EUR REV MED PHARMACOL SCI
2025; 29: 493-506

EXPLORING THE THERAPEUTIC AND REHABILITATIVE ROLE OF TRANSCRANIAL MAGNETIC STIMULATION IN MULTIPLE SCLEROSIS

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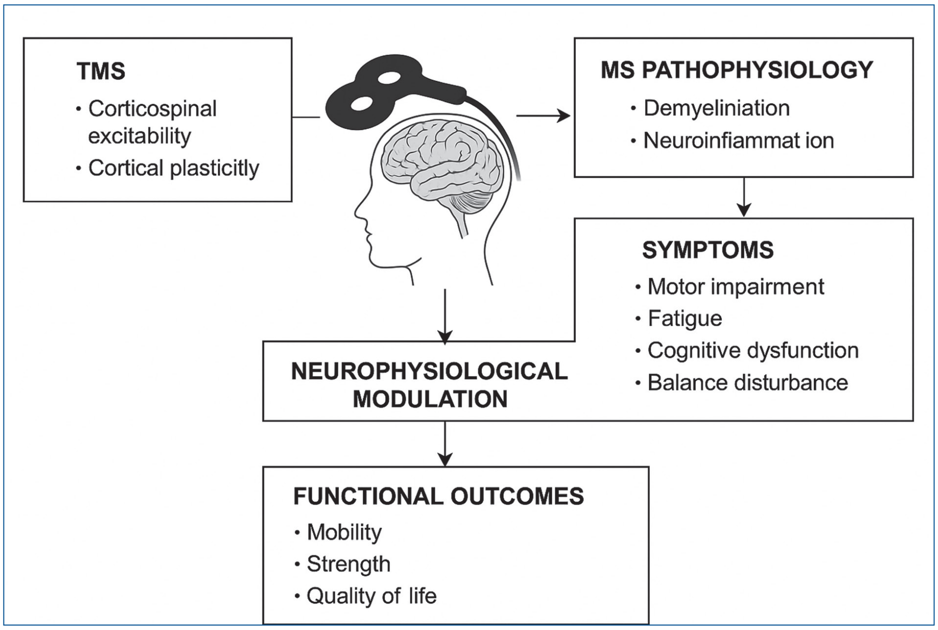
ABSTRACT – Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disease characterized by inflammation, lesions, demyelination, and axonal damage. Approximately 2.8 million people globally have MS. Many pharmacological agents can reduce relapsing-remitting episodes, but are ineffective on secondary progressive MS, causing symptoms to worsen over time. MS patients have significant impairment in neurophysiological factors such as demyelination and the balance between inhibitory and excitatory synaptic interactions. These impairments disrupt normal communication between neurons in the cerebral cortex, which contributes to the symptoms and disease progression. Transcranial Magnetic Stimulation (TMS) can identify and measure such neurophysiological parameters, including cortical excitability, linked with progression and the severity of disease. Thus, TMS could serve as a potential surrogate marker to monitor MS activity and severity. The review highlights the potential of TMS in managing MS, including enhanced cognitive functions, reduced fatigue, and improved spasticity, balance, and gait. In addition, TMS contributes to reducing neuroinflammation and oxidative stress while promoting neuronal repair and remyelination. However, further research is required for a better understanding of the stimulation- and site-specific effects of TMS in MS.

KEYWORDS: Multiple sclerosis, Transcranial magnetic stimulation, Evoked potentials, Demyelination, Experimental autoimmune encephalomyelitis, Relapsing-remitting MS.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating, and chronic autoimmune-mediated neurodegenerative disorder. MS causes non-traumatic neurological disorders and affects 2.8 million people worldwide[1,2]. MS is characterized by demyelination of neurons leading to altered nerve impulses, destruction of nerve fibers, variable axonal and neuronal loss, gliosis, formation of white matter lesions, and the resulting disruption within gray matter[3-5]. Cognitive dysfunction is also associated with progressive MS, which significantly affects the quality of life of patients, as well as their family members and caregivers.

In MS clinical trials, the efficacy of new drugs is assessed by the Expanded Disability Status Scale (EDSS) score[6] and magnetic resonance imaging (MRI)[7] of the central nervous system (CNS); however, these methods have some limitations. Sev-



Graphical Abstract. Schematic illustration exhibiting the employment of transcranial magnetic stimulation (TMS) to manage multiple sclerosis (MS).

eral scholars[8,9] have examined alterations in cortical excitability in multiple sclerosis (MS) using transcranial magnetic stimulation (TMS). These studies suggest that TMS can provide insights into cortical dysfunction and may hold promise as a marker of disease-related impairment.

