REVIEW

Acta Neurobiol Exp 2026, 86
DOI: 10.55782/yt66ak85

# Effects of transcranial direct current stimulation in multiple sclerosis: Recent findings of clinical studies and animal models

**Maedeh Hashemi[1], Mohammad Hassan Tajik[1,2], Parinaz Javanbakht[1], Fatemeh Taghizadeh[1], Davood Zarini[1], Sina Mojaverrostami[1*]**

*[1] Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
*[2] Department of Anatomy and Physiology, University of Melbourne, Parkville, Victoria, Australia*
** Email: smojaver@sina.tums.ac.ir*

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) affecting millions worldwide, leading to significant disability. Current treatments focus on symptom management and reducing disease exacerbations. Noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have emerged as potential therapies due to their ability to modulate cortical excitability and neuroplasticity. This review explores the therapeutic potential of tDCS in MS patients by summarizing human and animal studies investigating its effects. Literature was systematically reviewed from inception to October 2024 using PubMed and Google Scholar databases. Key findings include tDCS's ability to alleviate symptoms such as pain, fatigue, cognitive impairment, and motor dysfunction in MS patients. Mechanistically, tDCS is proposed to influence neurotransmitter modulation, inflammatory pathways, and neuronal networks, promoting neuroprotection and functional recovery. Moreover, preclinical studies in MS animal models suggest that tDCS may reduce inflammation, promote remyelination, and enhance neuronal survival. These insights underscore tDCS as a promising adjunctive therapy for MS, potentially improving quality of life and mitigating disease progression. Further research is warranted to elucidate optimal stimulation parameters, long-term effects, and broader applicability in clinical settings.

**Key words:** transcranial direct current stimulation, multiple sclerosis, remyelination, brain stimulation

## INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disorder of the central nervous system (CNS) that affects approximately 2.5 million individuals worldwide (Magyari & Sorensen, 2019). Several incapacitating symptoms may manifest throughout the illness, including motor and sensory dysfunction, visual issues, cognitive impairment, mood disruption, pain, and exhaustion. These functional deficiencies and symptoms significantly influence the patient's quality of life (Lopez-Diego & Weiner, 2008; Hsu et al., 2021). Throughout the preceding decades, various therapies were prescribed to alleviate symptoms and reduce the severity of MS exacerbations. Recently, immunotherapy, stem cell therapy and lifestyle changes have had significant roles in disease control and have led to a substantial reduction in CNS lesion formation and relapse rate. However, these treatments are largely inadequate to prevent the accumulation of permanent disability from axonal and neuronal damage, particularly during the progressive phase of the disease (Friese et al., 2014; Thompson et al., 2018; Javanbakht et al., 2023).

Many neurological and psychiatric illnesses, such as neuropathic pain, Parkinson's disease, and fibromyalgia, are believed to respond well to noninvasive brain stimulation (NIBS) (Lefaucheur et al., 2017; Cagnan et al., 2019). These treatments offer several advantages

*Received 30 December 2025, accepted 8 March 2026*

over invasive approaches, including the ability to adjust stimulation settings for maximum effectiveness, minimize side effects, and directly target the circuit pathophysiology underlying visible symptoms (Cagnan et al., 2019; Wang et al., 2024). The most common types of noninvasive brain stimulation (NIBS) include transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), transcranial random noise stimulation (tRNS), transcranial alternating current stimulation (tACS), cranial electrotherapy stimulation, and reduced impedance noninvasive cortical electrostimulation (Liu et al., 2019).

tDCS is a noninvasive brain stimulation technique that induces low-amplitude (2.0 mA or less) direct current into the brain using scalp electrodes to regulate cortical excitability. Clinical investigations have shown that tDCS is a safe and well tolerated procedure in patients with MS (Nitsche et al., 2008; Brunoni et al., 2012; Filmer et al., 2014). tDCS improved motor recovery in patients with various neurological disorders, including stroke and Parkinson's disease (Hess et al., 1987; Lazzaro et al., 2003). Several studies have shown that tDCS reduces pain feelings, raises the pain threshold, and relieves pain in patients with various clinical conditions (Lefaucheur et al., 2008; Csifcsak et al., 2009). In addition, tDCS has profound effects on neurotransmitters, glial cells, micro vessels, and regulation of inflammatory processes (Boggio et al., 2008; Iodice et al., 2017). tDCS has been increasingly employed in MS clinical research to improve motor function, spasticity, pain, sensory deficit, tiredness, and cognition (Cuypers et al., 2013; Ayache et al., 2016; Mattioli et al., 2016). Previous research has shown that tDCS instantly reduces fatigue levels in MS patients (Liu et al., 2019). MS patients with cognitive deficiencies experienced improvements after tDCS treatment in a separate clinical trial (Mori et al., 2010; Mattioli et al., 2016).

Recently, several review articles have addressed the effects of tDCS therapy in patients with MS. However, each of these studies has focused exclusively on a single therapeutic aspect in MS patients, such as motor function and balance, cognitive activity, fatigue, neuropsychiatric symptoms or etc. (Alashram, 2025; Chmiel et al., 2025; Zhang et al., 2025). To date, no comprehensive review has been published that examines the overall impact of this treatment across the various dimensions of MS in both animal and human studies (Hiew et al., 2022; de Souza Fonseca et al., 2024). Previous findings indicated the beneficial effects of tDCS in clinical and preclinical studies by affecting different aspects of MS disease such as alleviating pain, fatigue, mood, cognition and inflammation. Therefore, in this current review, we summarize the human and animal studies that investigated the effects of tDCS on MS to examine the most effective mechanisms of tDCS in the recovery of MS patients.

We designed a review based on previous clinical and preclinical studies. Google Scholar, PubMed, PubMed/Medline, and Scopus databases were searched in title and abstract using the following keywords: Multiple sclerosis [MeSH Terms], OR experimental autoimmune encephalomyelitis [MeSH Terms] OR demyelination model [MeSH Terms] AND tDCS [ MeSH Terms]. The literature search was performed from inception to 10 January 2026 to find relevant articles, the reference lists from all selected articles were completely checked. Preclinical and clinical studies that matched our keywords, including *in vitro*/*in vivo* animal models and human clinical trials, were reviewed. Original articles and case reports were included, while review articles, conference abstract and non-English articles were excluded.

## Neuroprotective features of tDCS

Several studies have shown that tDCS has favorable effects on regulating neuropsychiatric and neurological diseases, as well as regulating excitatory and inhibitory neurotransmitters (Liebetanz et al., 2002). The neuroprotective mechanisms of tDCS are still unknown; nevertheless, tDCS therapy may provide relief in several ways. One way is through changes in the activity of the Na+/Ca++ channel, N-methyl-D-aspartate receptor, brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (Huang et al., 2021). Additionally, the impact of tDCS may be associated with molecular processes such as boosting ischemia tolerance, neuroprotection, neurogenesis, angiogenesis, and anti-apoptosis, which may decrease inflammation, edema, or infarct size and alleviate neurological deficits after ischemic stroke (Boonzaier et al., 2018). Moreover, similar results have also been observed for tDCS-induced Na+ modulation (Liebetanz et al., 2002).

Another study revealed the immediate effects of tDCS on main pathophysiological pathways and apoptosis generated by cerebral ischemia (CI). In the mentioned study, cathodal tDCS could significantly reduce the levels of IL-1β, TNF-α, MDA, and NOS while increasing the level of SOD. Therefore, c-tDCS by controlling the pathophysiological pathways triggered during global CI could reduce neuronal death and apoptosis in the CA1 hippocampal region (Ran et al., 2019; Kaviannejad et al., 2022).

Non-neuronal tissues such as endothelial cells, lymphocytes, and glial cells, which were thought to be involved in the neuroinflammation process, were shown to be affected by tDCS (Gellner et al., 2016; Monai et al., 2016). It was discovered that tDCS dramatically de-

creased the levels of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) and raised the levels of an anti-inflammatory factor (IL-10) (Zhang et al., 2020). Thus, tDCS might considerably enhance the recovery of neurological impairment, brain damage, and apoptosis, suppress the activation of astrocytes and microglia, and reduce inflammatory markers in rats with middle cerebral artery occlusion (Liebetanz et al., 2002).

Some studies have shown that the noninvasive intervention affects both the superficial and deep components of the brain. Additionally, it alters the shape, orientation, development, and metabolism of neural stem cells and regulates immunological and inflammatory responses, neurogenesis, and angiogenesis (Zoghi & Jaberzadeh, 2023). Both anodal and cathodal tDCS, may influence brain injury and healing pathways. Anodal tDCS enhances cell activity, neuronal plasticity, and the release of substances such as BDNF (Pilloni et al., 2020); however, cathodal tDCS produces hyperpolarization and regulates cell activity (Akbari et al., 2024). All tDCS treatments significantly reduced hyperthermia, hyperglycemia, Bax, and Caspase-3 levels and increased Bcl-2 expression. The c/a-tDCS mode may increase the expression of apoptotic markers, improve memory function, manage hyperthermia and hyperglycemia and minimize DNA fragmentation in compared to other stimulating treatments (Ran et al., 2019).

