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK). A map for fractional anisotropy (FA) was also created and used as a reference when need. All DKI maps were checked for artifacts, intensity range problems, and general data quality. These maps were used to conduct tract-based spatial statistics [TBSS; (50)] analyses within FMRIB Software Library [FSL; (51)].

For TBSS, all participants' FA maps were put into a higher-resolution standard space using FSL's Non-linear Image Registration Tool [FNIRT; (64)]. First, a study-specific "target image" was created by aligning every FA image to every other one and then identifying the "most representative" image. The target image was then aligned into 1 × 1 × 1 mm MNI152 space using a combined non-linear transform and affine transform. Each participant's FA image was then aligned to this target. The mean of all FA images was calculated and thinned to create an FA skeleton, which encompasses the centers of all the white matter tracts common to the sample. The threshold for the FA skeleton was set to 0.2. This threshold value was chosen because it has been established as an appropriate threshold for segmenting white matter and gray matter (52). Prior to running the voxel wise cross-subject statistics, all aligned FA images were quality checked to ensure that there were no errors in registration, the FA skeleton was appropriately thresholded, and that each threshold within the FA skeleton could be matched to a white matter tract for each participant. Individual FA maps were then projected onto the mean FA skeleton. Once the reference FA skeleton was created, the "non-FA images" pipeline was used to apply TBSS to DKI maps (i.e., MK, AK, and RK).

Basal Ganglia Microstructure

The Harvard-Oxford subcortical atlas (53–56) was used to create masks for basal ganglia structures, including the right/left caudate, pallidum, and putamen. The structures were extracted and binarized using FSL's "fslmaths" function separately for the right and left sides, resulting in six separate masks in standard space (i.e., right caudate, left caudate, right pallidum, left pallidum, right putamen, left putamen). To account for partial volume effects, each mask was binarized using FSL and eroded by one voxel (i.e., −1) using Analysis of Functional NeuroImage's [AFNI; (57)] "dilate" function. To create the transformation matrices needed to transform the ROIs into each participant's native diffusion (i.e., MK, RK, AK) space, each participant's FA map underwent linear, followed by non-linear transformations using FMRIB's Linear Image Registration Tool [FLIRT; (58, 59)] and FNIRT. Then, FSL's "invwarp" was used to create an inverse warped coefficient using the warp coefficient image generated by FNIRT. Finally, FSL's "applywarp" was run to put each participant's basal ganglia ROI mask into their native diffusion space. Quality checking occurred after each

step within the pipeline to ensure all data were of good quality and without egregious artifacts/errors. Left and right caudate, pallidum, and putamen ROIs were combined to create single caudate, pallidum, and putamen masks for each participant. Each participant's binary caudate, pallidum, and putamen masks were then multiplied against each of their DKI maps (i.e., MK, AK, RK). Mean MK, AK, and RK values were then pulled from each of these basal ganglia structure x DKI maps using FSL's "fslstats" function. These mean MK, AK, and RK values were used in all analyses.

Statistical Analyses

Demographics

For the analysis of demographic variables, SPSS Statistics (v28) was used to conduct basic descriptive and frequency analyses on age, sex, disease duration, lesion load, race/ethnicity, and education. Expanded Disability Status Scale (EDSS) and current disease modifying treatment status were unavailable. All covariates for subsequent analyses were chosen apriori based on previous studies and availability, as such covariates vary based on the dependent variable of interest to ensure we accounted for the most pertinent confounds.

Fatigue Induction Task and Cognitive Fatigue Rate

Behavioral data from the fatigue induction task (i.e., RT, accuracy) and cognitive fatigue rate were inspected for normality. Only RT and accuracy were found to be skewed, and they were transformed using the Box-Cox method to ensure that assumptions of normality were not violated (60). Linear regression analyses were conducted with cognitive fatigue rate as the independent variable and RT and accuracy as the dependent variable (in separate analyses). Sex, age, disease duration, and education were included in the model as covariates. Cognitive fatigue rate was used as the primary independent variable in subsequent analyses.

Neuropsychological Measures

Neuropsychological data were inspected for normality and skewed scores were transformed using the Box-Cox method (60). Two scores required this transformation- CMDI Total and STAI State Total. Linear regression analyses were conducted with cognitive fatigue rate as the independent variable and behavioral score as the dependent variable. Sex, education, age, and disease duration were included in the model as covariates. Though MFIS Cognitive and CMDI Total are the primary variables of interest for our paper, additional subscales for these measures have been included for reference.

Whole Brain Lesion Volume

Whole brain lesion volumes were normally distributed. Linear regression analyses were conducted with cognitive fatigue rate as the independent variable and lesion volume as the dependent variable. Sex, age, and disease duration were included as covariates.

White Matter

To examine the relationship between white matter and cognitive fatigue rate in our MS sample, multiple regression analyses were conducted using FSL's General Linear Model (GLM) Setup utility and TBSS. First, a GLM script was created using the GLM Setup GUI by designating the variable of interest (i.e., cognitive fatigue rate) and covariates of no interest (age, sex, lesion volume, and disease duration). Missing disease duration scores ($n = 4$) were inputted while accounting for age. Two contrasts were included in each design matrix designating 1 or −1 to the variable of interest. This was done to help determine the direction of the relationship between the variable of interest and white matter skeleton. Voxel-wise regression analyses were run on MK, AK, and RK maps using the aforementioned statistical design matrix and FSL's Randomize tool. For the latter, a permutation-based inference (5,000 permutations) correction for multiple comparisons with a Threshold-Free Cluster Enhancement was implemented (Smith and Nichols, 2009). The demean option in Randomize (i.e., -D) was used to demean the data and model in all analyses. Lastly, a family-wise error (FWE) correction was used to correct for multiple comparisons.

The John Hopkins University DTI-based white matter atlases [i.e., ICBM-DTI-81 white matter atlas labels; (61–63)] were used to confirm the location of significant white matter tracts. All results were visualized using FSLeyes.

Basal Ganglia Microstructure

Basal ganglia microstructural data was inspected for normality and skewed scores were transformed using the Box-Cox method (60). Linear regression analyses were conducted with cognitive fatigue rate as the independent variable and mean caudate, pallidum, and putamen microstructural value (i.e., mean MK, AK, RK) as the dependent variable. Sex, age, and disease duration were included as covariates.

RESULTS

Fatigue Inducing Task Performance and Cognitive Fatigue Rate

Overall, the sample's ($n = 62$) mean total accuracy rate across seven runs of a fatigue inducing task was 87.4% (SD = 15.44, Median = 94.23, Range = 37.14–100). Mean reaction time was 885.3 ms (SD = 235, Median = 844.27, Range = 518.95–1,696.80). After accounting for disease duration, age, and education, results of linear regression analyses showed no significant relationships between cognitive fatigue rate and task accuracy or reaction time.