PATHOLOGY

MS is a complex demyelinating autoimmune neurodegenerative disorder. In CNS, myelin, formed by concentric wrapping, exerts protective and insulating characteristics because of its complex structure, thickness, lipid richness (i.e., 70% lipids and 30% proteins), and low water content[3]. Axonal loss and neurodegeneration are considered the causative factors for irreversible disability and MS. The axonal loss could be a result of demyelination[10]. Microglia and CD^{4+} helper cells initiate inflammation, consequently destroying axonal myelin sheath and causing gradual neuronal loss. Inflammation in the CNS significantly affects synaptic integrity[11], concentrations of neurotransmitter[12], redox status[3], synaptic transmission[4], and disrupts microtubule[13] which facilitates the survival and proper functioning of neurons. The immune cells attack myelinated axons, causing demyelination during MS lesions and dysregulate proliferator-activated receptor gamma (PPARγ) and WNT/β-catenin pathways[14,15]. Moreover, proinflammatory mediators released by astrocytes, microglia, and T cells also play a key role in neuroinflammation[16]. In MS, increased energy demand causes disruption of adenosine triphosphate (ATP), an energy-carrying molecule, which may contribute to disability in patients[17]. Thus, the severity of MS is mainly influenced by how well the CNS can maintain the proper functioning of neural pathways and mechanisms. While many studies recognized interruption of myelinated tracts as a symptom of MS[18], a certain part of neurodegeneration is demonstrated as independent of demyelination[19].

Furthermore, a recent study[20] also suggests that the entire CNS and peripheral nervous system (PNS) appear to be involved in MS. Gamma-aminobutyric acid (GABA) and glutamate are the vital inhibitory and excitatory neurotransmitters in the CNS and PNS. Glutamate is the mediator of excitatory signaling in the oligodendrocyte lineage and involves synaptic plasticity, synaptic transmission, sensory and motor processing, learning, and memory[21,22]. Glutamate mediates the crosstalk between neurons, astrocytes, oligodendrocytes, and microglia. The increase in extracellular glutamate concentration causes abnormal glutamate signaling, disturbed physiological functions, alterations in interactions of brain cells or nerve cells, thus leading to excitotoxicity[23]. Due to excitotoxicity, glutamate dysregulation causes neuronal degeneration, which is the principal pathological process of neurodegeneration in MS[23]. Recent studies demonstrate that GABA levels increased in the sensorimotor cortex of relapsing-remitting MS patients[24] and decreased in the hippocampus of secondary progressive MS, suggesting that GABA has a strong inhibitory impact in MS. The downregulated GABA concentration increases axonal firing, increasing energy demands, leading towards neurodegeneration[25].

Diagnosis

MS can be diagnosed with confirmation by observing the characteristic neurological lesions in the CNS[26]. McDonald criteria diagnose MS by combining clinical, imaging (e.g., MRI), and laboratory (e.g., CSF) findings[27]. MRI remains the primary diagnostic tool for both the diagnosis and monitoring of disease progression[5]. MRI scan could quantify brain atrophy[28] and reveal multiple lesions distributed throughout the anatomical CNS regions, including white and grey matter[26]. However, MS diagnosis could be complicated by the need to differentiate it from other similar conditions, such as optic nerves (neuritis), neuromyelitis optical spectrum disorders (NMOSD), lesions of the spinal cord, Susac syndrome, or even normal MRI scans showing MS-related anomalies[26].

Analysis of cerebrospinal fluid (CSF) is also a valuable approach for diagnosing MS, which may include CSF biochemistry, microbiological tests, cytopathological evaluation, or intrathecal immunoglobulin tests[29]. Many potential CSF tissue markers (i.e., myelin basic proteins, glial fibrillary acidic protein, neurofilaments, etc.) and immune markers (cytokines and their receptors, antiviral antibodies, T-cells, etc.) have been reported for MS diagnosis and differentiation of phenotypes[30-32]. Thus, CSF biomarkers could be employed to diagnose MS at early stages. However, long-term studies in large cohorts are required to establish the applications of biological markers in clinical practices[31]. Other investigations for MS diagnosis might include visual evoked potential[33], somatosensory evoked potential[34], optical coherence tomography[35], cognitive testing[2], etc.

Disease course

MS subtypes based on clinical impression include primary progressive MS (PPMS), secondary progressive MS (SPMS), relapsing-remitting MS (RRMS), progressive relapsing MS (PRMS), radiologically isolated syndrome (RIS), and clinically isolated syndrome (CIS)[36-38]. The main clinical course of MS at onset is RRMS in 85% of patients with episodic neurological dysfunction (relapses) followed by completed or partial remissions, which gradually advance into neurological impairment or SPMS in 10-15% without any relapses[29,39] (Figure 1). The progressive and differential nature of MS can confuse neurologists and complicate its management. Thus, diagnosing MS at early stages could be crucial for possible early treatment and preventing irreversible neurological impairment.