Furthermore, tDCS has shown promising neuroprotective effects in animal models of Parkinson's disease (PD). By modulating neuronal excitability and synaptic plasticity, tDCS can enhance dopamine release and reduce neuroinflammation, potentially slowing the progression of PD. Studies have demonstrated that anodal tDCS can improve motor function and reduce neuronal loss in the substantia nigra, a critical area affected in PD (Nitsche & Paulus, 2000; Kuo et al., 2014). Based on previous data, tDCS modulates the cAMP/PKA and NF-κB pathways *via* microglial activity, reducing neuroinflammation and oxidative stress in a people with PD. Moreover, tDCS, by activating the BDNF/TrkB pathway, enhances neuronal survival and synaptic plasticity, which are critical for maintaining dopaminergic function in the substantia nigra and striatum (Monte-Silva et al., 2013; Pikhovych et al., 2016).

In models of Alzheimer's disease (AD), tDCS has been found to mitigate cognitive decline and synaptic dysfunction. The neuroprotective effects are mediated through increased expression of neurotrophic factors like BDNF, which supports neuronal survival and synaptic plasticity (Márquez-Ruiz et al., 2012; Bystad et al., 2016). Additionally, tDCS can reduce amyloid-beta accumulation and tau phosphorylation, which are pathological features of AD. Behavioral improvements in memory and learning tasks have been observed following tDCS treatment in AD models (Márquez-Ruiz et al., 2012; Cotelli et al., 2014).

tDCS is also beneficial in epilepsy models and could reduce seizure frequency and severity in rats. The neuroprotective effects are associated with the modulation of cortical excitability and inhibition of hyperexcitability that characterizes epileptic networks. Cathodal tDCS, in particular, can decrease neuronal firing rates and enhance GABAergic inhibition, stabilizing neuronal activity and reducing epileptic episodes (Nitsche et al., 2004; Crespo et al., 2023). tDCS also increases the expression of BDNF, which activates the TrkB receptor, activating the PI3K/Akt and MAPK/ERK pathways. These pathways promote neuronal survival, reduce apoptosis, and enhance synaptic plasticity. Therefore, using tDCS in epileptic patients potentially reduces the likelihood of seizure occurrence and improves overall neurological function (Kasahara et al., 2023).

Research on tDCS in animal Huntington's disease (HD) models suggests that it can alleviate motor deficits and protect against neurodegeneration. The mechanisms include enhancing neurotrophic support, reducing mutant huntingtin protein aggregation, and improving mitochondrial function. tDCS may also promote the survival and function of striatal neurons in HD (Quartarone et al., 2004; Kasahara et al., 2023).

tDCS demonstrates significant effects as a non-invasive therapeutic intervention for various neuropsychiatric and neurological disorders. Despite the complexity of its neuroprotective mechanisms, which remain partially understood, tDCS appears to exert its effects through multiple molecular pathways. These include the modulation of Na+/Ca++ channels, N-methyl-D-aspartate receptors, and the enhancement of neurotrophic factors like BDNF and its receptor TrkB. The therapy shows promise in promoting ischemia tolerance, neurogenesis, angiogenesis, and anti-apoptotic processes, thereby reducing inflammation and neurological deficits following ischemic stroke.

The oxidative stress and inflammatory demyelinating processes in MS cause significant alterations in axonal conduction. First, nitric oxide, a type of inflammatory mediator, has the potential to activate persistent Na+ channels, causing a rise in intracellular Na+ and a depolarizing conduction block. Moreover, or by causing mitochondrial dysfunction and axonal ATP depletion (Bolaños et al., 1997; Filmer et al., 2014). Interestingly, according to one study, tDCS may influence these pathways by altering the activation of Na+ and Ca2+ channels (Nitsche et al., 2003). tDCS could be helpful in promoting the regeneration processes and ameliorating various MS symptoms in the course of the disease. In another study, tDCS was delivered to MS patients for five days straight who were experiencing fatigue. The

result showed that anodal tDCS might enhance axonal conduction along the demyelinated segments through a subthreshold polarizing effect. This might be used to improve MS fatigue (Chalah et al., 2015).

## tDCS effects on preclinical (animal) models of MS

Although there are some limitations, mainly linked to the difficulty or reproducing the entire range of clinical manifestations and neuropathological progression of human disease, animal models of MS provide an unique opportunity to study the pathophysiology of MS and the effects of pharmacological and non-pharmacological therapies for human MS at the cellular and molecular level. Based on published articles evaluating the effect of tDCS on preclinical MS disease (Table 2), tDCS has effect on inflammation, oxidative stress, axonal damage, and myelination (Marenna et al., 2022; Mojaverrostami et al., 2022). In one study done on female C57BL/6 mice, cathodal tDCS showed an anti-inflammatory effect and was able to prevent optic nerve damage.

In the experimental autoimmune encephalomyelitis (EAE), a preclinical MS model, optic nerve demyelination and delayed visual evoked potentials (VEPs) are also seen before motor symptoms. In EAE-Cathodal compared to EAE-Sham and EAE-Anodal after 5-days of tDCS treatment, there was significantly less axonal loss and a lower cell density of microglia/macrophages, but Luxol-fast blue staining revealed comparable levels of demyelination in all EAE groups. Additionally, immunofluorescence paranodal staining was done, and it showed that the EAE-Cathodal group, which was closer to healthy mice than the EAE-Sham and EAE-Anodal groups, had a significantly higher number of complete paranode domains as well. As a result, cathodal tDCS was associated with a lower number, closer to healthy, of single paranodes in contrast to EAE-Sham. Therefore, the effects of cathodal stimulation in preventing VEPs delays and optic nerve damage were already observed in the pre-motor onset EAE stage, and were associated with a lower density of inflammatory cells (Marenna et al., 2022).

In a recent study, 50 male C57 BL/6 mice were utilized to assess how tDCS enhanced stem cell therapy in a CPZ demyelination model. In this study used anodal tDCS (10 min, 0.1 mA) which was repeated daily with a custom-made constant current supply from week 12 to week 14 after demyelination. The outcome demonstrated that, following the induction of a chronic demyelination model, tDCS treatment may significantly increase remyelination capacity, improve motor coordination and balance performance, and produce neuroprotective benefits. Likewise, combining tDCS protocol and MSC transplantation was more effective than using either treatment separately. As a result, In a mouse model of CPZ demyelination, tDCS administration enhanced stem cell therapy by enhancing their migration and differentiation while reducing their apoptosis (Mojaverrostami et al., 2022).

In addition to the t-DCS method, other extracerebral stimulation methods have been performed to control MS symptoms, and electroconvulsive stimulation (ECS) is one of these methods of brain stimulating. In a study was done on female Biozzi mice model of EAE, ECS was applied *via* ear clip electrodes (ECS parameters were set on frequency, 100 Hz; pulse width, 0.5 ms; shock duration, 1 second). *In vivo* and *ex vivo* assays indicated that ECS suppressed microglial neurotoxicity by reducing inducible NOS expression, nitric oxide, and reactive oxygen species (ROS) production, and by reducing CNS oxidative stress. Thus, controlling microglial neurotoxicity reduced neuroinflammation. Immunofluorescence staining showed that ECS-treated EAE mice exhibited significantly less T cell infiltration (59% reduction). GFAP staining indicated a borderline significant ($P$=0.054) 35% reduction in astrogliosis in ECS-treated EAE mice as compared with control EAE mice. In addition, ECS reduces demyelination and axonal injury in chronic EAE. However, ECS does not affect the BBB permeability (Goldfarb et al., 2020).

An animal study on male rats analyzed tDCS's biochemical and genetic effects. This study used advanced metabolomics and transcriptomics techniques. The findings indicated that tDCS modulates metabolites crucial for neuroprotection, neuroplasticity, and inflammation and influences gene expressions associated with synaptic plasticity, myelination, and immune response. Moreover, results demonstrated that tDCS, by improving brain metabolism and influencing genetic pathways, could provide therapeutic advantages for individuals with MS. Enhancing mitochondrial efficiency and regulating calcium ion channels *via* tDCS could stimulate neuroplasticity, support remyelination, and alleviate neuroinflammation. These effects emphasize that tDCS could be used as a potential therapy for managing symptoms of MS alongside current treatment approaches (Agrawal et al., 2024). In a study by Rossi et al. (2024), 5 days anodal tDCS in C57BL/6 mice exposed to long-term cuprizone diet led to recovery of VEPs latency and optic nerve histology revealed higher myelin content and lower number of microglia/macrophage. In another study by Rossi et al. (2025), they found that 10 days of anodal tDCS and physical exercise in cuprizone-induced demyelination in C57BL/6 mice led to reduc-

tion of microglia/macrophage levels whilst effects on myelin by the first, and reduced cell death and BDNF protein were driven by the second. In a recent study, anodal tDCS (a-tDCS) at a current intensity of 250 μA for 12 minutes for four consecutive days increased remyelination, oligodendroglial survival and maturation in unilateral LPC-induced myelin injury in M1 cortex (Boda et al., 2026).