Behavioral and Cognitive Measures and Cognitive Fatigue Rate

Descriptive statistics of behavioral and cognitive measures can be found in **Table 1** ($n = 62$). Results of a multiple linear regression showed that there was a collective significant effect between sex, age, education, disease duration, and cognitive fatigue rate on MFIS Cognitive score [$F_{(5,52)} = 4.02$, $p = 0.004$, $R^2 = 0.28$], with cognitive fatigue rate being the only significant predictor in the model ($t = 3.20$, $p = 0.002$), meaning as trait cognitive fatigue increased, cognitive state fatigue rate also increased. In addition, multiple linear regression results showed that there was

a collective significant effect between sex, age, education, disease duration, and cognitive fatigue rate on SDMT performance [$F_{(5,50)} = 6.39$, $p < 0.001$, $R^2 = 0.39$], with sex ($t = 3.92$, $p < 0.001$) and years of education ($t = 2.83$, $p = 0.007$) as the significant predictors in the model. Another multiple linear regression showed that there was a collective significant effect between sex, age, education, disease duration, and cognitive fatigue rate on the CMDI Evaluative subscale [$F_{(5,52)} = 3.22$, $p = 0.013$, $R^2 = 0.24$], with disease duration ($t = -2.329$, $p = 0.024$) and education ($t = -3.10$, $p = 0.003$) serving as the significant predictors in the model. Models including sex, age, education, disease duration, and cognitive fatigue rate did not significantly predict MFIS Physical, MFIS Psychological, MFIS Total, CMDI Mood, CMDI Vegetative, CMDI Total, STAI State, or STAI Trait. After the *p*-value was adjusted for multiple comparisons, the model predicting MFIS Cognitive and SDMT remained significant.

Whole Brain Lesion Volume and Cognitive Fatigue Rate

After accounting for age, sex, and disease duration in our sample with usable neuroimaging data ($n = 56$), cognitive fatigue rate was not found to be significantly related to whole brain lesion volume.

White Matter Microstructure and Cognitive Fatigue Rate

Significant relationships between cognitive fatigue rate and white matter were found only for RK ($n = 56$). RK is a measurement of diffusivity radial to axonal fibers (i.e., perpendicular to the major axis of an axon), with increases in RK suggesting more compromised white matter microstructure. It has been proposed that increases in RK are related to dysmyelination and/or demyelination (65). After accounting for age, sex, lesion volume, and disease duration, results from multiple regression analyses showed cognitive fatigue rate to be positively correlated ($p < 0.05$) with RK in the corpus callosum (genu, body, splenium), anterior corona radiata (left, right), superior longitudinal fasciculus (right), external capsule (left, right), anterior limb of internal capsule (left, right), posterior limb of internal capsule (left, right), superior corona radiata (left, right), posterior thalamic radiation (right), and posterior corona radiata (right). The analyses were run with and without an apparent outlier without differences in results. Thus, presented results include the apparent outlier. Cluster details, including affected white matter tracts and total voxels of significant clusters within these tracts can be found in **Table 2**. Significant clusters and tracts demonstrating the linear association between RK and cognitive fatigue rate are presented in **Figure 1**. Plots demonstrating the linear association between RK and cognitive fatigue rate in the six tracts with the greatest volume of significant clusters can be found in **Figure 2**. Plots for remaining significant tracts (not pictured) show the same graphical pattern as the plots in **Figure 2**.

TABLE 2 | Number of voxels for significant clusters of RK × slope.

Region name	Number of voxels
Genu of corpus callosum	1,028
Right anterior corona radiata	855
Right superior longitudinal fasciculus	798
Left anterior corona radiata	707
Left external capsule	672
Left anterior limb of internal capsule	573
Splenium of corpus callosum	472
Right anterior limb of internal capsule	471
Body of corpus callosum	436
Left posterior limb of internal capsule	434
Right superior corona radiata	389
Right external capsule	379
Left superior corona radiata	305
Right posterior thalamic radiation	178
Right posterior corona radiata	166
Right posterior limb of internal capsule	125

Basal Ganglia Microstructure and Cognitive Fatigue Rate

Results of multiple linear regression analyses ($n = 56$) showed a collective significant effect between sex, age, disease duration, and cognitive fatigue rate on putamen RK [$F_{(4,47)} = 2.67$, $p = 0.044$, $R^2 = 0.19$]. Individual predictors were examined further and showed that cognitive fatigue rate ($t = 2.50$, $p = 0.016$) was the sole significant predictor in the model. That is, as cognitive fatigue rate increased, RK also increased (i.e., poorer white matter integrity). There was a trend for cognitive fatigue rate being associated with MK in the pallidum after accounting for sex, age, and disease duration [$F_{(4,47)} = 2.51$, $p = 0.054$, $R^2 = 0.18$], with cognitive fatigue rate ($t = 2.08$, $p = 0.043$) and disease duration ($t = -2.20$, $p = 0.033$) driving the model. That is, as cognitive fatigue rate increased, MK in the pallidum also increased (i.e., poorer white matter integrity). No models were significant for the caudate (MK, AK, RK) or aspects of the pallidum (AK, RK) and MK or AK of the putamen. After the *p*-value was adjusted for multiple comparisons, the models predicting putamen RK and pallidum MK were no longer significant.

DISCUSSION

The current study examined the relationship between cognitive fatigue rate and white matter and basal ganglia microstructure using advanced diffusion imaging in a group of pwMS. Our primary aim was to identify potential neural correlates that relate to how quickly or slowly a pwMS becomes cognitively fatigued. In addition, we investigated how cognitive fatigue rate relates to whole brain lesion volume, performance during a fatigue inducing task (i.e., RT, accuracy), and neuropsychological measures. We found cognitive fatigue rate to be related to several white matter tracts (i.e., corpus callosum, anterior

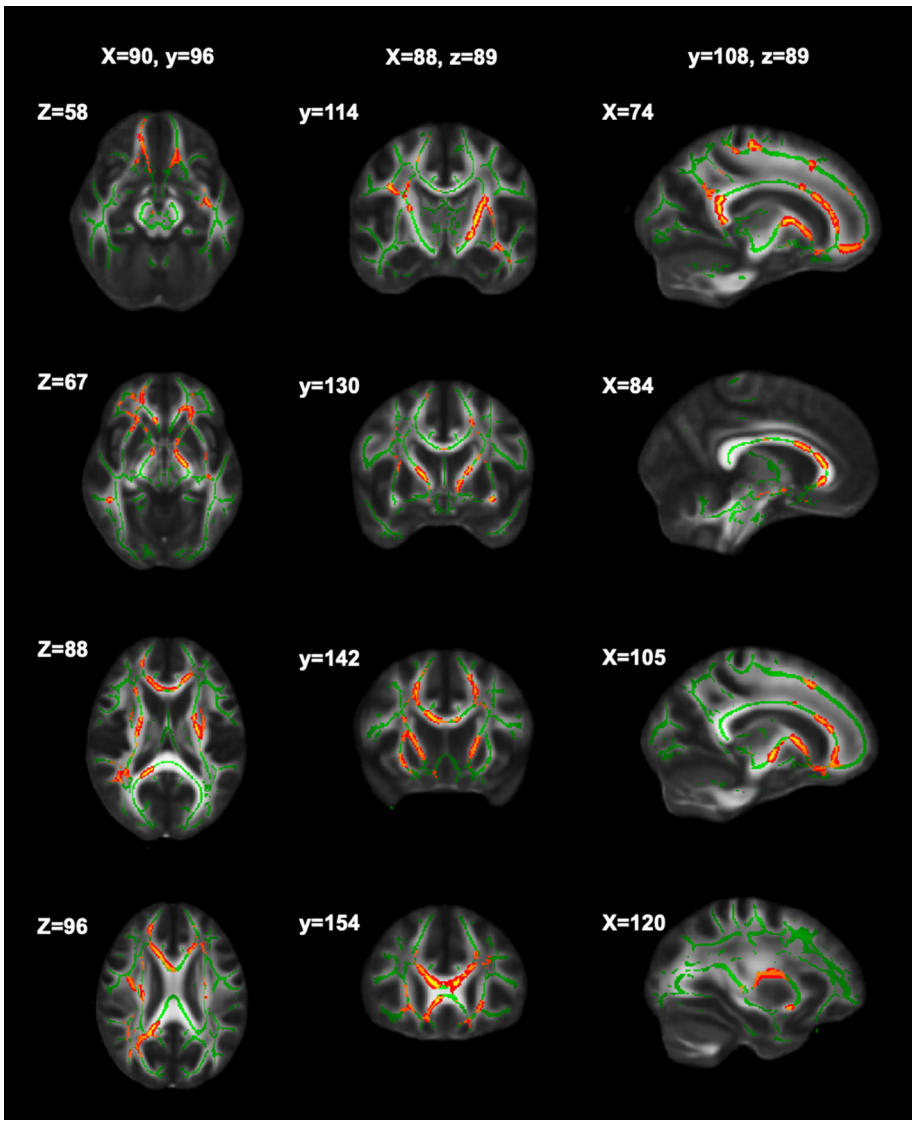

FIGURE 1 | Significant clusters of RK in relation to cognitive fatigue rate. Significant clusters (red) showing where RK is positively related to cognitive fatigue rate (i.e., as RK increases, cognitive fatigue rate increases).