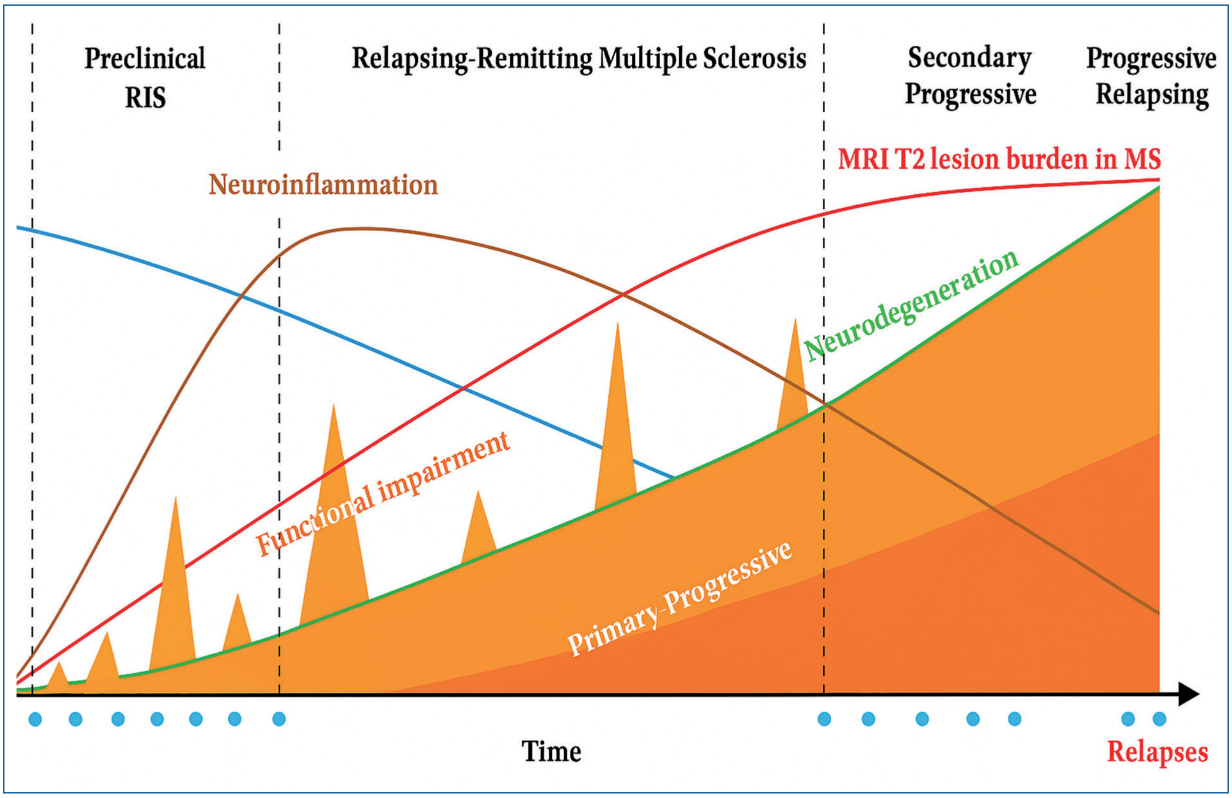


Figure 1. The clinical course description and spectrum of disease in Multiple Sclerosis (MS). RIS: Radiologically Related Syndrome, CIS: Clinically Isolated Syndrome, MRI: Magnetic Resonance Imaging.

Disease-modifying therapies (DMT) to manage MS are still at a progressive phase of development. Currently, several DMTs have been approved for MS treatment, which differ in their routes of administration, mechanisms of action, dosages, and potential side effects. The primary goal of DMT is to reduce the relapse frequency with fewer treatments available for neurodegeneration[40]. To a certain extent, a wide array of pharmacological agents slows clinical progression during relapsing-remitting stages; however, drug therapies do not show profound effects on the secondary progressive stage, in which neurological disability progressively worsens over time[41]. Moreover, DMT may also cause serious side effects, such as cardiomyopathy, acute leukemia, etc.[42].

TRANSCRANIAL MAGNETIC STIMULATION

The non-invasive brain stimulation (NIBS) techniques, specifically TMS and transcranial direct current stimulation (tDCS), are evolving and revolutionizing neuroscience research. NIBS are potential therapeutic tools that modulate molecular, biochemical and cellular processes by electromagnetic fields (EMFs). The seminal work establishing modern TMS is widely attributed to Barker et al[43], who in 1985 demonstrated that a rapidly changing magnetic field could noninvasively stimulate the human motor cortex, leading to observable motor responses. This revolution provided a noninvasive method to depolarize cortical neurons and assess corticospinal tract excitability and integrity, making it a promising tool in both clinical neurophysiology and neuroscience research[44,45]. TMS facilitates the understanding of neuronal circuit functionalities and modulation of neural excitability and neuroplasticity, thus paving the way for neuroscience research[45]. TMS encompasses several distinct modalities, each with unique stimulation parameters, neurophysiological effects, and clinical or research applications[46,47]. The principal modalities include single-pulse TMS, paired-pulse TMS, repetitive TMS (rTMS), and theta-burst stimulation (TBS)[47].

Single-pulse TMS delivers isolated magnetic pulses to the cortex, typically used to probe cortical excitability, map functional brain areas, or assess conduction times in motor pathways. It is primarily a diagnostic and research tool, not used therapeutically[48]. The single pulse induces a transient electric field, eliciting a motor-evoked potential (MEP) when applied over the motor cortex, allowing quantification of corticospinal excitability and conduction latency[49].

Paired-pulse TMS involves two pulses delivered in close succession, with variable interstimulus intervals (ISIs). This modality interrogates intracortical inhibitory and facilitatory circuits. Short ISIs (1-5 ms) assess intracortical inhibition, while longer ISIs (10-15 ms) probe intracortical facilitation[50]. Paired-pulse paradigms are essential in neurophysiological research to dissect cortical microcircuitry, but are not used therapeutically[48,49].

