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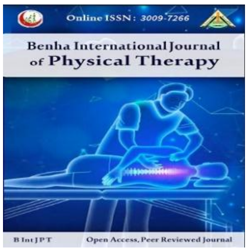

Original research

Relationship between Fatigue and Balance in Patients with Multiple Sclerosis: A narrative review

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Abstract

Background: Fatigue and balance dysfunction are common and debilitating symptoms of multiple sclerosis (MS), often affecting mobility and independence. These symptoms may be interconnected due to shared neural mechanisms. **Purpose:** This narrative review aimed to investigate how central fatigue contributes to impairments in various aspects of balance control, including static, dynamic, anticipatory, and reactive postural responses. **Methods:** A comprehensive search of Science Direct, PubMed, and Goggle Scholar was conducted using keywords such as multiple sclerosis, fatigue, balance impairment, neurorehabilitation, postural control, central fatigue. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from April 2006 to May 2025 were included, and only English language studies were reviewed due to lack of translation-related sources. Papers such as oral presentations, conference abstracts, unpublished manuscripts and dissertations that were not part of larger scientific studies were excluded. **Results:** Evidence suggests that central fatigue negatively affects balance control by disrupting sensory integration, slowing information processing, and reducing neuromuscular efficiency. Although several rehabilitative strategies such as vestibular rehabilitation, aquatic therapy, dual-task training, and non-invasive brain stimulation have shown promise, research remains limited by small sample sizes, inconsistent methodologies, and short follow-up periods. **Conclusion:** The relationship between fatigue and balance dysfunction in MS is complex and multifactorial. Addressing both symptoms concurrently may enhance functional outcomes. Future research should prioritize standardized assessment tools and long-term, integrative interventions targeting both physical and cognitive dimensions.

Keywords: Balance impairment, Central fatigue, Fatigue, Multiple sclerosis, Neurorehabilitation, Postural control.

INTRODUCTION:

Multiple Sclerosis (MS) is a chronic autoimmune, inflammatory, and neurodegenerative disease of the central nervous system (CNS), usually affecting teens, specially girls. It is characterised through demyelination, axonal injury, and subsequent neurological impairment that regularly progresses over time. The etiology of MS is multifactorial, concerning genetic susceptibility—specially HLA-DRB1*1501—and environmental factors such as vitamin D deficiency, Epstein–Barr virus (EBV) contamination, and smoking[1]

The disease typically follows one of several clinical courses, most commonly relapsing-remitting MS (RRMS), which may evolve into secondary progressive MS (SPMS). Less frequently, patients present with primary progressive MS (PPMS), which experience a progressive deterioration[2]. Common early symptoms include fatigue, optic neuritis, sensory disturbances, limb weakness, and impaired coordination. As MS progresses, it may result in cognitive decline, spasticity, and substantial disability[3].

Fatigue and balance impairments are two of the highest prevalent and disabling symptoms suffered by individuals diagnosed with multiple sclerosis (MS), often contributing to significant reductions in functional independence and quality of life. Fatigue in MS is multifaceted—encompassing physical, cognitive, and psychosocial domains, frequently emerging as the most debilitating symptom despite normal strength or mobility[4]. Balance disorder is not unusual in humans with MS and contributes to falls, mobility troubles, and reduced quality of life[5]. Recent evidence indicates that these two symptoms are closely interrelated: extra fatigue degrees notably predict poorer stability overall performance, in particular while primary sensory integration is challenged, suggesting shared neurological mechanisms possibly concerning cerebellar and brainstem circuits[6].

Furthermore, experimental studies have confirmed that inducing cognitive fatigue can directly delay impair balance manage in MS sufferers, specifically under eyes-open conditions that require active sensory processing[7]. Interventions which include aquatic therapy, vestibular rehabilitation, and postural education have shown promising outcomes in reducing both fatigue and stability deficits, similarly emphasizing their interconnected nature[8].