corona radiata, superior longitudinal fasciculus, external capsule, anterior and posterior limb of the internal capsule, superior and posterior corona radiata, posterior thalamic radiation), with many having been associated with basal ganglia connectivity or the previously proposed "fatigue network" (28). In addition, cognitive fatigue rate was associated with the microstructure within the putamen and pallidum (trend), though these did not survive multiple comparisons correction. Lastly, cognitive fatigue rate was found to be associated with trait cognitive fatigue, but not depression, anxiety, whole brain lesion volume, SDMT performance, or performance during a fatigue inducing task (i.e., RT, accuracy). The latter is consistent with previous examinations showing that performance measures, such as reaction time and accuracy, are weakly correlated with fatigue ratings (66–68).

One important finding from the current study is lower white matter integrity is associated with a faster onset of state fatigue (i.e., steeper cognitive fatigue rate), such that when white matter integrity is lower, pwMS show a faster onset of cognitive fatigue. Many of the tracts identified in our study have diffuse connections with brain areas that have been associated with fatigue in MS, including the thalamus, basal ganglia (e.g., caudate, putamen, ventral striatum), and frontal cortical areas. It has been suggested that disruption in networks that connect the cortex, particularly the frontal cortex, with deep gray matter areas such as the basal ganglia and thalami is what drives fatigue (13, 14, 69). Thus, our findings of compromised white matter along tracts that are associated with fatigue networks, such as the internal/external capsules and corona radiata, provide initial evidence that these networks may also be involved in the

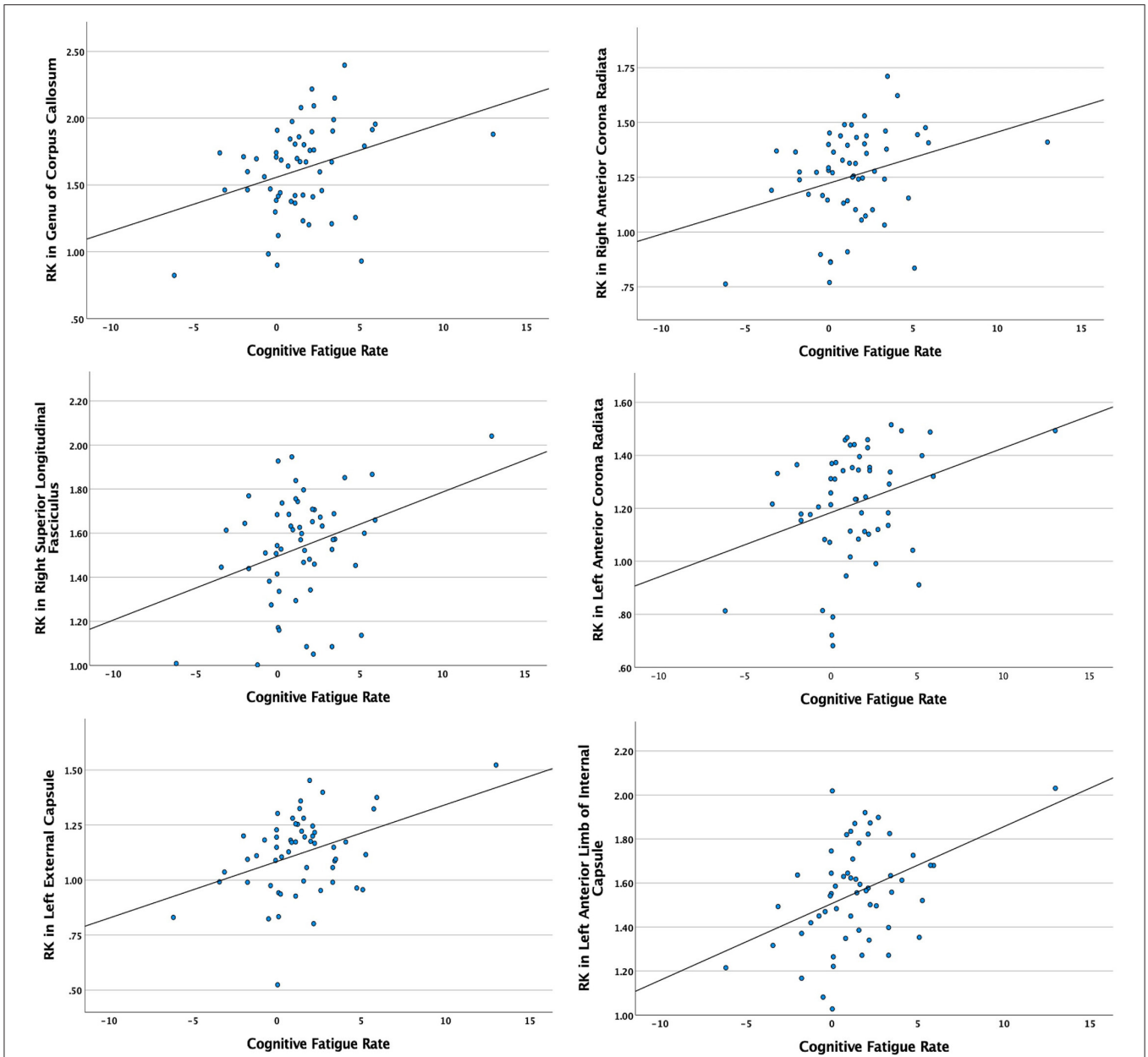

FIGURE 2 | Scatterplots demonstrating the linear relationship between cognitive fatigue rate and radial kurtosis (RK) in tracts with the six greatest volumes of significant clusters. Y-axes = RK in significant white matter tracts. X-axes = cognitive fatigue rate. Analyses were conducted with and without apparent outliers without significant changes in results.

development and experience of fatigue over time (i.e., cognitive fatigue rate).

Many of the white matter tracts found to be significantly associated with cognitive fatigue rate are consistent with other investigations of fatigue in MS. However, it should be noted that no other study to date has looked at cognitive fatigue *rate* in relation to structural brain outcomes. Nonetheless, the congruence of our findings with previous studies broadens our understanding of the structural neural correlates underlying the multifaceted characteristics of fatigue in MS. Tracts identified in our study, including the internal capsule, external capsule, corpus callosum, and corona radiata have all been linked to fatigue in MS (17, 18, 70, 71) and non-MS populations (21, 72). Other studies also identified additional tracts not significant in our analysis, which may be due to differing methodologies or our approach to quantifying fatigue (i.e., cognitive fatigue rate). Given we focused on state cognitive fatigue rate, rather than trait fatigue, the tracts identified in our analysis may be specific to the temporal properties of the onset and progression of fatigue over time, which offers a unique perspective to how we think about and study fatigue in MS.

