Cerebellar rTMS for Enhancing Coordination in Patients with Multiple Sclerosis: A Narrative Review

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ABSTRACT:
Purpose of Review: Cerebellar repetitive transcranial magnetic stimulation (rTMS) has gained attention as a potential therapeutic intervention for neurological disorders. Recently, there has been growing interest in its use to improve coordination in patients with multiple sclerosis (PwMS). This review aims to examine and discuss the current evidence on the effectiveness of cerebellar rTMS in enhancing motor coordination in individuals with MS.
Methods: A comprehensive search of Science Direct, PubMed, and Google Scholar was conducted using keywords such as multiple sclerosis, cerebellar repetitive transcranial magnetic stimulation, coordination, and neurorehabilitation. Articles published from January 2012 to July 2024 were included, and only English-language studies were reviewed. Unpublished manuscripts, conference abstracts, and studies not involving larger scientific investigations were excluded.
Results: The findings suggest that cerebellar rTMS, when combined with conventional rehabilitation methods, has the potential to improve coordination in PwMS. However, the available evidence is limited, and larger, more rigorous studies are needed to confirm these findings and establish standardized treatment protocols.
Conclusion: Current literature indicates that cerebellar rTMS holds promise as a supplementary intervention for improving coordination in PwMS. Further high-quality trials are required to support its clinical application and to better understand the underlying mechanisms.

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive, and disabling neurological condition that affects millions of individuals worldwide. MS results from the immune-mediated demyelination and neurodegeneration of the central nervous system (CNS), leading to various impairments, including motor dysfunction, balance issues, and coordination deficits (Woo et al., 2024). Among the numerous motor impairments, coordination problems, particularly ataxia, are prevalent and significantly impair the quality of life in PwMS (Chasiotis et al., 2023).

Cerebellar ataxia is one of the most prevalent and disabling manifestations of MS (Chasiotis et al., 2023). The coordination impairments seen in MS are primarily due to demyelinating lesions in the cerebellum and its connected pathways. Cerebellar dysfunction in MS can manifest as dysmetria, tremors, and gait instability, contributing to substantial motor impairment, in addition to affective and cognitive dysregulation (Billeri & Naro, 2021).

Given the complexity of coordination impairments in MS, traditional neurorehabilitation techniques, including physical and occupational therapy, have demonstrated benefits in improving balance and coordination, however, however, there is a pressing need for more rigorous studies to explore the full potential of these techniques (Chasiotis et al., 2023). With this, there is growing interest in adjunctive therapeutic interventions, such as repetitive transcranial magnetic stimulation (rTMS), which may offer further improvements by modulating neural pathways involved in motor control (Billeri & Naro, 2021; Xia et al., 2023).

Cerebellar repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising non-invasive neuromodulatory technique aimed at enhancing neuroplasticity and motor recovery (Somaa et al., 2022). rTMS involves the application of electromagnetic pulses to specific brain regions, inducing electrical activity that modulates neural circuits (Klomjai et al., 2015). rTMS was developed for the treatment of depression and other psychiatric disorders (Richter et al., 2023). Also, rTMS has shown potential in addressing motor impairments in various neurological conditions, including MS (Palm et al., 2014).

Recent studies have investigated the use of cerebellar rTMS for improving coordination in PwMS (Yassine et al., 2024), demonstrating promising results in reducing motor symptoms, balance and enhancing functional outcomes. However, evidence regarding its efficacy remains limited, and larger-scale studies are needed to validate its therapeutic role in this population. This narrative review aims to examine the current evidence on the use of cerebellar rTMS for improving coordination in PwMS and to discuss its potential as a supplementary therapeutic option in neurorehabilitation.

2. Overview of Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological technique that stimulates the human brain through electromagnetic induction, enabling the study of various neural interactions (Siebner et al., 2022). TMS generates electrical currents in the brain by creating a rapidly fluctuating magnetic field, which induces a secondary current in nearby neurons, leading to altered membrane potentials and subsequent action potentials (Brown et al., 2014).

TMS can be applied in three modes: single-pulse TMS, paired-pulse TMS, and repetitive TMS (rTMS). Single and paired-pulse techniques are primarily used for neurodiagnostic purposes, while rTMS involves delivering multiple stimuli in trains, with effects on cortical excitability that can be either inhibitory or facilitatory based on the stimulation frequency (Widhalm & Rose, 2019). Low-frequency rTMS (≤1 Hz) generally reduces cortical excitability, while high-frequency rTMS (>1 Hz) enhances it (Chung et al., 2015).

The mechanisms underlying the modulation of cortical excitability by rTMS beyond the duration of stimulation remain largely unclear. Long-term potentiation (LTP) and long-term depression (LTD) of cortical synapses have been proposed as potential explanations for the effects of high- and low-frequency rTMS, respectively. Research in both humans and animal models has shown that rTMS can induce significant alterations in neuronal circuits, reflected in behavioral changes and physiological parameters such as regional cerebral blood flow, motor evoked potential (MEP) size, neurotransmitter release, and gene transcription (Caipa et al., 2018). As rTMS techniques evolve, the integration of imaging methods like fMRI and EEG has further elucidated its mechanisms and expanded its therapeutic potential for various neurological and psychiatric disorders (Nasios et al., 2018).