Fatigue in multiple sclerosis (MS) is highly prevalent—affecting between 70 % and 90 % of patients— and is reported by 81 % of participants in a large Norwegian cohort, with greater frequency in women and those with more severe disability[15]. It is multidimensional, divided into primary fatigue directly caused by MS pathology and secondary fatigue arising from comorbidities such as depression, poor sleep, or medication side effects[16].

The pathophysiology of MS-associated fatigue is complex and remains under investigation. Central mechanisms—particularly disruptions in structural and functional brain networks—appear to dominate. Neuroimaging links fatigue more strongly to altered functional connectivity within regions like the cingulate cortex, basal ganglia, and prefrontal areas than to lesion burden, suggesting that network inefficiency and impaired cortico-subcortical communication underlie fatigue[17]. Moreover, reduced gray matter volume in subcortical nuclei (thalamus, basal ganglia) predicts long-term fatigue severity, pointing to a neuroanatomical substrate for the symptom[18].

A specific form—motor fatigue—stems from deficits in cortical motor pathways and abnormal muscle recruitment due to deconditioning and disrupted neuromuscular signaling. Key physiological processes for sustained muscle force (central drive, neuromuscular transmission, membrane excitability, muscle metabolism) are variably affected in MS: while membrane excitability may remain intact, impairments in central drive and metabolic coordination (including oxygen and fuel delivery across organs during exercise) are evident but not yet fully characterized[19].

Psychosocial factors—depression, anxiety, sleep disorders, and physical inactivity—further exacerbate fatigue through shared neurobiological pathways (dopaminergic and serotonergic systems), creating a self-reinforcing cycle of worsening symptoms[16]. Despite extensive study, no single treatment reliably alleviates MS-related fatigue, largely due to its heterogeneity and subjective nature. Consequently, multidimensional assessment strategies that integrate central neurobiological mechanisms with psychosocial contributors are critical for guiding the development of more effective interventions[20].

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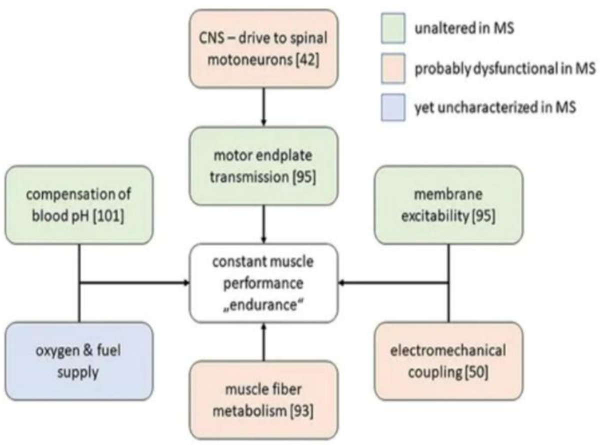

Figure 1. Selected physiological processes that are required to maintain stable muscle force production among MS-patients.

Multiple sclerosis fatigue (MS) is now understood to involve both central and peripheral mechanisms, with central fatigue—the inability of the CNS to generate or sustain adequate motor output—being predominant in most patients. Peripheral fatigue arises from dysfunction at the neuromuscular junction or within muscle fibers. In MS, demyelination and neuroinflammation disrupt signal transmission in corticospinal tracts and basal ganglia circuits, driving central fatigue[21]. Functional imaging has linked central fatigue to abnormal activation in the frontal cortex, thalamus, and basal ganglia, suggesting impaired sensorimotor integration and executive overload[22]. Experimental data show that fatigued MS patients exhibit reduced voluntary muscle activation compared to non-fatigued MS patients, even when maximal strength is similar[23]. While peripheral fatigue can contribute—especially during high-intensity tasks or in deconditioned individuals—MS patients demonstrate a smaller post-exercise reduction in peripheral twitch force than healthy controls, indicating a lesser role for peripheral mechanisms[24]. Notably, interventions targeting central fatigue, such as 8 weeks of quadriceps functional electrical stimulation (FES), significantly improve central fatigue scores and correlate with overall fatigue reduction without overloading the CNS[25].