Given the role of the basal ganglia in previous investigations of fatigue, we thought it important to also examine the microstructure of basal ganglia structures in relation to cognitive

fatigue rate. We did find relationships between putamen (RK) and pallidum (MK; trend) and cognitive fatigue rate, but they did not survive multiple comparison correction. This may be due to the methodology used or the size of our sample. Regardless, previous studies examining the structural and functional properties of basal ganglia structures have demonstrated a significant role of the basal ganglia to fatigue in MS (22, 23, 25, 26, 28), and our results suggest that future studies should investigate the relationship between the microstructure of the basal ganglia and cognitive fatigue.

Additionally, we found a positive association between cognitive fatigue rate and trait cognitive fatigue, as measured by the MFIS. To date, studies examining the relationship between state and trait fatigue have been mixed, with some studies demonstrating no relationship, while others show a small to medium relationship (12, 73, 74). Though we did find a significant association, it is notable that the amount of variance shared by the two variables was small (28%), suggesting that while state and trait fatigue both measure aspects of fatigue, the constructs they measure appear to differ considerably. The way in which state and trait fatigue are measured is also important to consider. In the current study, we took a novel approach by not only examining state fatigue during a fatigue inducing task, but we examined the rate at which pwMS became fatigued. Thus, it is likely we are capturing an aspect of fatigue that is missed by trait fatigue measures. Understanding these differentiations will be crucial for delineating cognitive fatigue and how best to measure it.

Our examination of microstructural neural correlates in relation to cognitive fatigue rate fills a gap in the current literature by showing how possible weakening of white matter pathways impacts the development of fatigue over time. Though investigations of trait fatigue measures have laid the foundation for our understanding of fatigue in MS, they fall short in their ability to adequately capture the in-the-moment experience of fatigue. Our study aimed to remedy this shortcoming by using a state fatigue measure that allowed us to calculate fatigue over time. The identification of white matter tracts related to cognitive fatigue rate has clinical implications, since disruptions of white matter tracts may contribute to dysregulation in previously established "fatigue networks." Thus, by understanding the structural connectivity underlying fatigue-associated brain functioning, we can develop interventions that modulate these fatigue networks.

LIMITATIONS AND FUTURE DIRECTIONS

Though our study produced important and novel results, several limitations exist. First, our sample size was relatively small and limited to individuals with a relapsing-remitting MS disease course, thereby impacting our statistical power and ability to generalize our results to more progressive subtypes. In addition, we did not have access to certain disease-related variables or pertinent comorbidities, such as EDSS, DMT, and sleep disorders/sleepiness and therefore could not determine how these variables may have played a role in our results. Our sample was largely white and highly educated which does not represent the diversity of individuals with MS and limits our ability to generalize our results to the larger MS community. Future studies should make it a priority to recruit more diverse samples to better understand how fatigue impacts individuals from more diverse backgrounds. Next, our analyses of brain metrics were restricted to individual tracts and brain areas, meaning we did not investigate neural network properties. Thus, future work would benefit from not only replicating the results of the current study with a larger, more diverse sample, but also incorporating network-based analyses (e.g., graph theory) to better understand the structural brain networks underlying rate of fatigue. Lastly, while within group studies have many benefits, they also carry limitations. As such, the current study is limited regarding the conclusions that can be made from the results. Future directions include the collection and inclusion of control data to conduct group comparisons.

CONCLUSION

Our results show the relationship between cognitive fatigue rate and microstructural properties in the white matter and in the basal ganglia in MS. We identified white matter tracts that connect brain areas that have been associated with fatigue (e.g., frontal cortical areas, thalami, basal ganglia), showing that specific white matter disruptions may be contributing to the rate at which pwMS become fatigued. Our approach of using cognitive fatigue rate, rather than trait fatigue, brings us closer to understanding how brain pathology may be impacting the experience of fatigue in the moment, which is crucial for developing interventions. These results hold promise for continuing to unpack the complex construct that is fatigue.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kessler Foundation Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CR, GW, JD, and BY contributed to the conceptualization of the manuscript. CR wrote the main manuscript. GW, JD, and BY reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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The pathophysiology of motor fatigue and fatigability in multiple sclerosis

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Multiple Sclerosis (MS) is a heterogeneous immune mediated disease of the central nervous system (CNS). Fatigue is one of the most common and disabling symptom of MS. It interferes with daily activities on the level of cognition and motor endurance. Motor fatigue can either result from lesions in cortical networks or motor pathways ("primary fatigue") or it may be a consequence of detraining with subsequent adaptions of muscle and autonomic function. Programmed exercise interventions are used frequently to increase physical fitness in MS-patients. Studies investigating the effects of training on aerobic capacity, objective endurance and perceived fatigability have yielded heterogenous results, most likely due to the heterogeneity of interventions and patients, but probably also due to the non-uniform pathophysiology of fatigability among MS-patients. The aim of this review is to summarize the current knowledge on the pathophysiology of motor fatigability with special reference to the basic exercise physiology that underlies our understanding of both pathogenesis and treatment interventions.

KEYWORDS

multiple sclerosis, motor fatigue, aerobic capacity, detraining, autonomic dysfunction

Introduction: Fatigue in multiple sclerosis

Multiple sclerosis (MS) is a clinically heterogeneous condition, often referred to as "a disease with a thousand different faces" (1, 2). Patients suffering from MS often experience a multitude of symptoms throughout their lifetime. Whereas, motor deficits are prominent and dominate both the social perspective on patient's disease and the clinically fundamental Expanded Disability Status Scale (EDSS), other symptoms are less easily accessible but nevertheless may have great impact on patients' quality of life and their self-reliance (3–8).

One of the most challenging non-motor complications of MS is the symptom complex termed "MS-fatigue" (1, 2, 9). It is frequent, occurring in a majority of MS patients at some point of disease (10, 11). And it is often hard to measure or even to define in individual patients, since it often occurs with comorbidities like depression or cognitive impairment and may be mimicked or overlayed with side effects of medications given for other MS-symptoms as spasticity of pain (12, 13).

Commonly, fatigue is classified as "primary fatigue" if it is considered to be the immediate result of immune-mediated damage to central nervous system (e.g., cortical lesions or lesions in the subcortical ascending arousal systems). In contrast, "secondary fatigue" results from factors that are indirectly related to MS, e.g., sleep disturbances, chronic urinary tract infections, the already mentioned pharmacological side effects or by deconditioning due to reduced physical activity levels (1).

A common distinction in studies on the pathophysiology of fatigue in patients with MS is made between "motor fatigue" and "cognitive fatigue" (9). Quantitative assessment instruments [e.g., the Modified Fatigue Impact Scale (14) or the Fatigue Scale for Motor and Cognitive Functions (15)] have been developed to differentiate fatigue and to facilitate future studies on the etiology and treatment responses of fatigue subtypes. However, a study analyzing questionnaires which were supposed to reflect the respective dimensions of MS-fatigue failed to confirm the assumed factor structure of three widely applied scales (16).

Regarding the clinical appearance of fatigue, three distinct prototypical manifestations of MS-fatigue have been deduced from pathophysiological considerations by Iriarte et al. (17): First, general adynamia or asthenia might result from inflammation, analogous to the well-known "cytokine induced sickness behavior" seen in the acute stage of many infectious diseases (18). Second, the long-known Uhthoff-phenomenon, a worsening of symptoms triggered by patients' engagement in physical activities, may be attributed to impaired action potential conduction in demyelinated axons that occurs with increased temperature (19, 20). Third, pathological mental and physical exhaustibility may occur independently of body temperature due to lesions in neuronal networks which reduce their functional efficiency and perseverance in task handling (21, 22).