## Effects of tDCS on MS patients

In the present study, we describe data from both animal and human studies reporting the effects of tDCS on different aspects of MS disease (Table 1 and Table 2). tDCS may alter human CNS function by generating localized, sustained, reversible excitability alterations (Ayache et al., 2016; 2022; Hanken et al., 2016; Mori et al., 2010; Solaro et al., 2013; Rossi et al., 2017; Stagg et al., 2018). Anodal stimulation of the motor cortex left, and right inferior frontal gyri (IFG) revealed that tDCS significantly affects brain network connectivity and modifies cortico-striatal and thalamocortical circuits (Amato et al., 2013). Beneficial effects of tDCS on MS patients are listed below (Fig. 1).

## Neuropathic pain and other sensory deficits

Although the effects of tDCS on the specific brain networks involved in pain processing are poorly understood, an application of tDCS in MS is the treatment of neuropathy (Ayache et al., 2016). Pain is a major consequence of MS, and the incidence of chronic pain in MS has been reported to range from 29 to 86%, and tDCS may be used to decrease pain in MS patients (Solaro et al., 2013; Ayache et al., 2016; Workman et al., 2020). Central neuropathic pain is affected by supraspinal functional alterations in multiple pain-perception-related components. In addition, recent developments in neuroimaging and neurophysiological techniques have shown the essential function of the dorsolateral prefrontal cortex (DLPFC) in the pain circuitry. The efficacy of five tDCS treatments (2 mA, 20 minutes/day) on chronic, drug-resistant pain in right-handed individuals between the ages of 18 and 70 who have had neuropathic pain for more than three months was studied. Nineteen patients with relapsing-remitting (RR) MS were randomly assigned to undergo either sham tDCS or anodal tDCS. After anodal stimulation, but not sham stimulation, there was a substantial reduction in pain as measured by the Visual Analog Scale (VAS) for pain and the McGill

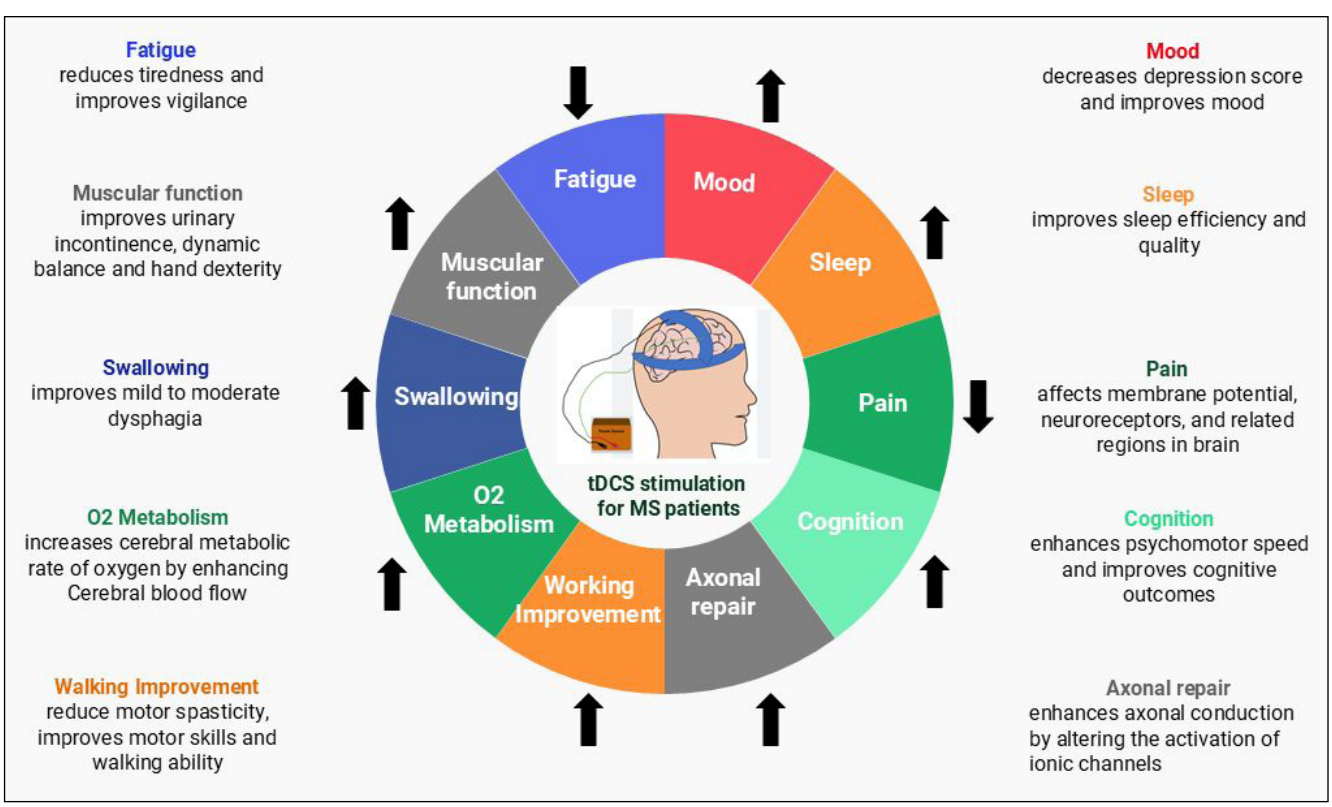


Fig. 1. Beneficial effects of tDCS on different aspects of MS disease.

Table 1. The studies reporting the effects of tDCS on MS patients.

| Author and year | Study Design | Patients | Treatment Method | Results |
|---|---|---|---|---|
| Cinbaz et al., 2025 | double-blind, randomized, sham-controlled clinical trial | Twenty-two pwMS | Patients received 6 sessions of 20-minute trans spinal cathodal tsDCS (n=11) or sham tsDCS (n=11) in addition to a physiotherapy program | Incorporating cathodal tsDCS into a physiotherapy program improved walking function and fatigue in pwMS |
| Akbari et al., 2025 | double-blind, randomized, and sham control | 57 participants with an EDSS score ranging from 3.5 to 5 | One group a-tDCS over cerebellum, another a-tDCS over DLPFC, and the third sham a-tDCS. Subjects in the a-tDCS experimental groups underwent 1.5 mA stimulation over a 20-minute duration alongside postural training. The stimulation was stopped following 30 seconds. Treatment was conducted for ten sessions over four weeks | The results showed that a-tDCS targeting the cerebellum could enhance balance and postural stability in MS patients |
| Charvet et al., 2025 | double-blind, sham-controlled, randomized clinical trial | 61 participants for active tDCS 45 female and 16 male, age=53.65±9.74 | 30 remotely supervised tDCS treatment sessions from their home on consecutive business days (Monday through Friday) for 6 weeks. Stimulation was applied to the DLPFC for 20 minutes at an intensity of 2.0 mA | tDCS did not provide any additional benefit over cognitive training alone in reducing fatigue, but confirmed the feasibility and tolerance of this home-based intervention |
| Pagliari et al., 2025 | Multicenter, rater-blinded, active-controlled, randomized trial | 20 subjects with MS (age=51.60±8.46, 13 female and 7 male) | Anode electrode was placed over the left DLPFC, constant current of 2 mA was applied with a ramping period of 15 s | The combination of remotely supervised tDCS with telerehabilitation enhanced gait and balance capabilities, without impacting cognitive functions. Although no statistical effects on fatigue or depression were observed |
| Shibuya et al., 2025 | double-blind, randomized, crossover trial | Five patients with CNS demyelinating disease (three with MS and two with NMOSD). Mean age=59.2 | Patients received 10 sessions of tDCS combined with rehabilitation, A constant current of 1.0 mA was applied for 900 s | A significant improvement was observed in working memory and information-processing ability |
| Ferrazzano et al., 2025 | A randomized, double-blind, sham-controlled, pilot study | 60 MS patients with cognitive complaints and enrolled 36 pwMS meeting the following criteria: age 18-55 years | γ-tACS over the left dorsolateral prefrontal cortex or precuneus, Stimulation lasted 30 minutes with no direct current offset, a 1.5-mA peak-to-peak amplitude, 3-second ramp-up and ramp-down periods, and a frequency of 40Hz | γ-tACS improved working memory, information processing speed, and verbal memory in MS patients |
| Tecchio et al., 2025 | A multicenter pilot study, randomized double-blind cross-over study | 17 PwMS with relapsing-remitting (RRMS) clinical subtype (14 female, 3 male) | bilateral S1 anodal tDCS with constant current of 1.5 mA delivered for 15 min, 5 consecutive days | The treatment improved fatigue symptoms by an average of 27%, to levels comparable with previous studies. Similarly, mild depressive symptoms improved by an average of 38% |
| Akbari et al., 2024 | double-blind, randomized, sham-controlled trial | 46 individuals (n=16 in experimental groups and n=14 in control group) age=49 | a-tDCS with a current of 1.5 mA for a period of 20 min. While, in the sham group, tDCS was only activated for 30 s and then turned off. The treatment included 10 sessions for four weeks | There was found a significant reduction in fatigue in the group receiving a-tDCS over the prefrontal cortex with postural training compared to the other two groups |
| Cinbaz et al., 2024 | double-blind, randomized, sham-controlled clinical trial | 35 pwMS (25 female, 10 male) | 12 sessions of 20 min anodal tDCS (n=11), cathodal tsDCS (n=12), or sham treatment (n=12) | Both cathodal tsDCS and anodal tDCS effectively improved gait function and reduced fatigue in pwMS |