This review aims to synthesize current research on the relationship among fatigue and balance in multiple sclerosis, emphasizing the importance of assessing and controlling fatigue as a key component of balance rehabilitation techniques.

METHODS

This systematic review was elaborated based on the methods outlined in the Cochrane handbook , and we also adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines reporting standards. The purpose of this systematic review was to identify the relationship between fatigue and balance in patients with multiple sclerosis.

Assessment Tools for Fatigue in MS

Fatigue in multiple sclerosis is a highly subjective and multifaceted symptom, making its assessment particularly challenging. Traditional approaches have relied primarily on self-report questionnaires, which remain essential due to the lack of a definitive objective biomarker. Among the most widely used instruments is the Modified Fatigue Impact Scale (MFIS), particularly its abbreviated version—the MFIS-5—which demonstrates strong psychometric properties and practical ease of use in clinical settings. A study confirmed its reliability, unidimensionality, and high internal consistency (Cronbach's alpha = 0.90), making it suitable for tracking the impact of fatigue on physical, cognitive, and psychosocial functioning[26].

For more extensive evaluation, the Fatigue Scale for Motor and Cognitive Functions (FSMC) has achieved traction due to the ability to distinguish between cognitive and motor fatigue domains. It is validated in large years and provides a cut -off value to classify the severity level and help clinical decision -making[27]. Another strong tool is the Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS), developed using elements from installed parameters and validated to assess both physical and cognitive fatigue components[28].

Recognizing the boundaries of self -report equipment is the purpose of recent progress to determine cognitive exhaustion objectively. Such a unit is a Cognitive Fatigability Assessment Test (cFAST)—a smartphone-based application that traces the real -time changes during the reaction time during a cognitive work. In a pilot study, exhausted MS patients saw a significant performance on cFAST compared to non-fatigued controls, reflecting its ability as a reliable, accelerated and scalable frequent monitoring tool[29].

Experts emphasize that no units capture full range of fatigue, a combination of subjective self -report with targeted performance -based or digital assessment can provide the most accurate and functional assessment. This approach supports the increasing trend against individual and distance monitoring strategies in MS fatigue management[16].

Assessment tools for balance in MS

The main types of balance affected in MS include static, dynamic, anticipatory, reactive, and sensory-oriented balance, each representing a distinct physiological domain.

a) Static Balance

Static balance refers to the ability to maintain the body's center of mass within its base of support while stationary. Tests like single-leg stance and Romberg tasks assess static postural stability. People with MS often show increased sway and reduced stability limits during these tasks due to deficits in proprioceptive feedback and central processing[30].

b) Dynamic Balance

Dynamic balance involves maintaining postural control during voluntary movement, such as walking or reaching. It is often assessed through tests like the Timed Up and Go (TUG), six-spot step test, or figure-of-8 hop test. MS patients exhibit slower gait speed and compensatory trunk movements, particularly under cognitive load, reflecting impaired sensorimotor integration[31].

c) Anticipatory Balance

Anticipatory postural adjustments occur before voluntary movement to maintain stability. In MS, this control is often compromised due to delayed activation of trunk and limb muscles. The Balance Evaluation Systems Test (BESTest) and Berg Balance Scale capture some aspects of anticipatory balance and have demonstrated reliability in MS populations[32]

d) Reactive Balance

Reactive balance is the automatic response to unexpected external perturbations, such as tripping or slipping. MS patients show delayed or inappropriate postural responses, increasing fall risk. However, this component is less frequently addressed in rehabilitation protocols, even though recent reviews recommend its inclusion in balance interventions[33].

e) Sensory-Oriented Balance

This type involves adaptation to changes in visual, vestibular or somatosensory inputs. Many MS patients depend on too much on the visual input due to reduced proprioception, which becomes clear during the eye -closed balance tasks. Tools such as computerized dynamic posturography and BRU ™ posturography can detect these sensory dependence patterns[34].