Considering the concepts of primary and secondary MS-fatigue, it seems likely that both central and peripheral alterations are relevant in the pathophysiology of physical exhaustibility and generalized "motor fatigue."

An assessment of the central component of fatigue is especially challenging due the intrinsic physiological complexity of CNS network function and the dependence on indirect readouts to analyze it. From the multitude of potential factors, three are of special relevance in the context of this review:

First, given the high incidence of depression and other mood disorders in MS, it is difficult to distinguish their genuine impact on the course and characteristics of reported fatigue (2, 23, 24). In imaging studies, lesions in specific brain areas were correlated with depression and fatigue in MS, suggesting a common elements in their pathophysiology (25, 26). It is nevertheless possible to define specific characteristics of concomitant depression and fatigue in MS patients on the basis of a parallel assessment of perceived "action control" (27). Despite the frequent coincidence of both symptoms in MS, there is no convincing data to support specific beneficial effects of antidepressant medications on MS-fatigue (28, 29).

Second, both increased and decreased connectivity between brain regions may give rise to motor fatigue. Functional magnetic resonance imaging (fMRI) studies could demonstrate that functional connectivity between brain regions is increased, although structural connectivity is decreased in patients with MS with cognitive deficits. Changes in functional connectivity may thus be maladaptive and lead to functional deficits even beyond isolated reduced performance in neuropsychological tasks (30). A transcortical magnetic stimulation study in RRMS–patients found an attenuated connectivity between premotor- and primary motorcortex which was significantly correlated with reported motor fatigue. In contrast, corticospinal connectivity was retained (31).

Third, a reduced or non-stable volitional drive to descending motor pathways will impede performance in motor tasks. Volitional drive is usually upregulated over time to keep constant force despite peripheral muscle fatigue in persistent submaximal contractions (32). With ongoing effort and exhaustion, feedback signals from peripheral muscles increase and make it more difficult to maintain volitional motor drive. Since MS-patients frequently suffer from depression, emotional stress and chronic pain, it seems justified to assume that their abilities to keep up adequate motor drive are reduced when compared to healthy controls (33, 34). Although the conduction pathways between brain and spinal cord are stable in MS-patients (35), a rundown in the actual motor output is supported by studies on central fatigue (36, 37).

Nevertheless, even with regular cortical network function and volitional drive, an important prerequisite for physical performance and endurance is an appropriate oxygen and energy supply which is physiologically adapted rapidly by appropriate changes of cardiac, pulmonary and vascular function parameters (38). Furthermore, effective movements rely on an accurate orchestration of motor units which is a complex computational task for the CNS (39). Finally, the muscle fibers themselves differ in their size, contractility and metabolism with respect to their utilization, i.e., training level (40, 41).

Considering this complex integration of peripheral and central factors, the intention of this review is to summarize our current knowledge on the interdependent pathophysiology of motor fatigue, fatigability and changes of physiological exercise responses in MS-patients.

Abbreviations: CNS, Central Nervous System; EDSS, Expanded Disability Status Scale; MS, Multiple Sclerosis; OUES, Oxygen Uptake Efficiency Slope; VO_2max, maximum oxygen uptake; VO_2peak, peak oxygen uptake.

Current concepts of motor fatigue in MS: Definitions, assessment, pathophysiology and training interventions

In this section, we will discuss the existing knowledge and concepts of motor fatigue and fatigability in MS with a special focus on its pathophysiology. To avoid ambiguity, we will briefly discuss their definitions and operationalization first.

Basic definitions of motor fatigue and fatigability in MS

By definition, the individual perception of being exhausted is purely subjective. In contrast, observable changes motor task performance can rather easily be detected and quantified. Therefore, the term "objective fatigability" can be used to address motor symptoms of MS-fatigue more specifically (42). On the other hand, the objective changes in motor functions may not fully reflect the degree of subjective impairment. Therefore, data from questionnaires assessing motor fatigue are still relevant, especially when it comes to judging the overall benefit of therapeutic interventions and for estimating the prevalence of fatigability in larger patient samples. As a consequence, studies engage both clinical tests and fatigue questionnaires (43).

Assessment of self-perceived fatigue

Fatigue is reflected to a variable degree by the overall MS-fatigue scores, e.g., the Fatigue Severity Scale and the Modified Fatigue Impact Scale (44, 45). The Fatigue Scale for Motor and Cognitive Function (FSMC) is another well validated instrument for addressing fatigue (15). Based upon FSMC, a recent Norwegian survey among 1,454 patients, found equally high prevalence of motor (82%) and cognitive (72%) fatigue. Despite these already high rates of *subjective motor fatigue*, the prevalence of *objective fatigability* may be even higher since in the absence of subjective fatigue, functional testing may still reveal alterations in motor performance (46). The scores of common fatigue questionnaires correlate with each other, but they may be confounded by general disability and are intended to reflect the multitude of dimensions of fatigue rather than to focus on specific aspects that may be related to pathophysiological changes in exercise responses (10, 47–50).

Assessment of objective fatigability in response to task performance

From the high prevalence of perceived fatigue in questionnaires one would likewise expect objective fatigability in patients with MS. Although objective fatigability is indeed prevalent in patients perceiving fatigue, the levels of objective and perceived fatigue are only weakly correlated (51). Studies that engaged patients in rather artificial motor tasks, e.g., repeated voluntary contractions of hand- or leg muscles over defined periods and at defined force levels gave conflicting results regarding the correlation of task performance and perceived fatigue scores within the defined scores, although perceived exertion during the task itself was clearly increased in MS-patients (50, 52, 53).

An alternative to the study of fatigability during isolated movements (which are at best fragments of meaningful, intention-guided motor sequences) is testing the patients' performance in more complex tasks which may more closely resemble challenges patients undergo in daily life. One of the most extensively studied and rather easily accessible parameters is walking endurance, defined as the decline of walking speed between the first and the last minute of a 6-min-walking task. Patients with MS show increased objective fatigability in this test when compared to healthy subjects. Furthermore, walking leads to force reductions in distinct muscle groups and to impaired (54).

Besides the retrospectively stated perceived fatigue which is measured in classic fatigue scores ("trait fatigue") and the objective measurements of functional parameters (e.g., force or velocity), interoceptive signals occurring during physical activity may hamper *ad-hoc* task performance by inducing the feeling of growing exhaustion or difficulty. This so-called "state fatigue" is commonly estimated using visual analog scales during the exercise itself (43). Studies testing muscle force, walking and cognitive tasks could demonstrate clear increases in state fatigue during tasks, but again these increases were only weakly correlated with the objective worsening of performance, i.e., fatigability (55, 56). To explain the fact that classic objective measures of fatigability neither correlate with "state" or "trait"–fatigue, Enoka et al. (43) recently suggested that increasing "extra demands on the nervous system of persons with MS" during task performance lead to fatigue perception. In other words, it is more demanding for MS patients to maintain the nervous drive to activate muscle that is required for movements and maintaining this drive contributes a major part to the perceived fatigability. This hypothesis is in line with previous findings of other groups that studied state fatigue and the effects of training interventions on fatigue parameters, muscle strength and activation parameters (57, 58).

Assessment of objective fatigability in response to exercise

A critical parameter in the assessment of exercise responses in both healthy and diseased subjects is the duration and the intensity of exercise, the latter usually defined as percentage

of the individual's maximum output in that particular task. A special difficulty in MS is that due to the heterogeneity of motor deficits among patients, the results of standard exercise tests show a high degree of variance and are only valid if disability does not interfere directly with engagement in the task, e.g., paresis of the legs with riding on a standard bicycle ergometer or severe ataxia with a simple walking test.