Repetitive TMS (rTMS) applies trains of pulses at a fixed frequency, typically ranging from 1 Hz (low frequency) to 20 Hz (high frequency), over a defined period[51]. rTMS can induce lasting changes in cortical excitability – low-frequency (≤1 Hz) rTMS is generally inhibitory, while high-frequency (≥5 Hz) rTMS is excitatory[52]. rTMS is FDA-cleared for several neuropsychiatric indications, most notably treatment-resistant depression (TRD), and is delivered in daily sessions over several weeks. Standard protocols include 10 Hz stimulation for 37.5 minutes (e.g., 3,000 pulses/session) or 1 Hz for 16 minutes (e.g., 960 pulses/session)[53,54].

Theta-burst stimulation (TBS) is a patterned form of rTMS that delivers bursts of high-frequency pulses (usually 3 pulses at 50 Hz) repeated at 5 Hz (theta frequency)[55]. There are two main TBS protocols: intermittent TBS (iTBS), which is excitatory, and continuous TBS (cTBS), which is inhibitory. iTBS typically consists of 2-second trains of bursts repeated every 10 seconds, while cTBS delivers bursts continuously for 40 seconds. TBS protocols are significantly shorter in duration (e.g., iTBS can be completed in 3-10 minutes) but deliver a similar number of pulses as standard rTMS[55]. Accelerated TBS (aTBS) involves multiple TBS sessions per day to potentially enhance and expedite clinical response, though evidence for its efficacy and safety is still emerging[56].

TMS works on the principle of electromagnetic induction and produces electromagnetic fields (EMF) that penetrate the brain tissue, non-invasively regulating brain activity and stimulating nerve tissues (spinal nerves, peripheral nerves, cerebral cortex, and central motor pathways)[57]. Several experimental studies in animal models and MS patients demonstrated promising results in treating many neurological diseases[58], including multiple sclerosis[59]. However, the molecular mechanisms underlying its therapeutic effects remain elusive. However, it is still an experimental therapy when discussed in the context of MS. Extensive research indicates the potential of TMS in managing MS[59]. Although the number of studies on TMS in MS is still sparse, the application of TMS as a disease-modifying tool opens a field for research workers to investigate its molecular mechanism further (Table I).

The repetitive TMS (rTMS) therapy facilitates neurophysiological and neurochemical functions by regulating molecular, biochemical, and cellular mechanisms through the induction of EMF, triggering long-term depression (LTD) and long-term potentiation (LTP) of synaptic plasticity, thereby improving the accurate and precise functioning of neurons in MS[57]. The different stimulation parameters or frequency of rTMS, i.e., high-frequency and low-frequency rTMS, have opposite, but potentially therapeutic effects on brain regions, for instance, regulating corticospinal excitability either by increasing or decreasing it[60]. High-frequency rTMS (10-20 Hz) and high-frequency rTMS (≥5 Hz) increase cortical excitability and MEP amplitude by inducing LTP-like effects, promoting excitatory neuroplasticity. In contrast, low-frequency rTMS (LF-rTMS) (1-5 Hz) decreases cortical excitability and MEP amplitude through LTD-like effects, facilitating inhibitory neuroplasticity[61]. TMS regulates corticospinal excitability, neural functionality, and promotes neuroplasticity. In addition, TMS can induce long-lasting therapeutic effects and neuroplastic changes across interconnected cortical and subcortical structures, the cortex, and the spinal cord[62].

TMS-based neurophysiological measurements

TMS-based neurophysiological measurements, such as MEP, cortical silent periods (CSP), and central motor conduction time (CMCT), could serve as potential markers of disability in MS by assessing cortical excitability, motor pathway integrity, and neural response (Table II). Such measurements provide insight into the functioning of the CNS, enabling the detection of abnormalities or impairments in conditions such as MS, where they reflect alterations in neural pathways and motor control. Application of TMS modulates neurophysiological measurements in MS patients. For instance, alterations in short-interval intracortical inhibition (SICI), resting motor thresholds (RMT), MEP[63], CMCT[63,64], and CSP[65] are reported in MS patients. Moreover, abnormalities in MEP and CMCT are associated with disability in MS patients[66]. Reduced MEP amplitudes compared to healthy controls indicate impaired neuronal recruitment and synaptic efficiency in MS patients[67]. These markers have the potential to correlate with clinical measures of disability, such as the EDSS, making them valuable tools for tracking disease progression.

Furthermore, MS-related conduction block, axonal depletion, motor neuron lesions, conduction impedance, and reduced signal velocity may be associated with reduced MEP and altered CMCT[68,69]. A recent study[70] highlights CMCT as a specific but not highly sensitive marker for MS, with potential to improve diagnostic accuracy and differentiate between relapsing and progressive forms of the disease. A consensus opinion emphasizes that TMS effects in MS, such as increased CMCT, reduced MEP amplitude, and altered cortical inhibition markers, provide valuable insights into the disease's progression and severity. These abnormalities, particularly in CMCT[71] and Triple-stimulation technique (TST)[72], are highly sensitive in detecting subclinical corticospinal lesions and correlate with motor impairment and disability. These findings illustrate the utility of TMS in detecting central and peripheral neurophysiological changes in MS and their correlation with disease progression and motor function. Furthermore, such changes in cortical inhibition may also indicate alterations in brain plasticity, which potentially assess treatment efficacy and long-term disability risk in MS patients. These neurophysiological measures provide insights into MS pathophysiology and the effectiveness of therapeutic interventions. While TMS has limited diagnostic utility, it holds potential for prognostic use, with its interpretation influenced by disease type, treatment, and fatigue.