| Author and year | Study Design | Patients | Treatment Method | Results |
|---|---|---|---|---|
| Muccio et al., 2024 | Prospective observational study | 20 patients with a diagnosis of MS (age=45.4±12.3 years, 7 males) | Pre-tDCS phase: 15-20 min MRI imaging, during-tDCS phase: 2 mA for 15 min and identical MRI, post-tDCS phase: 15–20 min MRI imaging | tDCS induces acute neuronal response in MS patients and increase cerebral blood flow |
| Zakibakhsh et al., 2024 | Randomized, double-blind, parallel-group study | 37 patients (mean age=37.30, SD=6.21, 27 females, 10 males) | 1.5 mA of stimulation for 20 min, and completed the FSS, VAS, and BDI questionnaires | Quality of life, sleep difficulties, psychological distress, and cognitive functions improved |
| Ibrahim et al., 2024 | Randomized controlled study | 38 MS patient, Age ranged from 25 to 40 years old | 2 mA of stimulation for 20 min, assessment of sleep by PSQI, PSG and ESS | Improvement of sleep in patients with MS |
| Pilloni et al., 2024 | Home-based randomized, double-blinded, sham-controlled clinical trial | 65 right-hand dominant participants with PMS | 2 mA of stimulation for 20 min, over 4 weeks, 9-HPT and DMMPUT tests was used for clinical outcome | Improving and preserving hand dexterity |
| Charehjou et al., 2024 | Blind randomized clinical trial study, with pre and post-assessment | 30 patients with MS aged 18-55 years | 2 mA of stimulation for 20 min over five consequtive days, also Patients performed the VR program three sessions per week for two weeks | VR can improve fatigue, balance and walking speed, with more excessive effect in combination with tDCS |
| Muñoz-Paredes et al., 2023 | Cross over pilot study | 15 patients with relapsing–remitting or secondary progressive MS, ages ranged from 35 to 66 years | Applicants receive tDCS (was applied by a specialized physiotherapist during 10 sessions lasting 20 min) and exercise program | 12 patients (5 female, 7 male) showed significant improvement in 6MWT test and 2MWT after the exercise program |
| Linnhoff et al., 2023 | Placebo-controlled study in two phases | 18 participants (male=3) aged 23 to 65 years diagnosed with clinically definite MS according to the McDonald criteria | tDCS was induced by a direct current with an intensity of 1.5 mA for 30 min (4 weeks), sham tDCS condition was induced by 15 s fade in – 30 s stimulation – 15 s fade out approach | tDCS could alleviate MS-associated fatigue and fatigability |
| Akbari et al., 2023 | Double-blind randomized controlled trial | 20 MS patient, Age ranged from 25 to 45 years old | 2 mA of stimulation for 20 min, TUG and BBS tests was used for dynamic balance assessmet | tDCS can use in combination with physical therapy to treat balance disorders in MS patients |
| Charvet et al., 2023 | Blind randomized sham-controlled clinical trial | 60 PPMS or SPMS patients (52% female, ages 37-72 years) | 2 mA of stimulation, manual dexterity was measured with the Nine-Hole Peg Test (9HPT) and Dellon-Modified Moberg Pick-Up test (MMPUT) | Hand impairment was Significantly improved after At-home manual dexterity training paired with tDCS |
| Charvet et al., 2023 | Blind randomized sham-controlled clinical trial | 106 MS patients aged 20 to 72 years, 81% female, with 63% relapsing subtype | 2 mA of stimulation for 20 min over six weeks, the Brief International Cognitive Assessment in MS (BICAMS) was administered | Active tDCS resulted in significantly better cognitive outcomes |
| Zoghi et al., 2023 | Randomised controlled study | 72 MS patients with secondary progressive, with impaired dominant hand functions (right side) | Applicants receive tDCS with 10-25-10 protocol for 5 consecutive days on the M1 area | tDCS improve hand movement and may help learn a new motor skill |
| Chalah. et al., 2022 | Pilot study | 7 PwMS patients | Patient received 1.5 mA tDCS on left and right dorsolateral prefrontal cortices for 5 days | Significant improvement in sleep, but did not yield any effect on objective sleep measures |

| Author and year | Study Design | Patients | Treatment Method | Results |
|---|---|---|---|---|
| Ramezani et al., 2022 | Parallel, double-blind, randomized controlled trial | 30 patients with a mean age of 38.83±5.43 years | Experimental group (n=15), receiving multiple sessions of active M1 a-tDCS concurrently with PFMT 2. Sham group (n=15), receiving multiple sessions of sham M1 a-tDCS and PFMT concurrently | Concurrent active M1 a-tDCS and PFMT could significantly improve the PFM and decrease urinary incontinency |
| Pilloni et al., 2020 | Double-blind, parallel-arm, randomized, sham-controlled trial and assigned to 10 sessions (5 d/wk for 2 weeks) | 15 participants (9 in the active and 6 in the sham)- aged 18-70 years with RRMS or secondary progressive (SP) subtype | 2.5 mA anode over the left primary motor cortex (C3) and the cathode over the supraorbital area (Fp2) | Anodal tDCS paired with aerobic exercise can lead to improvements in gait velocity, step length, and walking |
| Fietsam et al., 2020 | Single-blind, sham-controlled, randomized, cross-over study | 2 women with a positive RR MS – age 18-70 years | The anode was placed over the motor cortex area, and cathode was placed over the supraorbital area (3 mA for 20 min) | tDCS decreased glucose uptake and improved lower limb asymmetries during walking. Moreover, tDCS increased neural drive to the muscle and lowered energetic demands and perceived exertion |
| Workman, 2020 | Double blind, sham-controlled, and randomized crossover | 6 moderately disabled PwMS (relapsing-remitting MS; 3 female; age=46.7±14.1 yrs.) | 2 mA of stimulation for 20 min, and completed the FSS, VAS, and BDI questionnaires | Less knee extensor fatigability, less perception of fatigue, and decreased pain |
| Clayton et al., 2018 | Case study report | A 54-year-old woman with a 20-year history of secondary progressive subtype MS | The patient undergone with RS-tDCS; 2.0 mA 20 minutes, dorsolateral prefrontal cortex left anodal montage | Depression Rating Scale score dropped-mood improved-Cognitive tests (Cogstate Battery and Symbol Digit Modalities Test) and learning memory tasks for verbal learning significantly improved |
| Cosentino et al., 2018 | A pilot open-label study | 6 MS patients with mild to moderate dysphagia | 5 sessions of anodal tDCS (20 min at a 2 mA)applied in consecutive days over the right swallowing motor cortex | Anodal tDCS has therapeutic potential in the treatment of swallowing problems in patients suffering with MS |
| Hanken et al., 2016 | Randomized double-blind placebo-controlled study | 52 healthy participants, 46 MS patients | anodal tDCS 1.5 mA was delivered to the right parietal cortex or the right frontal cortex for 20 min before 40 and 20 visual vigilance task in healthy and MS participants respectively | Stimulation had a significant effect on vigilance decrement in mildly to moderately cognitively fatigued MS patients |
| Ayache et al., 2016 | Prospective, randomized, cross-over, sham-controlled study | 16 MS patients (aged between 18 and 70 years) which had history of neuropathic pain more than 3 months | Patients randomly received two anodal tDCS blocks (active or sham). the current was ramped up during the first 15 s to a maximum of 2 mA that was maintained throughout the 20-min stimulation session | tDCS ameliorate specific symptoms, particularly neuropathic pain. result However, Attention, mood, and fatigue were not improved in this work |
| Iodice et al., 2015 | Single-centre randomized, double-blind, sham-controlled study | 20 RR MS patients | Patients received anodal tDCS stimulation to the primary motor cortex for 20 minutes/day for 5 consecutive days. Moreover, 10 patients received sham tDCS stimulation. Spasticity was assessed by using the modified Ashworth scale (MAS), the self-scoring MSSS-88 (Multiple Sclerosis Spasticity Scale) and Multiple Sclerosis Walking Scale (MSWS-12) at baseline and at the end of protocol stimulation. | Did not observe any improvement in lower limb spasticity |