Patients with MS walk slower and their speed declines faster over time than that of healthy controls (59, 60). In contrast, some, although not all studies that assessed isolated muscle fatigability did demonstrate significant differences in force decline during voluntary contractions between MS patients and healthy controls (52, 57, 61). In studies on muscle contractions evoked by peripheral electric stimulation, responses to repeated stimulation have been reported to be reduced in MS patients compared to controls, especially in lower extremity muscles (62–64). Beyond abnormal recruitment responses during voluntary contractions, there clearly is a peripheral component of muscle fatigue that seems to be independent of neurotransmission at the neuromuscular endplate or of sarcolemmnal excitation, since compound motor action potentials are usually unchanged. Nevertheless, the buildup of force during evoked tetanic contractions is reduced and relaxation prolonged (61, 65). Remarkably, also intracellular pH and phosphocreatine have been reported to drop faster in fatiguing muscle of MS patients (65).

From these findings, the question arises whether motor fatigability in MS may be due to insufficient oxygen- or nutrient supply or whether they are caused by changes in neuromuscular structure and function. Before discussing integrative pathophysiological concepts of fatigability in MS, the current knowledge on aerobic capacity as a central component of physical fitness will be summarized.

Assessing exercise responses of MS patients using spiroergometry

Common measures of physical fitness are derived from parameters measured during spiroergometry challenges. From the analysis of breath gases under and heart rate (maximum heart rate, HRmax), the oxygen uptake rate (VO_2max or aerobic capacity), the respiratory ratio (RER) and the oxygen uptake efficiency slope (OUES) can be estimated. Oxygen costs for performing daily activities as stair climbing, walking, sitting or standing up or even rolling in bed are higher in MS patients than in age and sex matched controls. The increased oxygen consumption is correlated with higher perceived fatigue (66). This may be the result of less effective movements in MS patients due to altered motor programs. In other words, when compared to healthy controls, MS patients require more energy and thus depend on a better physical fitness to perform equal motor tasks.

Especially the aerobic capacity VO_2max has widely been used to characterize exercise responses and energy expenditure in MS patients. It is defined as the maximum amount of oxygen an individual can use in a given time and can easily be measured by subtracting the amount of oxygen in the inspired from that in expired air. A strong correlation exists between an individual's VO_2max and its ability to engage in endurance motor tasks, but also in many other kinds of physical activities (67, 68). Aerobic capacity is thus not identical with physical fitness, but besides strength, flexibility and other parameters it is one of its central components.

To be extracted from the inspired air, oxygen has to be utilized by working muscle or other tissues. In healthy humans, the amount of oxygen which would be utilized if all muscles were intensely activated at the same time by far exceeds the amount of oxygen that can be delivered to them by the cardiovascular system. Therefore, it is the capacity of the cardiovascular system to deliver oxygen that sets the upper limit for aerobic endurance performance in motor tasks. In neurological disorders, however, the activation of muscles and therefore their cumulative oxygen utilization may be restricted. In such a situation, which may also occur in MS, a reduced VO_2max may reflect limitations of physical activity by disability itself rather than the limitations of the cardiovascular system response. Therefore, it is of critical importance to apply the rather strict criteria for the estimation of VO_2max that have been introduced by Midgley et al (69) and which were applied in the studies by Langeskov–Christensen et al. (73, 79). These require that

1. The measured O_2-uptake remains constant despite increasing workload.
2. The achieved heart rate is close to the expected heart rate calculated from the individual's age,
3. The measured RER is above 1.1 and that the subjective rating of exertion exceeds predefined values (e.g., Borg's rating of perceived exertion > 16).

Fulfillment of criterion 1 means that the individual is shifting to anaerobic metabolism to provide energy for the increasing muscle work, since no additional O_2 can be delivered. Criterion 2 relies on the fact that oxygen consumption depends on oxygen transport through the circulation and thus cardiac output, as reflected by the strict correlation between HRmax and VO_2max (68). Criterion 3 means that the amount of CO_2 that is expired per time is above that of inspired O_2. The additional release of CO_2 from plasma bicarbonate stores is reflects the acidification of the blood during anaerobic metabolism, i.e., lactic acidosis [criterion 1, (70)].

Spiroergometry has been thoroughly validated for the use among ambulant MS patients (71–73) and used extensively to study the effects of training and other interventions on MS patients' physical fitness (74). A systematic review and meta-analysis identified 40 studies that altogether analyzed data

of 1,029 MS patients and 165 healthy controls (73). When comparing the results of classic whole-body spiroergometry, the mean value reported in studies was 25.2 ± 5.2 ml·kg^{-1}· min^{-1} for MS patients and 30.9 ± 5.4 ml·kg^{-1}·min^{-1} for controls. For spiroergometry restricted to upper limb muscles, the respective values of the single study (75) that compared both groups, the respective values were 10.2 ± 4.7 ml·kg^{-1}·min^{-1} (MS patients) vs. 14.3 ± 1.6 ml·kg^{-1}·min^{-1} (controls).

As a result of their 2015 meta-analysis, Langeskov-Christensen et al. (73) report a significant reduction of the VO_2max among MS patients over the pooled sample. Three of the five included studies reported significantly lower VO_2max values among MS patients compared to controls (76–81). Lower mean values of VO_2max in the studied patient samples correlated with higher mean disability and increased age (73).

Additional studies published after the abovementioned meta-analysis added further evidence to support the relevance of reduced aerobic capacity in MS. The work of Klaren et al. included 162 MS patients and 80 controls and reported significantly lower values for VO_2max, RER, HRmax and other parameters among MS patients. Furthermore, when MS patients were classified according to their scores on the patient determined disease steps (PDDS)–scale, significant differences in VO_2max could be observed between those defined to have mild, moderate and severe disability, with the lowest values seen in the group with the highest degree of disability (82). Likewise, a study by Driehuis et al. found reduced VO_2max in MS patients compared to reference values. However, in the studied sample there was no correlation between VO_2max and physical activity. A correlation with fatigue as measured by the "Checklist for Individual Strength 20r" was reported by the authors (83) whereas two other recent studies and another meta-analysis reported only weak or even lacking correlations between reductions of VO_2max and fatigue (84–86).

Taken together, different independent studies indicate that VO_2max is reduced in MS. Although the relevance of this reduction in aerobic capacity is less clear we will subsequently discuss their pathophysiology in the context of reduced physical activity and autonomic function.

Pathophysiological concepts of reduced aerobic capacity in MS

Basically, two different and at least partly conflicting pathophysiological concepts of MS-related limitations in cardiorespiratory parameters exist and will be discussed here. First, the mere lack in physical activity may be considered the central or even the only causative factor. We will thus refer to this concept as the *deconditioning hypothesis*. Second, CNS-lesions causing alterations in autonomic function on the level of cardiac, respiratory and vascular control can be considered to hamper the appropriate physiological adaptive responses during exercise, a concept which may be termed the *central dysregulation hypothesis*. Despite the fact that a combination of both seems likely to appear in reality, a dominance of one of the components is suggested by some authors (87). A brief summary of the involved factors is given in Figure 1.

In more detail, the deconditioning hypothesis implies that reduced VO_2max is caused by a decreased metabolic activity of contracting skeletal muscle, i.e., an alteration of muscle metabolism that cannot be explained by an acute innervation deficit of the activated muscle. Instead it is suggested that the chronic lack of exercise and muscle activation would cause a loss in the oxidative capacity of muscle fibers due to altered mitochondrial function, thereby reducing oxygen utilization (87). However, even under regular physiological conditions, a considerable part of skeletal muscle fibers is not capable of a fully oxidative metabolism and releases lactate to the blood which is either metabolized by other tissues or converted to glucose by the liver and then returned back to the muscle (88, 89). As a consequence, oxygen utilization by the liver increases during exercise in healthy subjects (90–92).