The Balance Evaluation Systems Test (BESTest) is a comprehensive clinical tool that evaluates six domains for postural control: Biomechanical barriers, stability limits, anticipatory postural adjustments, reactive positive reactions, sensory orientation and waking stability. It has shown excellent validity and reliability of people with MS and can distinguish between MS patients and healthy controls based on sway and displacement parameters[35]. The internal consistency and ability to detect subtle deficits makes it suitable for individual balance treatment planning[36].

Other variety used tools include Berg Balance Scale (BBS) and TIME UP and GO (TUG) tests. These are simple and valid for use in the MS population, with high interrater reliability (ICC = 0.99 for BBS)[37]. BBS is especially effective for detecting stable and dynamic balance losses, while TUG assesses the risk of dynamics and falls. New studies confirm that these tests can be administered externally through tele-assessment with high agreement levels (ICC> 0.95)[38].

For a detailed evaluation of dynamic and stable postural stability in individuals with multiple sclerosis (MS), tools such as Berg Balance Scale (BBS) and computerized posturography systems like the NeuroCom SMART Balance Master are often used. These systems provide objective, quantitative data on self, stability and sensory integration[39]. In study by **Fjeldstad et al.**[39], MS patients demonstrated significantly more postural instability than healthy contros, even in the early stages of the disease, measured by BBS and various

NeuroCom subtests including the Sensory Organization Test and Step/Quick Turn test.

For more detailed evaluation of dynamic balance in individuals with multiple sclerosis (MS), functional tests such as Six-Spot Step Test and the Figure-of-8 Hop test have been shown to provide valuable insights. These tests are recognized for their ability to evaluate dynamic postural controls under the status of real-life movement[30]. According to **Sedaghati et al.**[30] these tests are the most effective for measuring dynamic balance in patients with MS, along with Timed Up and Go (TUG) test. Their use can complement the static evaluation of several balance items and contribute to the comprehensive evaluation of functional stability in this population.

Rehabilitation Strategies for Improving Balance in MS

Rehabilitation aimed at enhancing the balance of multiple sclerosis (MS) which is a key component of symptom management and prevention of fall. Various approaches-included task-specific training, vestibular therapy, cognitive-motor practice and virtual reality-have shown effectiveness. A recent meta -analysis of 71 randomized controlled trials confirmed that neurological rehabilitation significantly improves the balance results in patients, with a medium pool effect size (SMD = 0.41) and with a remarkable benefit on the Berg Balance Scale (mean improvement = 3.58 points). High-intensity, task-specific intervention were found to be more effective, especially when sessions included functional, goal -controlled activities[40].

The vestibular rehabilitation has proven to be another promising strategy, especially for patients with central vestibular dysfunction. In a randomly controlled study, patients who underwent vestibular therapy showed significant improvements not only in balance, but also in fatigue and activities in daily life, which have an impact on a follow-up effect of 30- and 60 days. It highlights sensory integration, energy efficiency and context of positive control in MS rehabilitation[8].

Cognitive rehabilitation also plays a role in improving balance, especially when information processing deficits contribute to postural instability. A study showed that integrating cognitive training into occupational therapy significantly enhanced balance performance (eta-squared = 0.59), reinforcing the idea that higher-level brain functions can influence physical outcomes[41].

Additionally, home-based programs—such as those involving digital balance training systems or game-based interventions—have shown feasibility and benefit, particularly for patients with moderate disability. Tailored, supervised use of such systems can lead to clinically meaningful improvements in balance, though gait improvements may be limited unless gait-specific elements are included[42].

Overall, the most effective rehabilitation programs combine high intensity, task specificity, and multi-sensory engagement, and they benefit from personalization based on disability level and patient goals[43].