3. Uses and clinical implications of transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has been explored in a growing number of clinical trials for its therapeutic potential across a wide range of neurological and psychiatric conditions, including depression, schizophrenia, addiction, posttraumatic stress disorder, pain, migraine, stroke, autism, multiple sclerosis (MS), and neurodegenerative diseases like Alzheimer's and Parkinson's (Nasios et al., 2018; Lefaucheur et al., 2014). In experimental models of MS, rTMS has been shown to influence synaptic plasticity and modulate neuroinflammatory processes by affecting astrocytosis, cell density, and lipopolysaccharide levels. These findings suggest rTMS may hold promise as a treatment for neuroinflammatory conditions such as MS (Nasios et al., 2018). However, the effectiveness of rTMS is not universal and depends on several protocol-related factors, such as the cortical target, stimulation intensity, frequency, number of sessions, and session duration. Additionally, patient-specific factors like age, symptom severity, and the underlying cause of the symptoms also play a role in determining the response to rTMS (Lefaucheur et al., 2014).

4. Uses and Application of transcranial magnetic stimulation in Multiple Sclerosis

Transcranial Magnetic Stimulation (TMS) has gained recognition as a potential non-invasive symptomatic therapy for MS, showing promise in alleviating fatigue, pain, psychiatric symptoms, and spasticity (Uygur-Kucukseymen et al., 2023). While transcranial direct current stimulation (tDCS) improves MS-related fatigue in the short term, repetitive TMS (rTMS) has demonstrated more significant effects in reducing fatigue over time (Liu et al., 2019; Uygur-Kucukseymen et al., 2023). Although, Limited data support that high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) showed potential analgesic effects, while intermittent theta burst stimulation (iTBS) lacked strong evidence (Korzhova et al., 2019).

Significant effects were found in psychiatric outcomes such as depression and anxiety in MS with non-invasive brain stimulation, particularly transcranial direct current stimulation (tDCS), but potentially limited by study power. The dorsolateral prefrontal cortex (DLPFC) is commonly targeted area and plays a crucial role in addressing hypoactivity observed in depression among patients with MS (Uygur-Kucukseymen et al., 2023).

In the treatment of spasticity, both rTMS and intermittent theta burst stimulation (iTBS) have shown effectiveness in managing spasticity in MS. Studies combining TMS with physical therapy suggest that TMS may alleviate spasticity by modulating corticospinal projections to spinal inhibitory interneurons (Korzhova et al., 2019). Conversely, tDCS did not yield significant improvements in spasticity in MS (Iodice et al., 2015).

There is some evidence supporting the effectiveness of non-invasive brain stimulation techniques on cognitive and motor performance in MS (Li et al, 2023). Despite suggestions that stimulating regions with challenging neuroplasticity may enhance effectiveness. Similarly, the limited data from TMS studies highlighted the need for additional investigation (Uygur-Kucukseymen et al., 2023). Also, variability in study outcomes, session durations, and the widespread presence of CNS lesions in MS complicate efforts to enhance cognition. Further researches are essential to clarify their roles in MS cognition (Nasios et al., 2018; Uygur-Kucukseymen et al., 2023).

Coordination is a very challenging aspect in PwMS. Yassine et al. (2024) conducted one of the few randomized controlled trials (RCTs) utilizing cerebellar rTMS to improve balance in patients with relapsing-remitting MS (RRMS). The study found a significant improvement in balance after 12 sessions of high-frequency cerebellar rTMS administered over four weeks. However, limitations in this study included the small sample size and the need for further investigation into the effects on postural control, activities of daily living, and the durability of long-term effects.

5. Side effects and contraindications of transcranial magnetic stimulation.

The most common side effect of transcranial magnetic stimulation (TMS) is headache and/or neck pain, reported in 20–40% of subjects. This pain varies depending on individual susceptibility, coil design, stimulation location, intensity, and frequency, often caused by muscle tension or posture during prolonged protocols. A single dose of acetaminophen or aspirin may be recommended if pain persists beyond stimulation duration (Rotenberg et al., 2014).

Seizures are a rare but serious side effect of rTMS, particularly when high frequencies and short intervals are used. Seizures can occur either during or immediately after rTMS trains, or post-stimulation due to cortical excitability modulation. As of 2008, 16 seizures were reported in TMS studies, with only four additional cases since then, placing the seizure risk at approximately 1 in 1,000 applications. It is important to establish a plan prior to treatment to address any possibility of an induced seizure. In the event of a seizure, the treatment should be stopped immediately, and the patient should be managed as any other individual experiencing a witnessed seizure (Rotenberg et al., 2014).

Syncope is rare and may result from anxiety or physical discomfort rather than the stimulation itself. Subjects should be closely monitored for symptoms such as dizziness or faintness, and stimulation should be stopped if syncope occurs. Although dental pain is uncommon, it may signal an underlying dental issue and should prompt cessation of stimulation and referral for a dental evaluation (Rotenberg et al., 2014).

TMS is contraindicated in patients with ferromagnetic or conductive implants, such as cochlear implants, aneurysm clips, or pacemakers as it has the potential to affect devices or objects implanted in the head or that cannot be removed to more than 30 cm from the treatment coil. Dental fillings and bridgework are generally safe, but caution is advised in individuals with pacemakers and implantable defibrillators (Rossi et al., 2021).

6. Conclusion

Cerebellar rTMS shows promise in improving coordination in patients with multiple sclerosis. However, further studies with larger sample sizes and extended follow-up periods are necessary to confirm these findings and assess the durability of the benefits.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

Authors state no conflict of interest.

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