TMS-derived neurophysiological metrics, particularly those obtained from MEPs, are increasingly recognized as potential biomarkers for both disease progression and therapeutic response in MS[73,74]. For instance, prolonged MEP latency and reduced amplitude are indicative of demyelination and axonal loss within the corticospinal tract, correlating with clinical disability as measured by the EDSS and motor function scores[73]. Recent studies[75,76] using navigated TMS have shown that patients with higher disability (EDSS ≥3) exhibit not only altered MEP parameters but also enlarged and less densely distributed cortical motor maps (CMMs), reflecting both neurodegeneration and compensatory neuroplasticity. These changes are more pronounced in progressive MS compared to relapsing-remitting forms, and MEP metrics correlate with objective measures of strength and dexterity, supporting their role as functional biomarkers of disease severity and progression. Additionally, quantitative mapping of the cortical representation of limb muscles *via* navigated TMS reveals that increased CMM volume and altered MEP distribution are associated with greater disability[76]. All together, these findings suggest that CMM metrics can serve as objective markers of motor system reorganization and disease burden, potentially tracking progression over time or in response to therapy[74,76]. With regard to therapeutic response predicting and monitoring, changes in TMS-derived metrics, such as improvements in MEP latency or amplitude, or normalization of CMM characteristics, may reflect remyelination or neuroplasticity in response to disease-modifying therapies[75]. Therefore, quantitative neurophysiological monitoring offers noninvasive, objective tools to assess and predict treatment efficacy[77].

Altered neurophysiological measures such as CMCT and CSP in patients with multiple sclerosis (MS) reflect disruptions in central nervous system pathways that have direct implications for daily functioning[73,78,79]. Prolonged CMCT, as consistently observed in MS, indicates delayed conduction along the corticospinal tract due to demyelination and axonal injury. This delay is associated with impaired voluntary muscle activation, reduced muscle strength, and increased central fatigue, all of which contribute to difficulties in performing activities of daily living, such as walking, manipulating objects, and maintaining balance[80]. These impairments are more pronounced in central than peripheral pathways, and neurophysiological abnormalities in CMCT correlate with clinical disability measures in MS[81].

CSP is frequently prolonged in MS and reflects increased GABAergic inhibitory activity within the motor cortex[82-84]. Prolonged CSP has been independently associated with greater subjective fatigue, reduced cardiorespiratory fitness, and impaired motor dexterity in MS patients[83,84]. Specifically, longer CSP duration predicts worse performance in tasks requiring fine motor control, such as those assessed by the Multiple Sclerosis Functional Composite (MSFC) and upper limb dexterity tests[65]. This increased intracortical inhibition may represent maladaptive plasticity or a compensatory response to cortical damage, but functionally it is linked to greater motor impairment and fatigue, which are major contributors to reduced quality of life and limitations in activities of daily living[83,84].

Furthermore, alterations in these neurophysiological measures are not only markers of disease burden but also provide mechanistic insight into the central origins of motor fatigue and impaired motor adaptability in MS[83,84]. For example, altered interhemispheric inhibition (IHI), as measured by silent period metrics, may influence gait adaptability, with reduced inhibition correlating with better gait adaptation, suggesting that neurophysiological imbalances can either hinder or facilitate motor learning and compensation strategies in MS[85].

In summary, prolonged CMCT and CSP in MS are robustly linked to impaired voluntary motor control, increased fatigue, reduced dexterity, and diminished adaptability, all of which significantly impact daily functioning and independence[81,83-85].

THERAPEUTIC EFFECTS OF TMS ON MS

Several studies[57] highlight the potential effects of TMS on MS. TMS therapy treats neuroinflammation and modifies astrocytes, cell density, and lipopolysaccharide levels[86].

Translating the molecular mechanisms underlying the therapeutic effects of TMS from experimental autoimmune encephalomyelitis (EAE) models to clinical practice in MS might require a focus on several convergent pathways identified in preclinical studies[87,88]. For example, attenuation of reactive gliosis and promotion of remyelination; in EAE animal models, TBS was found to have a significant role in reducing reactive gliosis and downregulating vimentin expression, which contribute to restoration of myelin sheaths and improved clinical outcomes[87,88]. These findings suggest that TMS may promote remyelination and neuroprotection, which are central goals in MS therapy[86,88]. Another molecular mechanism is improvement in muscle involvement and neurogenic lesions, in which TMS ameliorates muscle atrophy and neurogenic muscle lesions in EAE, with effects superior to those of medications in preclinical models[89]. This suggests potential for TMS to address secondary complications of MS, such as muscle weakness and atrophy, through both central and peripheral mechanisms[89]. Moreover, modulation of myelin plasticity is another critical molecular mechanism in EAE preclinical models; thus, activity-dependent myelin plasticity, which can be induced by neuromodulation modalities, is increasingly recognized as a mechanism for promoting remyelination[86]. TMS may enhance these pathways to promote endogenous repair processes in MS[86,87].