DISCUSSION

Fatigue and balance impairments are two of the most disabling symptoms in people with multiple sclerosis (MS), and increasing evidence suggests a significant interaction between the two. One foundational study by **Hebert and Corboy**[6] demonstrated a strong negative correlation between self-reported fatigue, measured by the Modified Fatigue Impact Scale (MFIS), and balance performance, assessed via dynamic posturography using Sensory Organization Testing (SOT). The total MFIS score significantly predicted balance deficits ($r = -0.78$, $p < 0.001$), with fatigue explaining up to 62% of the variance in balance outcomes. Notably, individuals with cerebellar and brainstem lesions experienced worse fatigue and poorer balance, supporting the idea that central nervous system structures mediating sensory integration play a critical role in this relationship.

A more recent randomized crossover trial by **Perucca et al.**[44] compared the effects of endurance and balance training on fatigue and postural stability in MS patients. Both interventions led to significant reductions in fatigue symptoms; however, only balance training resulted in measurable improvements in balance performance, as assessed by the Equiscale and computerized posturography. These findings support the concept that while general physical activity can reduce fatigue, specific balance-focused interventions have a dual impact on both symptoms, offering a more comprehensive therapeutic benefit.

Innovative neuromodulation techniques have also been explored to address this fatigue–balance relationship. In a double-blind randomized trial, **Akbari et al.**[4] Combined postural training with transcranial direct current stimulation (tDCS) targeting either the cerebellum or dorsolateral prefrontal cortex. Their findings showed that prefrontal tDCS led to the greatest reductions in fatigue, while cerebellar stimulation was most effective in improving balance. This suggests that distinct brain regions mediate different components of MS symptomatology and can be targeted for more effective, symptom-specific interventions.

In addition, the role of cognitive fatigue on balance was detected in a study by **Turan et al.**[7]. In this study, MS patients performed a cognitive tired work after the balance test. The assessment after the task give significant decline in static balance in eyes-open balance, but there is no big difference in dynamic functions or eyes-closed conditions. These findings mean that cognitive fatigue specifically interferes with balance domain that depend on active sensory integration, and more emphasizes the complexity of fatigue–balance link in MS.

Finally, an observation study added another dimension by examining the interaction between fatigue, respiratory function and postural stability. They found that high fatigue score is negatively correlated with balance, while better respiratory performance (e.g., FEV1) and strong core muscles were associated with better postural control. This study supports a systemic approach to the effect of fatigue on balance, suggests that not only the neural, but also muscles and respiratory factors mediate the relationship[45].

Limitations

Despite growing evidence linking fatigue to balance impairments in multiple sclerosis (MS), several research limitations remain. Many existing studies use small, heterogeneous samples or cross-sectional designs, limiting their ability to capture causal relationships or long-term intervention effects. There is also a lack of standardization in how fatigue and balance are assessed, with variability in clinical scales, subjective measures, and instrumented tools. Few studies have investigated the combined impact of fatigue-targeted and balance-targeted rehabilitation using objective, real-time monitoring such as posturography or sensor-based assessments. Future research should focus on large-scale, longitudinal trials that integrate multimodal evaluation—combining neurophysiological, biomechanical, and cognitive metrics. Investigating how neuroplasticity in motor and sensory pathways influences the fatigue–balance relationship could lead to more tailored and effective rehabilitation approaches for individuals with MS.

CONCLUSION

Fatigue and balance dysfunction are two of the most maximum and disabling symptoms experienced by individuals with multiple sclerosis (MS), often coexisting and compounding functional impairment. Emerging proof supports a significant, multidimensional relationship between these symptoms, involving shared neural mechanisms and sensorimotor disruptions. Evaluation tools that catch both subjective and objective aspects of fatigue and balance are important for exact diagnosis and treatment planning. Rehabilitation plans—particularly those combining cognitive, physical, and sensory training—show agreement in improving both domains. A deeper knowledge of their interaction will be great for developing individual, integrated interventions that increase mobility, reduce fall risk, and enhance quality of life for people living with MS.

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Conflicts of Interest

There is no conflict of interest

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