| Author and year | Study Design | Patients | Treatment Method | Results |
|---|---|---|---|---|
| Mattioli et al., 2015 | Single-centre randomized, double-blind, sham-controlled study | 20 RR MS patients aged 18-65 years | anodal tDCS (2 mA, 20 min/day) over the left DLPFC for 10 daily sessions, and patient follow up for six months | Improvement in the SDMT and WCST after treatment, and in the PASAT and WCST six months later |
| Ferrucci et al., 2014 | Sham-controlled, and randomized crossover study | 25 MS subjects (22 RR MS) | The stimulating current was delivered for 15 minutes once a day for 5 consecutive days over the motor cortex. Fatigue Impact Scale (FIS), and the Back Depression Inventory (BDI) were evaluated before and after stimulation. | tDCS improved fatigue in 65% participants of MS patients. Furthermore, r FIS scores improved by about 30% and the tDCS-induced benefits persisted at one and three weeks after stimulation. |
| Saiote et al., 2014 | Sham-controlled, double-blind intervention study | 13 RR MS patients | 1 mA anodal tDCS was applied over the left prefrontal cortex of MS patients with fatigue for five consecutive days. Symptoms were tracked for 1 month *via* questionnaires | Did not find an overall significant improvement in fatigue score, but there was a correlation between response to treatment regarding subjectively perceived fatigue and lesion load in the left frontal cortex |
| Tecchio et al., 2014 | Randomized, double blind sham-controlled, cross-over study | 10 fatigued MS patients | A constant current of 1.5 mA intensity was applied for 15 min a day for five consecutive days | tDCS effect against fatigue in MS patients with mild disability |
| Mori et al., 2013 | Randomized, double blind, sham-controlled study | 20 patient (12 women, 8 men) with RR MS (aged 25-61 years) | Patients received sham or real anodal tDCS of the somatosensory cortex for 5 consecutive days (2 mA intensity was applied for 20 min) | tDCS is a possible tool for the treatment of sensory deficit in MS patients |
| Mori et al., 2010 | Randomized, double blind, sham-controlled study | 19 patients (11 females, 8 males, mean age 44.8±27.5 with relapsing remitting MS (RRMS) | Patients received sham tDCS or real tDCS (2 MA) for 5 day | Anodal tDCS is able to reduce pain scales and improve quality of life in MS patients as assessed through scores obtained at VAS (for pain, SF-MPQ (the short form McGill questionnaire), and MSQoL54 (), and that this effect outlasts the period of stimulation, leading to long-lasting beneficial clinical improvement |

Table 2. The studies reporting the effects of tDCS on animal models of MS.

| Author and year | Study Design | Treatment Method | Results |
|---|---|---|---|
| Boda et al., 2026 | Unilateral LPC-induced myelin injury in M1 cortical gray matter of C57BL/6 mice | 7 days after LPC-mediated lesion, mice were subjected to anodal tDCS (A-tDCS) at a current intensity of 250 μA for 12 minutes for four consecutive days between 10 and 12 am | A-tDCS accelerated remyelination and increased oligodendroglial survival and maturation in the lesioned cortex. |
| Rossi et al., 2025 | Cuprizone induced demyelination in C57BL/6 mice | 10 days of anodal tDCS and physical exercise | Anodal tDCS and physical exercise may synergically confer protection from demyelination via BDNF signalling. Anodal tDCS and physical exercise reduced microglia/macrophage levels whilst effects on myelin by the first, and reduced cell death and BDNF protein were driven by the second. |
| Rossi et al., 2024 | Cuprizone induced demyelination in C57BL/6 mice | Anodal tDCS was applied for 5 days after inducing demyelination | Anodal tDCS in freely moving mice induced recovery of visual nervous conduction and increased remyelination potential |
| Marenna et al., 2022 | EAE model in C57BL/6 mice | 5-day cathodal or anodal tDCS treatment started 3 days post-immunization | Cathodal tDCS led to lower number of single paranodes in contrast to EAE-Sham. The effects of cathodal stimulation in preventing VEPs delays and optic nerve myelin damage were observed. |
| Mojaverrostami et al., 2022 | Cuprizone induced demyelination in C57BL/6 mice | Anodal tDCS was applied for 4 weeks after inducing demyelination | Anodal tDCS treatment improved remyelination capacity, enhance motor coordination and balance performance. Also, combination treatments of Mesenchymal stem cells transplantation and tDCS protocol was more effective than use of each treatment alone. |

questionnaire, as well as an improvement in overall quality of life up to 3 weeks following the conclusion of therapy. In contrast, there was no influence on anxiety and sadness (Mori et al., 2010).

In a similar way, recent research examined the effects of anodal tDCS on the DLPFC. Sixteen MS patients with persistent neuropathic pain were included in a crossover, randomized, placebo-controlled study. Participants underwent two tDCS blocks (active or sham) separated by three weeks. Each block consisted of three consecutive daily sessions. Anodal tDCS (2 mA, 20 min/day) had significant analgesic effects on VAS and brief pain inventory (BPI) global scales compared to sham. Neither block had any impact on mood, weariness, or concentration. Based on these findings, the authors concluded that anodal tDCS over the left DLPFC appeared to function selectively and might alleviate certain symptoms, including neuropathic pain (Ayache et al., 2016). These studies suggest that tDCS relieves pain by modifying function of brain regions that are essential to the etiology of neuropathic pain. tDCS modifies pain perception and reduces chronic neuropathic pain by acting on cortico-subcortical and corticocortical pain-related pathways (Mori et al., 2010; Ayache et al., 2016).

It has been reported that tDCS causes polarity-dependent shifts in the resting membrane potential, which may alter neuronal excitability at the site of stimulation and in functionally connected regions (Workman et al., 2020). tDCS at 2.0 mA for five days decreased pain and felt weariness (FSS). Anodal tDCS administered for five days (2 mA, 20 min/day) across the somatosensory cortex might help decrease tactile sensory impairments by raising the visual analog scale for sensory scores in 20 patients with RR MS (Mori et al., 2013).

## Walking improvement

More than sixty percent of MS patients with motor-related symptoms exhibit spasticity (Eisen & Odusote, 1979). This elevated muscle tone (or hypertonia) is a consequence of damage to the corticospinal system and the unmodulated firing of local spinal neurons and sensory afferent pathways. It may result in discomfort, spasms, decreased mobility, a restricted range of motion, and contractures if not properly controlled (Bethoux & Marrie, 2016).

tDCS may boost neuronal drive to leg muscles and reduce glucose absorption while walking in patients with MS with low physical activity levels (Fietsam et al., 2020). Iodice et al. (2015) evaluated whether a five-daily session of anodal tDCS (2 mA, 20 min/day) administered to M1 contralateral to the more afflicted leg successfully reduced lower limb motor spasticity in a randomized, double-blind, controlled experiment. However, they discovered no change in clinical spasticity ratings or between active and sham stimulation (Iodice et al., 2015). Another research demonstrated that anodal direct current stimulation of the M1 immediately after completion of a motor sequence training session enhanced consolidation of the acquired ability in healthy persons but not in MS patients (Rumpf et al., 2018).

In a crossover pilot study conducted on twelve patients with MS, tDCS was administrated using an HDC-stim stimulator on the DLPFC. The International Physical Activity Questionnaire Short Form (IPAQ-SF) was used, and findings indicated that exercise combined with tDCS could improve MS patients' walking capacity and weariness during 2- and 6-minute walks. Moreover, tDCS was found to decrease fatigue but did not significantly improve walking ability (Muñoz-Paredes et al., 2023). Moreover, the study was done by Pilloni et al. (2020) showed that tDCS combined with 10 sessions aerobic exercise lead to improvements in gait velocity, step length, and walking after 4 weeks of treatment.