To our best knowledge, despite the well-known associations between altered liver function and fatigue in other medical conditions, there are no studies addressing hepatic function during exercise among MS patients.

In contrast, as already stated above, alterations of muscle function in MS have been described even decades ago on the level of altered contraction dynamics and muscle architecture and strength (93, 94). In addition to that, fibers of the tibialis anterior muscle from MS patients are smaller, have an impaired oxidative capacity (which is frequently interpreted as impaired mitochondrial function) and rely more on anaerobic metabolism than those obtained from healthy controls (95, 96), but myosin-ATPase activity is not increased in MS patients compared to controls (97). This finding indicates that fatigability during exercise in MS patients is unlikely to be the result of increased energy demands of the activated muscle. Within the deconditioning hypothesis, this is an important complementary information since it allows the conclusion that the reduced VO_2max is indeed reflecting reduced muscle activity. Otherwise, it could be argued that increased energy demands of rather few activated fibers might lead to local metabolic decompensation and rapid exhaustion despite a globally decreased energy and oxygen consumption. Functional measurements by Kent-Braun et al. (98) indeed gave no evidence for metabolic failure in contracting muscles of MS patients. Whereas, deconditioning can be expected to be prominent in the leg muscles of MS patients with impaired ambulation, one would not expect it to occur in non-affected upper extremity muscles. Thus, the results of two recent studies that demonstrated reduced oxidative capacity in both

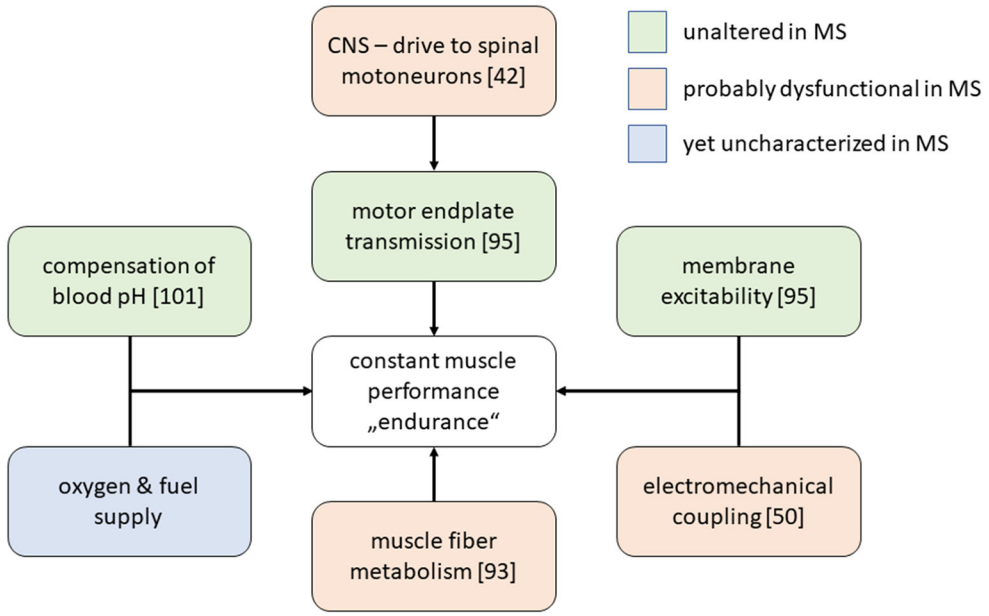

FIGURE 1
Selected physiological processes that are required to maintain stable muscle force production. Among MS-patients, most of these processes have been described in MS patients samples and, according to the given in the figure legend, were found to be altered or not. The metabolic integration between muscle, liver and other organs during exercise has not yet been characterized thoroughly by appropriate experiments in MS patients.

leg (gastrocnemius) and wrist flexor muscles of MS patients compared to controls raise a challenge to the deconditioning hypothesis (99, 100).

The central dysregulation hypothesis assumes that the limited ability of MS patients to exercise is impaired due to altered cardiac, circulatory, respiratory or thermoregulatory responses (101).

Whereas, cardiac and circulatory responses in MS have been addressed by various studies, rather few have covered respiratory and thermoregulatory responses. On average, pulmonary function in terms of spirometry responses is not altered in MS, although individual patients may show signs of impaired respiratory muscle strength (102). During exercise, ventilatory dysfunction has been reported in MS patients, i.e., the efficiency of ventilation seems to be rather low and could not be improved by a 6-month training intervention (103). The relevance of this finding with respect to fatigability still remains to be defined. At least, lactate levels do not differ significantly between MS patients and controls during exercise, indicating that there is probably no increased demand for respiratory compensation to avoid relevant pH-shift (104).

The sweating response to exercise is impaired in MS patients due to impaired sudomotor function, leading to larger increases in body temperature during exercise with potential detrimental effects on performance. Results of studies that aimed to quantify this effect gave conflicting results (105–108).

The pathophysiological link between cardiovascular dysregulation and impaired exercise performance is rather straightforward. Briefly, the insufficient cardiac inotropy or chronotropy would prevent the necessary increase in cardiac output to permit delivery of dissolved oxygen to the tissues. On the other hand, a failing vasomotor response may lead to an inadequate allocation of cardiac output with a relative perfusion deficit in working muscle or to systemic hypo- or hypertension during exercise. Clinical data point to a rather high prevalence of autonomic dysfunction in MS (109). In particular, cardiac function seems to be altered in MS patients compared to controls and even severe neurogenic cardiomyopathy has been reported to occur (110, 111). Heart rate variability is an easily available parameter that reflects cardiac autonomic control and indeed gives pathological findings in MS patients, with a majority of studies indicating a correlation with CNS lesions in regions that are associated with autonomic regulation of cardiac rhythm (112–116). In studies investigating exercise effects on aerobic capacity of MS patients, abnormal heart rate responses were reported which in some studies were ameliorated to training, whereas they abnormal in others (87, 117, 118). Another recent finding is that the recovery of heart rate following exercise *via* parasympathetic pathways is impaired in MS patients. This is in line with other data indicating parasympathetic dysfunction in MS (100, 101). Besides heart rate modulation, an increase in stroke volume is a regular response to exercise. This

response was shown to be diminished in a cross-sectional study comparing MS patients and controls and was not reversed by a 6-month-training intervention. Instead, MS patients keep their systemic blood pressure by increasing vascular resistance with potential negative effects on cardiac workload (119, 120).

Although the evidence suggests that both deconditioning and autonomic dysfunction are frequent in MS and may even potentiate each other, it is rather difficult to specify their contribution to clinical fatigability or perceived fatigue in individual patients. Neither aerobic capacity nor autonomic dysfunction are strongly–if at all–correlated with classic fatigue scores or quality of life (85, 86, 121, 122).

Training effects on cardiorespiratory fitness

The question whether it is possible to raise the reduced VO_2max in MS patients by training is relevant in the light of the discussion whether altered the cardiorespiratory fitness of MS patients is a consequence of autonomic dysregulation or other primary sequela of the immune mediated disease, or whether it is merely a consequence of deconditioning and lack of exercise.