Many clinical trials and human studies assess the efficacy of TMS therapy on MS patients, suggesting the modulation of cortical excitability, improvement of cognition, normal brain function[6], brain activation, and functional connectivity[90], dexterity[91], spasticity[92], and spasm frequency[93]. Studies[94] also confirm the effective and safe use of TMS on patients suffering from MS. TMS also exerts therapeutic effects on MS patients by reducing the manifestations of fatigue, the main neurological symptoms, and its cognitive and psychosocial components[94].

TMS treatment significantly improves gait, balance, and muscle involvement in MS patients (Table I). A recent study[95] finds that muscle responses evoked by TMS and the long-latency part of stretch reflexes were remarkably delayed in MS patients with dysmetria, compared to MS patients with tremor. TMS treatment also facilitates walking and postural stability in MS. The high-frequency rTMS significantly improves walking speed, walking endurance, and spasticity[96]. High-frequency rTMS (6 Hz) over the left prefrontal cortex of relapsing-remitting MS patients improves walking speed[97]. TMS also reduces lower limbs spasticity in MS patients[98].The 5-Hz rTMS over the motor cortex in MS patients with cerebellar impairment improves hand dexterity and treats cerebellar symptoms[99]. Scholars[100] also evidence that the experimental paradigm of TMS, tDCS, also exerts therapeutic effects on MS. However, the underlying mechanism of rTMS effects on gait is unclear. Burhan et al[97] suggest that left prefrontal cortex excitability is associated with gait, whereas Strafella et al[101] suggest that increased dopaminergic transmission in the caudate could be the possible mechanism behind rTMS effects on gait improvement.

TMS, particularly repetitive TMS, and tDCS are the two most studied non-invasive neuromodulation techniques in MS[102]. Each modality has distinct advantages and limitations, both in terms of clinical efficacy and practical considerations.

Current evidence suggests that TMS, particularly rTMS, may be more effective for improving motor function and alleviating pain in MS, while tDCS appears to have greater utility in reducing fatigue and enhancing certain aspects of cognitive performance[102-104]. For example, rTMS has shown promise in improving motor outcomes and pain, whereas tDCS has demonstrated benefits in ameliorating fatigue and cognitive symptoms, with some studies also reporting improvements in quality of life, particularly with prefrontal cortex stimulation[105]. However, both modalities show heterogeneity in results, and the overall quality of evidence remains limited by small sample sizes and methodological variability[103,104].

Direct head-to-head comparisons, such as in neuropathic pain, indicate that both rTMS and tDCS can be effective, with rTMS sometimes providing a slightly greater magnitude of symptom relief[106]. Importantly, individual response profiles vary, and a significant proportion of patients may respond to only one modality, suggesting that both should be considered before declaring non-responsiveness[106].

tDCS is generally more accessible, less expensive, and easier to administer, including the potential for home-based protocols, which may be advantageous for patients with mobility limitations[105]. In contrast, rTMS requires specialized equipment and trained personnel, limiting its availability to specialized centers[103,104]. Safety profiles for both techniques are favorable, with mild and transient adverse effects being most common[102].

The main limitations for both rTMS and tDCS in MS are the heterogeneity of stimulation protocols, small sample sizes, and inconsistent outcome measures across studies, which complicate direct comparisons and generalizability[103,104]. There is also a lack of long-term efficacy data and standardized protocols tailored to individual neuroanatomy, though advances such as high-definition tDCS and network-based targeting may address some of these issues in the future[103].

In summary, rTMS and tDCS offer complementary, non-invasive options for symptom management in MS, with rTMS favored for motor and pain symptoms and tDCS for fatigue and cognitive dysfunction. Choosing such modality should be tailored and individualized, considering symptom profile, accessibility, and patient preference, while recognizing the need for further high-quality, multicenter, longitudinal clinical research to optimize and standardize these intervention parameters and effects[106].

Variability in TMS responses among patients with MS is multifactorial and can be attributed to several contributors, such as disease stage and duration, lesion burden, and baseline disability[81]. Disease duration is associated with progressive microstructural and volumetric changes in both grey and white matter, which accumulate over time and influence neurophysiological responses to TMS[81,107]. Longer disease duration correlates with more widespread microstructural disintegration and atrophy, particularly in cortical and deep grey matter brain regions, which in turn are associated with altered TMS measures such as increased motor thresholds and delayed MEP latencies[107]. These changes reflect both direct demyelination and secondary neurodegeneration, leading to reduced corticospinal excitability and impaired intracortical inhibition/facilitation[81,107]. Lesion burden or load, especially within the corticospinal tracts, is a key determinant of TMS response variability[81]. Lesion volume fraction in the brain, brainstem, and spinal cord portions of the corticospinal tracts correlates with both baseline disability and progression over time[108]. Notably, spinal cord lesion burden exerts the strongest independent effect on physical disability and is closely linked to prolonged central motor latencies[111] and reduced MEP amplitudes[110]. Lesion location is also critical; lesions in strategic motor pathways disproportionately affect TMS-derived measures of motor system integrity[108]. Moreover, baseline disability, as measured by scales such as the EDSS, is robustly associated with TMS measures abnormalities[111]. Higher disability correlates with increased frequency of abnormal TMS findings, including prolonged central motor latencies, abnormal transcallosal inhibition, and altered intracortical excitability parameters[83]. Patients with higher EDSS scores or progressive MS phenotypes exhibit more pronounced changes in TMS measures, such as enlarged but less dense cortical motor maps, delayed MEPs, and impaired inhibitory and facilitatory circuits[75,76]. Collectively, these findings suggest that TMS responses reflect the cumulative impact of demyelination, axonal loss, and maladaptive plasticity associated with advancing disability[65,76,111].