Furthermore, tDCS might help to learn a new ability in MS patients. In a randomized controlled experiment, 72 MS patients with secondary progressive disease were divided to determine how tDCS affected their ability to use their hands. The results showed that those who received a-tDCS on the M1 area during rehabilitation had better recovery than those who received only rehabilitation or tDCS. The 10-25-10 protocol involves, 10 min of tDCS intervention, followed by 25 min of rest, and then another 10 min mA DCS for 5 consecutive days. Furthermore, tDCS might make it easier to learn a new motor skill (Zoghi & Jaberzadeh, 2023). In 2025, a multicenter study demonstrated that telerehabilitation (TR), whether combined with active remotely supervised (RS)-tDCS, which involved five initial sessions of RS-tDCS targeting the left DLPFC followed by an additional five-week TR period, led to marked improvements in both balance and walking ability as detected with MiniBest test. The add active tDCS could increase effect of TR rehabilitation intervention in the mobility, considering that the effect falls between small to medium range in the a-tDCS group (Pagliari et al., 2025). Also, in another study 12 sessions of 20 min both cathodal tsDCS and anodal tDCS effectively improved gait function and reduced fatigue in pwMS. The lack of differences between tsDCS and tDCS on gait and fatigue outcomes suggests that tsDCS may offer comparable therapeutic benefits (Cinbaz et al., 2024). In a recent study, trans-spinal cathodal tsDCS in pwMS patients received 6 sessions of 20-minute stimulation and phys-

iotherapy program increased walking speed. Also, they found that incorporating cathodal tsDCS into a physiotherapy program improved walking function and fatigue in pwMS (Cinbaz et al., 2025).

## Swallowing

Swallowing difficulties are a common symptom of MS. The research concluded that anodal tDCS offers therapeutic promise for treating swallowing difficulties in MS patients. Six patients (4 SP-MS and 2 RR-MS patients, mean age 50 ± 9.6 years) who presented with mild to moderate dysphagia underwent 5 sessions of anodal tDCS applied on consecutive days over the right swallowing motor cortex (20 min at a 2 mA intensity). Patients were followed-up at 1 week, 1 month and 3 months after treatment, and Dysphagia Outcome and Severity Scale (DOSS) score indicated that in all patients the tDCS treatment determined a one-point improvement in the DOSS score at 1 week and 1 month after treatment, with return to baseline at 3 months follow-up (Cosentino et al., 2018).

## Fatigue

tDCS can alleviate fatigue in MS patients (Ayache et al., 2022; Saiote et al., 2014). Regarding tiredness complaints, the impact of tDCS was evaluated in six sham-controlled experiments. Recently, Hanken et al. (2016) tested whether anodal tDCS (1.5 mA) across the right parietal in 46 MS patients counteracted fatigue-associated vigilance decrement and subjective exhaustion. Patients received 20 minutes of tDCS before completing a 20-minute visual vigilance test. They discovered that anodal tDCS across the right parietal cortex substantially improved alertness in cognitively tired MS patients with mild to moderate fatigue (Hanken et al., 2016). Interestingly, a prior research indicated that anodal tDCS (1.5 mA, 15 min/day) administered over the left M1 for five days in 25 MS patients (22 relapsing-remitting, RR) improved fatigue impact scale (FIS) ratings by around 30% in 65% of participants (Ferrucci et al., 2014). These improvements persisted three weeks after the conclusion of therapy.

Saiote et al. (2014) examined 13 RRMS patients with chronic tiredness that had been clinically stable for at least eight weeks and did not take psychiatric medications. A total of five sessions of 1 mA anodal tDCS were administered to the left DLPFC. Compared to sham tDCS, active tDCS did not result in a statistically significant improvement in fatigue score or change in perceived exhaustion. Nevertheless, a sample of patients observed a connection between subjectively experienced tiredness response to therapy and lesion burden in the left frontal brain (Saiote et al., 2014). Individuals who responded well to anodal tDCS had a larger lesion burden than those who did not. Furthermore, other authors discovered that five-day sessions of bilateral anodal tDCS across the main somatosensory cortical regions reduced tiredness (modified FIS scores) in ten MS patients (Tecchio et al., 2014).

People with MS and tiredness benefit from a home intervention that combines aCT with left DLPFC tDCS for improved attentional vigilance. Therefore, vigilance provides an objective measurement of MS's cognitive fatigue. In a research involving 24 MS patients (63% female, ages 22 to 71), 2.0 mA tDCS was given over DLPFC for 20 minutes; the results revealed no appreciable improvement on the Symbol Digit Modality Test (SDMT). However, the vigilance composite score and reaction time specific both improved as a result of the active tDCS and aCT combination intervention (Charvet et al., 2023b). In recent double-blind, randomized, sham-controlled trial, researchers investigated the comparative effects of tDCS targeting the cerebellum and prefrontal cortex, paired with postural training, in 60 individuals diagnosed with RRMS. Participants were divided into experimental groups receiving active tDCS (2 mA) and a control group receiving sham stimulation. Assessments focused on balance metrics such as sway area and sway velocity, alongside measures of fatigue using standardized scales. Results indicated significant improvements in balance, with reductions in sway area by approximately 25% and sway velocity by 20% compared to sham stimulation. Moreover, fatigue levels were notably reduced following cerebellar and prefrontal tDCS interventions. Importantly, no significant adverse effects were reported during or after the sessions. These findings underscore the potential of tDCS as an adjunctive therapy for enhancing balance and alleviating fatigue in MS rehabilitation protocols (Akbari et al., 2024).

A recent clinical trial study was conducted on 30 patients with MS aged 18-55 years to evaluate the combined effects of virtual reality (VR) and tDCS. The tDCS group received daily 20-minute sessions (2 mA) for five consecutive days and the VR group participated in a VR program using the VR BOX headset for three sessions per week over two weeks. The results of this study showed that all three groups, including those receiving tDCS, VR, and a combination of tDCS and VR, experienced a significant reduction in fatigue levels after the intervention compared to before. However, better results were recorded for the VR and combined tDCS-VR groups. Additionally, the study revealed that balance and walking time improved in both the VR+tDCS and

the VR groups from pre-test to post-test. In contrast, the tDCS group did not show any significant changes in these studies. The authors concluded that combining tDCS with VR therapy can result in a more pronounced effect on fatigue reduction, balance, and walking time (Charehjou et al., 2024).

In another randomized, sham-controlled trial study, 18 participants were randomly assigned to anodal tDCS or a sham tDCS group. The anodal tDCS group received a direct current of 1.5 mA for 30 minutes, with a 15-second fade-in and fade-out period, two times a week for four weeks. The sham group received a 15-second fade followed by a 30-second stimulation and then a 15-second fade out approach. Interestingly, both the tDCS and sham groups reported a significant reduction in subjective trait fatigue, regardless of the stimulation condition. The observed results in the sham group suggest that this improvement may be related to the placebo effect (Linnhoff et al., 2023). In a recent study, a-tDCS with a current of 1.5 mA for a period of 20 min included 10 sessions for four weeks over cerebellum and dorsolateral prefrontal cortex (DLPFC) reduced fatigue in the group receiving a-tDCS over the prefrontal cortex with postural training compared to the other two groups. Also, a significant improvement was found in balance in the group receiving a-tDCS over the cerebellum concurrent with postural training (Akbari et al., 2024). Also, in a recent study, patients with MS-related fatigue, but without depression, were stratified by neurologic disability using the EDSS and randomized to complete 30 daily sessions over 6 weeks of either active or sham tDCS paired with online cognitive training. The primary outcome was the change in PROMIS Fatigue score from baseline to the end of the intervention. In both groups showed significant reductions in fatigue, with no significant difference between them. This suggests that tDCS does not provide any additional benefit over cognitive training alone in reducing fatigue (Charvet et al., 2025). Tecchio et al. (2025) indicated that a 5-days bilateral S1 anodal tDCS is feasible within the cooperation of two centers in the Italian territory. They found that the treatment improved fatigue symptoms by an average of 27%, to levels comparable with previous studies. Similarly, mild depressive symptoms improved by an average of 38%.

## Sleep

In a study conducted on seven patients with MS five-day sessions of anodal and cathodal bifrontal tDCS were found to decrease daytime drowsiness, but had no impact on actigraphy measurements. The current findings suggest that tDCS improves sleep efficiency in MS patients, as evidenced by a reduction in daytime drowsiness (Chalah et al., 2022).

In a recent study, 38 female MS patients were treated with either active tDCS receiving 2.0 mA for 20 minutes or sham tDCS in which the current was discontinued after a few seconds. The researchers observed that the results of the Epworth Daytime Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) tests were significantly increased in both groups, indicating improvement in sleep quality. However, the active tDCS group showed a greater improvement in sleep efficiency compared to the sham group, suggesting the effectiveness of tDCS in improving sleep in MS patients (Rehab et al., 2024).

## Mood

In a case report of a 54-year-old lady with a 20-year history of MS who had RS-tDCS at 2.0 mA for 20 minutes, the dorsolateral prefrontal cortex exhibited an anodal montage. After completing all sessions, the Hamilton Depression Rating Scale score decreased from 15 to 11, and mood improved, as seen by linear positive affect improvements throughout treatment. During the baseline and follow-up visits, cognitive testing consisted of information processing tests (Cogstate Battery and Symbol Digit Modalities Test) and narrative and list learning memory tasks for verbal learning. After completing tDCS study sessions, the scores on all measures improved considerably and uniformly from their initial values (Clayton et al., 2018).