In contrast to earlier recommendations to restrict physical activity in MS patients, cardiorespiratory fitness in patients with MS can be increased safely and effectively by appropriate training and exercise (123). Endurance- and resistance training of moderate intensity are recommended for patients with mild to moderate disability (124). Classic types of endurance training are bicycle ergometry, combined arm-leg or isolated arm ergometry and treadmill walking. Individual circumstances should nevertheless be considered: Patients receiving oral or intravenous glucocorticosteroids are at an increased risk for acute hypertension and hyperglycemia, so a monitoring of these parameters is recommended before and during exercise. Relevant critical events or severe deteriorations of mental or physical health have hardly ever been reported to occur in physical exercise programs for multiple sclerosis and relapses do not occur more frequently in MS patients on exercise programs. An instructive review on practical aspects of exercise training in MS is given by Learmout and Motl (125).

Beneficial effects on fatigue scores and QoL can be achieved for patients participating structured training programs (122, 126–128). Aerobic exercise has been especially well-studied with this respect. In their recent meta-analysis, Andreu-Caravaca et al. analyzed 43 studies that had investigated effects of aerobic training or control interventions on functional parameter (i.e., walking speed and endurance) as well as on parameters reflecting cardiorespiratory fitness (i.e., VO_2max). In the meta-analysis, significance for improved cardiorespiratory fitness could only be demonstrated for interventions that applied moderate intensity bicycle training at least 3 days a week on moderate intensity. Furthermore, most likely due to heterogeneity in study protocols and studied patient samples, the pooled analysis of studies could not detect a difference between aerobic training and control interventions, most of which applied some kind of exercise training as well.

As already mentioned, the extent of improvement in cardiorespiratory fitness varied widely, depending on the applied interventions: Whereas, for instance, a study by Mostert and Kesselring (129) found no increase in VO_2max following a rather short intervention period of 3 weeks with 30 min of training for 5 days a week, Ponichtera-Mulcare et al. (130) and Rodgers et al. (131) reported an almost 20%-increase in ambulatory, but of only 5% in non-ambulatory MS-patients following a 6-month intervention of aerobic exercise on every second day for 30 min.

Whereas, physical activity is usually beneficial when conducted in a safe framework and at an individually optimized intensity, some patients may report even increased fatigue or a worsening of other symptoms. To improve the applicability of aerobic training in such patients, special modifications have been developed to avoid potential detrimental effects of training. Increases in body temperature during training which might lead to a worsening of MS symptoms in predisposed patients are prevented in special aquatic exercise programs. Studies that investigated the effects of exercise while immersed in water (usually 28°C) found beneficial effects on QoL and fatigue (132, 133) as well as on cardiorespiratory fitness (134). Furthermore, to achieve larger effects on endurance with lesser intensity of training, e.g., in patients that have severe fatigability, normobaric hypoxic endurance training might be an alternative strategy since it takes advantage of the same physiological mechanisms that are applied in high altitude training (135, 136), although by now, none of the studies investigating hypoxic endurance training could prove superiority to standard exercise. Treadmill walking and strength training seem to be less suitable to increase cardiorespiratory fitness (137). A very recent meta-analysis concluded that combined endurance and resistance exercise programs have the highest probability to improve both subjective fatigue and objective fatigability (138). Besides potential positive effects of physical activity on cardiovascular fitness and fatigue, patients may be encouraged to participate in other exercise programs with potential benefits for quality of life, e.g., by improving bladder control (139).

Taken together, the existing literature gives evidence that training interventions of appropriate duration and intensity can increase cardiorespiratory fitness in MS patients. However, even with sophisticated and well-instructed interventions of 6-month training, the reported VO_2max values of MS-patients are clearly lower than those reported for general population samples (e.g., median values for 50-50 year old males: 38.5 $ml \cdot kg^{-1} \cdot min^{-1}$; females: 31.0 $ml \cdot kg^{-1} \cdot min^{-1}$) (140). Compared to these general reference values, the *ad-hoc* VO_2max of healthy controls that are reported in the literature appear rather low. To our

knowledge, there are no studies that have directly compared the training-induced increases in VO_2max of healthy controls and MS patients, which would be helpful to answer the question whether detraining or MS itself contribute more to the impaired cardiorespiratory fitness of MS patients.

Summary and conclusion

Motor fatigue is a frequent and disabling symptom of MS. It can be assessed using questionnaires that in general assess the perceived quality, intensity and temporal aspects in a retrospective manner ("trait fatigue"). In contrast, the perceived exhaustion during motor task performance or at other defined time points can be estimated using instantaneous ratings, e.g., *via* visual analog scales ("state fatigue"). Objective functional measurements, e.g., walking distance or force generation clearly demonstrate change of performance indicating fatigability in MS patients. These are, however, not strictly correlated with perceived state or trait fatigue. Physical disability that is related to the primary CNS lesions in MS, e.g., paresis and ataxia, have a major influence on fatigue parameters and constitute methodological problems for defining the pathophysiology of the observed phenomena since they overlay with prominent secondary factors as deconditioning of peripheral muscle and autonomic reflexes as well as with other more subtle primary CNS-related sequelae, e.g., damage to autonomic regulatory pathways or complex cortical networks involved in motor planning and interoception. As a result of combined deconditioning and altered autonomic function including pathological cardiovascular function, the aerobic capacity is clearly reduced in MS-patients which inevitably reduces physical fitness, although the observed degree of correlation between the degree of impaired aerobic capacity varies widely between studies, most likely due to confounding effects of general disability and other factors affecting trait fatigue. Based upon the hypothesis that deconditioning due to a deficit in physical activity is a major factor in the pathogenesis of motor fatigue, training interventions have been extensively studied and have been shown to be safe and effective for improving physical fitness in MS-patients. Training effects on fatigue vary widely between studies and again depend on the patient's disability, comorbidities and on the applied training protocol. An integrated and personalized approach is thus necessary for addressing motor fatigue in MS patients.

Author contributions

RP and UZ conceptualized the study, collected and discussed the literature, and prepared the manuscript. Both authors approved the final version.

Conflict of interest

Author RP has received research grants from Novartis. Author UZ received research support as well as speaking fees and travel funds from Almirall, Alexion, Bayer HealthCare, Bristol Myers Squibb, Biogen, Janssen, Merck Serono, Novartis, Octapharma, Roche, Sanofi Genzyme, and Teva.

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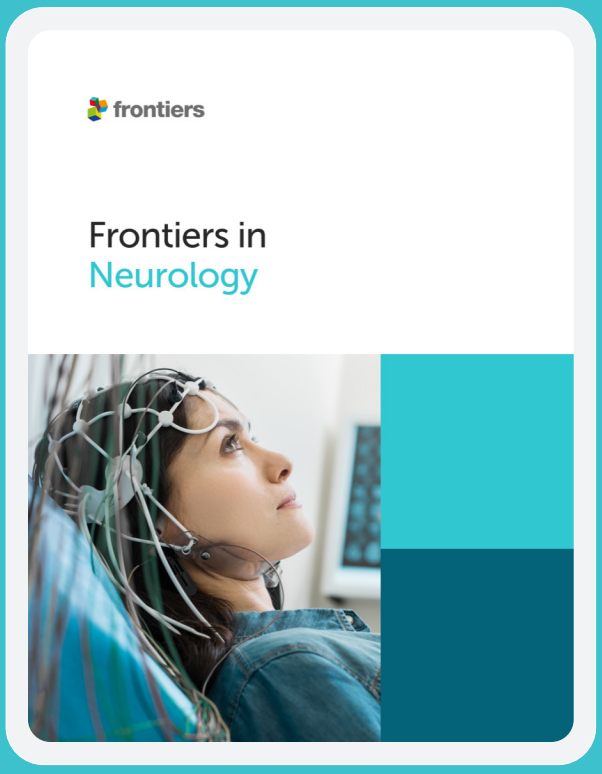

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