TMS therapy on working memory and cognition in MS

The brain undergoes structural and functional changes through the disease course, causing cognitive impairment. Although DMTs help manage disease progression and reduce relapses, they do not directly address the cognitive deficits associated with MS, such as memory, attention, and processing speed impairments. TMS and tDCS have emerged as a therapeutic and painless neurostimulation approach that improves working memory and cognitive performance in healthy patients[112,113], and also in neurodegenerative disorders[114,115]. Recently, Hulst et al[90] reported that 10 Hz rTMS over right DLPFC decreases frontal hyperactivation and increases task-related functional connectivity. The real rTMS treatment induces changes in network efficiency in MS patients, *via* biochemical, molecular, and cellular alterations[115-118] (Table I), hence exerting a beneficial role in motor and cognitive rehabilitation in MS patients[119,120] (Table II). Therefore, further research is needed, either using animal models of MS or appropriate human subjects, to clarify the therapeutic role of TMS or tDCS on cognition and memory in MS patients.

CONCLUSIONS

TMS could potentially be used in the clinical context of MS as a beneficial NIBS technique that can facilitate early diagnosis of neurological disorders, including MS. Changes in cortical connectivity have already been confirmed in MS, with alterations in neurophysiological measures such as CMCT and cortical silent periods CSP reflecting these changes. However, in clinical practice, other neurological parameters such as MRI findings, relapse rates, and EDSS scores are more commonly employed to measure disease severity and progression. These traditional measures are widely used due to their established clinical relevance, despite their limitations in detecting subtle changes in cortical function and connectivity, which may be more accurately identified through advanced techniques such as TMS. This review suggests that TMS enhances corticospinal excitability, modulates interhemispheric excitability, may promote recovery through neuroplastic and molecular mechanisms, and improves cognitive functioning in MS patients.

TMS potentially improves functional recovery and reduces symptoms in MS, suggesting its therapeutic benefits in addressing this neurodegenerative disease. Furthermore, studies of TMS on animal models or human subjects demonstrate that TMS induces a change in biochemical, molecular, and cellular processes in MS. Future research should concentrate on understanding the effects of TMS on various factors, including oxidative stress and non-neural/glial cells, such as oligodendrocytes, microglia, astrocytes, and neural stem cells. In addition, the impact of NIBS on Ca^{2+}, neurotrophic factors, neurotransmitters, and apoptosis-related proteins should be explored. Moreover, it is critical to investigate the influence of TMS on gene expression, metabolites, and enzymatic activity.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethics Approval and Informed Consent

Not applicable.

Funding

The authors extend their appreciation to the King Salman Center for Disability Research for funding this work through Research Group (No. KSRG-2024-302).

Authors' Contributions

Turki Abualait: Conceptualized the study, analyzed the data, and wrote the manuscript.
Shama Mukhtar: Curated and analyzed the data.
Ghulam Murtaza: Acquired data and contributed to writing and revising the manuscript.
Fawaz Al-hussain: Wrote and critically revised the manuscript.
Eman Nassim Ali: Contributed to data curation and writing the manuscript.
Shahid Bashir: Supervised the study and wrote the manuscript.

AI Disclosure

Figure 1 was generated by artificial intelligence (OpenAI GPT-5). All outputs were examined and evaluated by the authors.

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Table I. Molecular mechanism behind the therapeutic effects of TMS on Experimental Autoimmune Encephalomyelitis (EAE).