## Cognition

Cognitive issues are prevalent in MS and may be predicted by lesions and atrophy of the cortex (Langdon, 2011; Rossi et al., 2017). Mattioli et al. (2016) investigated the possible significance of anodal tDCS in conjunction with particular cognitive training for treating cognitive deficits in RRMS patients. Twenty patients with reduced attention/speed information processing were randomly randomized to ten daily mental training sessions during anodal tDCS (2 mA, 20 min/day) over the left DLPFC or cognitive training during sham tDCS. Neuropsychological tests were performed at the beginning of the study, following therapy, and six months afterward. Patients demonstrated significant improvement on the SDMT and Wisconsin Card Sorting Test (WCST) after treatment and on the Paced Auditory Serial Addition Test (PASAT) 2" and WCST six months later when anodal tDCS rather than the sham was applied during cognitive training. In addition, patients reached the

most demanding activity level much faster than with placebo therapy (Mattioli et al., 2016). Combining tDCS with cognitive rehabilitation thus looks to be a viable technique for maximizing the therapeutic benefits on MS patients. Two case studies evaluating the long-term effects of tDCS on MS patients' attention, IPS (information processing speed), and linguistic learning are intriguing (Ayache et al., 2017; Chalah et al., 2017).

In a recent randomized, double-blind study, mental health and cognitive performance were evaluated in 20 MS patients who received active tDCS and 20 MS patients who received sham tDCS. The active tDCS group received an electrical current (1.5 mA) for 20 minutes with a 30-second ramp-up and ramp-down period. The sham group received a similar stimulation protocol but with the electrical current turned off after 30 seconds, generating the same sensation as the active condition without the participants' knowledge. The results of the psychomotor speed assessment revealed that active tDCS significantly improved movement time and performance compared to sham tDCS (Zakibakhsh et al., 2024).

In another sham-controlled randomized clinical trial study, 106 MS patients underwent either active (2.0 mA) or sham tDCS paired with adaptive cognitive training (aCT) for 30 daily 20-minute sessions over six weeks. The authors reported that active tDCS resulted in significantly better cognitive outcomes compared to sham tDCS (Charvet et al., 2023a). Shibuya et al. (2025), assessed 5 patients with demyelinating disease received 10 sessions of tDCS combined with rehabilitation, with assessments at baseline and poststimulation, and a second session under the alternate condition followed with the anodal electrode was placed over M1 (C3 in the 10–20 system), and the cathode over Fp2, delivering 1.0 mA for 900 s. They found no adverse effects related to tDCS while a significant improvement was observed in working memory and information-processing ability, as assessed by using the Paced Auditory Serial Addition 2-s version after active stimulation compared to sham stimulation (Shibuya et al., 2025). Ferrazzano et al. (2025), indicated that gamma transcranial alternating current stimulation (γ-tACS) over the left dorsolateral prefrontal cortex or precuneus improved working memory, information processing speed, and verbal memory in 36 pwMS patients.

## Muscular function

Muscular dysfunction, including muscle weakness, spasticity, and loss of postural balance, fine skills, and hand function, significantly impacts the quality of life in MS patients.

In a study by Charvet et al. (2023), the effectiveness of tDCS combined with manual dexterity training on improving hand dexterity impairment in MS patients was evaluated. The results demonstrated that combining active tDCS (2.0 mA) with at-home manual dexterity training is a well-tolerated approach for enhancing hand skills in these patients (Charvet et al., 2023c).

Pilloni et al. (2024) investigated the impact of active or sham M1-SO tDCS combined with manual dexterity training over four weeks. Electrodes were positioned over the motor cortex and the contralateral supraorbital region for tDCS induction. The results indicated that the active tDCS group demonstrated significant improvement in left-hand dexterity compared to baseline (Pilloni et al., 2024).

In another study, active tDCS was applied to the DLPFC or cerebellum, in combination with balance training to assess postural balance in 20 MS patients. Both groups received 20 minutes of tDCS at a 2 mA intensity and 10 minutes of balance training. The dynamic balance assessment using the Berg Balance Scale (BBS) revealed a significant improvement in both groups. However, the cerebellum group demonstrated better performance overall (Akbari et al., 2023).

Another common symptom in MS patients is urinary incontinence, which often results from pelvic floor muscle dysfunction. Ramezani et al. (2023) studied the combined effects of pelvic floor muscle training (PFMT) and tDCS on female MS patients. The active tDCS group received concurrent active M1 a-tDCS and PFMT, while the sham group received concurrent sham a-tDCS and PFMT. The results showed that active tDCS could effectively improve pelvic muscle dysfunction and reduce urinary incontinence, even up to one month after treatment (Ramezani et al., 2023).

## $O_2$ metabolism

MS is characterized by glial plaques that often surround blood vessels and impair oxygen metabolism (D'haeseleer et al., 2015). Muccio et al. (2024) recently studied the impact of tDCS on the cerebral metabolic rate of oxygen (CMRO2) in MS patients. For active tDCS, the anode was placed over the left DLPFC, F3, and the cathode was placed over the right DLPFC (2.0 mA). Participants underwent MRI imaging three times during the experiment: before tDCS, during tDCS, and after tDCS induction. Cerebral blood flow and CMRO2 were calculated using an axial PC-MRI sequence. The study found that tDCS induces an acute neuronal reaction in MS patients and that these effects accumulate over time (Muccio et al., 2024).

## CONCLUSION

The lack of relevant side effects or harmful interactions with pharmacotherapy, especially certain disease-modifying medications used in MS, makes tDCS a particularly appealing approach. Prior research mostly utilized 1.5 and 2 mA for 15 to 20 minutes. The prefrontal, frontolateral, and parietal cortex were the areas that were most stimulated. Although the beneficial effects of anodal and cathodal tDCS have been properly reported in clinical models of MS, there is still a need to confirm these positive findings in preclinical studies. According to clinical research, tDCS may be effective for treating sensory symptoms like pain, motor symptoms, exhaustion, spasticity, and mental and cognitive problems; moreover, in animal studies, while beneficial effects are sparse, mostly based on small sample size or open-label studies, and there are not sufficient studies. However, tDCS could improve myelination, axonal regeneration, and cell protection. Therefore, the preclinical indications of tDCS should be further developed in the coming years, with an emphasis on the significance of the pathophysiological and molecular processes underlying the symptoms to be treated.

## REFERENCES


Agrawal, B., Boulos, S., Khatib, S., Feuermann, Y., Panov, J., & Kaphzan, H. (2024). Molecular Insights into Transcranial Direct Current Stimulation Effects: Metabolomics and Transcriptomics Analyses. *Cells*, *13*(3), 205.

Akbari, N. J., Tahan, N., Naimi, S. S., Baghban, A. A., Moghadam, N. B., & Zoghi, M. (2024). Comparing the effects of cerebellar and prefrontal anodal transcranial direct current stimulation concurrent with postural training on balance and fatigue in patients with multiple sclerosis: a double-blind, randomized, sham-controlled trial. *Experimental Brain Research*, *242*(5), 1087–1100.

Akbari, N. J., Yousefi, M., & Tahan, N. (2023). Comparing the effects of multi-session cerebellar and prefrontal trans-cranial direct current stimulation on postural balance in patients with multiple sclerosis. *Gait & Posture*, *106*, S90.

Alashram, A. R. (2025). Transcranial direct current stimulation for cognitive rehabilitation in people with multiple sclerosis: A systematic review of randomized controlled trials. *Applied Neuropsychology: Adult*, 1–12.

Amato, M. P., Langdon, D., Montalban, X., Benedict, R. H., DeLuca, J., Krupp, L. B., Thompson, A. J., & Comi, G. (2013). Treatment of cognitive impairment in multiple sclerosis: position paper. *Journal of neurology*, *260*, 1452–1468.

Ayache, S. S., Lefaucheur, J. P., & Chalah, M. A. (2017). Long term effects of prefrontal tDCS on multiple sclerosis fatigue: A case study. *Brain stimulation*, *10*(5), 1001–1002.

Ayache, S. S., Palm, U., Chalah, M. A., Al-Ani, T., Brignol, A., Abdellaoui, M., Dimitri, D., Sorel, M., Créange, A., & Lefaucheur, J.-P. (2016). Prefrontal tDCS decreases pain in patients with multiple sclerosis. *Frontiers in Neuroscience*, *10*, 147.

Ayache, S. S., Serratrice, N., Abi Lahoud, G. N., & Chalah, M. A. (2022). Fatigue in multiple sclerosis: a review of the exploratory and therapeutic potential of non-invasive brain stimulation. *Frontiers in Neurology*, *13*, 813965.

Bethoux, F., & Marrie, R. A. (2016). A cross-sectional study of the impact of spasticity on daily activities in multiple sclerosis. *The Patient-Patient-Centered Outcomes Research*, *9*, 537–546.