Author/Yr	Animal model of MS/EAE induction	Clinical investigation(s)	Type of stimulation and parameters	Effects	Study outcomes
Medina-Fernandez et al[92] (2017)	Rats were injected with a single dose of 150 µg of myelin oligodendrocyte glycoprotein	Effects of TMS on cell and oxidative damage	Extremely low-frequency electromagnetic fields (60 Hz and 0.7 mT) for 2 h in the morning, once a day, 5 days a week, for 3 weeks	Significant TMS reduces lipid peroxidation, oxidative protein products, lactate dehydrogenase, caspase-3 in brain and spinal cord	Decreases oxidative stress, reduces cell loss, and recovers cells density
Dragic et al[94] (2020)	Acute EAE in rats was induced by injection of 0.1 mL encephalitogenic emulsion, comprising equal volumes of rat spinal cord tissue homogenate and complete Freund's adjuvant in right hind foot	Effects on neuroinflammatory activation of microglia and astrocytes and remyelination	iTBS and cTBS above the frontal cranial bone, in close contact with the scalp of manually immobilized animal	Increases myelin basic protein, reduces the number of Iba-1+ cells, reactive astrogliosis, and vimentin expression	Indisputably attenuates reactive astrogliosis and demyelination. Moreover, promotes remyelination
Dragić et al[121] (2021)		Effects on the adenosine-mediated signaling system in the context of neuroinflammatory activation of glial cells	cTBS over frontal cranial bone for 10 consecutive days	Downregulates IL-1β, NF-κB, CD73, and increases IL-10. A_1R-*ir* is restored and increases at the glial, while A_{2A}R expression on glial cells decreases	Neuroprotection
Stevanovic et al[123] (2019)	Subcutaneous injection of 0.1 ml solution of rat spinal cord tissue homogenate suspended in complete Freund's adjuvant containing 1 mg/ml *mycobacterium tuberculosis*	iTBS or cTBS-induced changes of BDNF expression in lumbar spinal cords	iTBS and cTBS for 10 days	Significantly increases in BDNF and decreases GFAP, Ki67, IBA1, and GABA	Neuronal survival and attenuate reactive astrogliosis
Medina- Fernandez et al[122] (2018)	Single dose of myelin oligodendrocyte glycoprotein (MOG) in tail of rats	Effects of transcranial magnetic stimulation (TMS), natalizumab (nata), dimethyl fumarate (DMF) and dexamethasone (DEX) on clinical score and oxidative stress	Extremely low electromagnetic fields of 60 Hz and amplitude of 0.7 mT applied for 2 hours, once a day, 5 days a week, for 3 weeks	TMS + nata, DMF, and DEX restore glutathione redox ratio, inhibit lipid peroxidation, and carbonylated proteins in the brain, spinal cord, and blood	Significant antioxidant and neuroprotective action of TMS as compared to other clinical treatments

TMS (Transcranial Magnetic Stimulation), IL-1β (Interleukin-1 beta), NF-κb (Nuclear Factor kappa-light-chain-enhancer of activated B cells), CD73 (Cluster of Differentiation 73), c-TBS (Continuous Theta Burst Stimulation), i-TBS (Intermittent Theta Burst Stimulation), EAE (Experimental Autoimmune Encephalomyelitis), BDNF (Brain-Derived Neurotrophic Factor), GFAP (Glial Fibrillary Acidic Protein), Ki67 (Ki67 Antigen), IBA1 (Ionized Calcium-Binding Adapter Molecule 1), GABA (Gamma-Aminobutyric Acid).

Table II. TMS effects on muscle movement or mobility in MS subjects.

Author/Yr	Study type	Sample and clinical status	Clinical investigation(s)	Type of stimulation and parameters	Effects	Study outcomes
Leocani et al[103] (2012)	Randomized controlled trial	23 progressive MS patients with lower limb spasticity, undergoing inpatients rehabilitation	Walking abilities in patients with spasticity associated with multiple sclerosis (MS)	10-min sessions of deep high-frequency rTMS with H-coil for 3 weeks following rehabilitation sessions.	rTMS improves walking tests and reduces MAS score	Improved walking ability, with speed and endurance
Burhan et al[104] (2015)	Research study	51-year-old Caucasian male with chronic relapsing/ remitting MS with residual disabling attention and gait symptoms.	Gait parameters	3-consecutive daily sessions of high-frequency rTMS (6 Hz) over the left dorsal lateral prefrontal cortex (DLPFC)	The significant enhancement in ambulation time, gait velocity, and cadence	Significant increase in cadence, ambulation time, and walking speed
Tramontano et al[126] (2020)	Randomized controlled trial	20 MS patients undergoing vestibular rehabilitation (VR)	Gait and balance	c-iTBS over left and right cerebellum before each daily VR session	c-iTBS-VR shows improvement in Tinetti Balance and Gait scale	Significant improvement in gait and balance
Koch et al[106] (2008)	Clinical trial	8 clinically stable patients with MS and dysmetria affecting predominantly the dominant right upper limb	Hand dexterity	5-Hz rTMS over motor cortex	rTMS reduces the time required to complete the nine-hole pegboard task with the affected limb.	Improvement in hand dexterity in cerebellar patients
Oveisgharan et al[124] (2019)	Randomized double-blind clinical trial	13 patients with MS and walking disability	MS-related walking disability	anodal tDCS stimulation at 1 cm anterior to the C_z point for 30-minute daily sessions in 7 consecutive days	Real tDCS stimulation spent 2.7 seconds less for walking the 25 feet. Real tDCS not improves the Multiple Sclerosis Walking Scale-12 (MSWS-12).	Significant increase in walking speed
Pilloni et al[125] (2020)	Research study	15 MS patients with either relapsing remitting or secondary progressive subtype	tDCS + aerobic exercise on walking function	10 sessions (5 d/wk for 2 weeks) of tDCS coupled with 20 minutes cycling	Increase gait speed and distance covered during the 2-minute walking test.	Significant increase in gait speed
Hulst et al[97] (2017)	Research study	17 MS patients	Working memory performance, while measuring task-related brain activation and task-related brain connectivity	real-rTMS (10 Hz) applied to the right DLPFC	rTMS improves N-back task accuracy, diminishes task-related brain activation and task-related brain connectivity increases	Cognitive rehabilitation following rTMS

rTMS (Repetitive Transcranial Magnetic Stimulation), MAS (Modified Ashworth Scale), c-iTBS (Continuous Intermittent Theta-Burst Stimulation), tDCS (Transcranial Direct Current Stimulation).

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