Boda, E., Marchiotto, F., Pigozzi, A., Buffo, A., Buffelli, M., & Cambiaghi, M. (2026). Transcranial direct current stimulation (tDCS) promotes myelin repair and plasticity in the mouse motor cortex. *bioRxiv*, 2026.2001. 2020.700602.

Boggio, P. S., Zaghi, S., Lopes, M., & Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European journal of neurology*, *15*(10), 1124–1130.

Bolaños, J. P., Almeida, A., Stewart, V., Peuchen, S., Land, J. M., Clark, J. B., & Heales, S. J. (1997). Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases. *Journal of neurochemistry*, *68*(6), 2227–2240.

Boonzaier, J., van Tilborg, G. A. F., Neggers, S. F. W., & Dijkhuizen, R. M. (2018). Noninvasive Brain Stimulation to Enhance Functional Recovery After Stroke: Studies in Animal Models. *Neurorehabil Neural Repair*, *32*(11), 927–940. https://doi.org/10.1177/1545968318804425

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D. J., Valero-Cabre, A., Rotenberg, A., & Pascual-Leone, A. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation*, *5*(3), 175–195.

Bystad, M., Grønli, O., Rasmussen, I. D., Gundersen, N., Nordvang, L., Wang-Iversen, H., & Aslaksen, P. M. (2016). Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial. *Alzheimer's research & therapy*, *8*, 1–7.

Cagnan, H., Denison, T., McIntyre, C., & Brown, P. (2019). Emerging technologies for improved deep brain stimulation. *Nature biotechnology*, *37*(9), 1024–1033.

Chalah, M. A., Grigorescu, C., Kümpfel, T., Lefaucheur, J.P., Padberg, F., Palm, U., & Ayache, S. S. (2022). The effects of transcranial direct current stimulation on sleep in patients with multiple sclerosis–a pilot study. *Neurophysiologie Clinique*, *52*(1), 28–32.

Chalah, M. A., Lefaucheur, J.-P., & Ayache, S. S. (2017). Long-term effects of tDCS on fatigue, mood and cognition in multiple sclerosis. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *128*(11), 2179–2180.

Chalah, M. A., Riachi, N., Ahdab, R., Créange, A., Lefaucheur, J.-P., & Ayache, S. S. (2015). Fatigue in multiple sclerosis: neural correlates and the role of non-invasive brain stimulation. *Frontiers in cellular neuroscience*, *9*, 460.

Charehjou, B., Moghadas Tabrizi, Y., & Minoonejad, H. (2024). The Combination of Transcranial Direct Current Stimulation and Virtual Reality Training on Fatigue, Balance and Walking in Patients With Multiple Sclerosis. *Physical Treatments-Specific Physical Therapy Journal*, *14*(3), 171–182.

Charvet, L., Best, P., Lustberg, M., Pilloni, G., Shaw, M., Zhovtis, L., Li, X., Goldberg, J., Gutman, J., & Krupp, L. (2023a). Cognitive Functioning in Multiple Sclerosis (MS) Improves with At-Home Online Training Paired with Transcranial Direct Current Stimulation (tDCS): Results from a Sham-Controlled Randomized Clinical Trial. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *16*(1), 344.

Charvet, L., Goldberg, J. D., Li, X., Best, P., Lustberg, M., Shaw, M., Zhovtis, L., Gutman, J., Datta, A., & Bikson, M. (2025). Home-based transcranial direct current stimulation paired with cognitive training to reduce fatigue in multiple sclerosis. *Scientific Reports*, *15*(1), 4551.

Charvet, L., Masters, L. W., Choi, C., Muccio, M., Ge, Y., Krupp, L., & Pilloni, G. (2023b). Vigilance Improves in People with Multiple Sclerosis (MS) and Fatigue following Repeated Dorsolateral Prefrontal Cortex Transcranial Direct Current Stimulation (tDCS) Sessions Paired with Cognitive Training Delivered at Home (S38. 003). *Neurology*, *100*(17_supplement_2), 3018.

Charvet, L., Pilloni, G., Lustberg, M., Malik, M., Feinberg, C., Gutman, J., Krupp, L., & Raghavan, P. (2023c). Hand Dexterity Improves in Patients with Progressive Multiple Sclerosis (MS) with Telerehabilitation Using Transcranial Direct Current Stimulation (tDCS). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *16*(1), 280.

Chmiel, J., Kurpas, D., & Stępień-Słodkowska, M. (2025). The potential of transcranial direct current stimulation (tDCS) in improving quality of life in patients with Multiple sclerosis: a review and discussion of mechanisms of action. *Journal of Clinical Medicine*, *14*(2), 373.

Cinbaz, G., Sarı, Z., Oğuz, S., Hanoğlu, L., Fernández-Pérez, J. J., & Gómez-Soriano, J. (2025). Effects of Trans-spinal Direct Current Stimulation on Gait Function in People With Multiple Sclerosis. *Journal of Neurologic Physical Therapy*, 10.1097. https://doi.org/10.1097/NPT.0000000000000534

Cinbaz, G., Sarı, Z., Oğuz, S., Tombul, T., Hanoğlu, L., Fernández-Pérez, J. J., & Gómez-Soriano, J. (2024). Effects of Transcranial and Trans-Spinal Direct Current Stimulation Combined with Robot-Assisted Gait Training on Gait and Fatigue in Patients with Multiple Sclerosis: A Double-Blind, Randomized, Sham-Controlled Study. *Journal of Clinical Medicine*, *13*(24), 7632.

Clayton, A. M., Howard, J., Dobbs, B., Shaw, M. T., & Charvet, L. E. (2018). Remotely supervised transcranial direct current stimulation after ECT improves mood and cognition in a patient with multiple sclerosis: a case study. *The journal of ECT*, *34*(1), e15.

Cosentino, G., Gargano, R., Bonura, G., Realmuto, S., Tocco, E., Ragonese, P., Gangitano, M., Alfonsi, E., Fierro, B., & Brighina, F. (2018). Anodal tDCS of the swallowing motor cortex for treatment of dysphagia in multiple sclerosis: a pilot open-label study. *Neurological Sciences*, *39*, 1471–1473.

Cotelli, M., Manenti, R., Brambilla, M., Petesi, M., Rosini, S., Ferrari, C., Zanetti, O., & Miniussi, C. (2014). Anodal tDCS during face-name associations memory training in Alzheimer's patients. *Frontiers in aging neuroscience*, *6*, 38.

Crespo, P. C., Martins, L. A. M., Dos Reis, C. C., Medeiros, L. F., Scarabelot, V. L., Gamaro, G. D., Soares, M. S. P., Spanevello, R. M., Stefanello, F. M., & De Souza, I. C. C. (2023). Transcranial direct current stimulation effects in the pain threshold and in oxidative stress parameters of neuropathic pain rats. *Neuroscience letters*, *803*, 137179.

Csifcsak, G., Antal, A., Hillers, F., Levold, M., Bachmann, C. G., Happe, S., Nitsche, M. A., Ellrich, J., & Paulus, W. (2009). Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain medicine*, *10*(1), 122–132.

Cuypers, K., Leenus, D. J., Van Wijmeersch, B., Thijs, H., Levin, O., Swinnen, S. P., & Meesen, R. L. (2013). Anodal tDCS increases corticospinal output and projection strength in multiple sclerosis. *Neuroscience letters*, *554*, 151–155.

D'haeseleer, M., Hostenbach, S., Peeters, I., Sankari, S. E., Nagels, G., De Keyser, J., & D'hooghe, M. B. (2015). Cerebral hypoperfusion: a new pathophysiologic concept in multiple sclerosis? *Journal of Cerebral Blood Flow & Metabolism*, *35*(9), 1406–1410.

de Souza Fonseca, B. H., de Andrade, P. H. S., & Luvizutto, G. J. (2024). Does non-invasive brain stimulation improve spatiotemporal gait parameters in people with multiple sclerosis? A systematic review and meta-analysis. *Journal of bodywork and movement therapies*, *37*, 350–359.

Eisen, A., & Odusote, K. (1979). Amplitude of the F wave: a potential means of documenting spasticity. *Neurology*, *29*(9_part_1), 1306–1306.

Ferrazzano, G., Maccarrone, D., Guerra, A., Collura, A., Satriano, F., Fratino, M., Ievolella, F., Belvisi, D., Amato, M. P., & Centonze, D. (2025). The effects of gamma-tACS on cognitive impairment in multiple sclerosis: A randomized, double-blind, sham-controlled, pilot study. *Multiple Sclerosis Journal*, *31*(6), 728–739.

Ferrucci, R., Vergari, M., Cogiamanian, F., Bocci, T., Ciocca, M., Tomasini, E., De Riz, M., Scarpini, E., & Priori, A. (2014). Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. *NeuroRehabilitation*, *34*(1), 121–127.

Fietsam, A. C., Workman, C. D., Ponto, L. L. B., Kamholz, J., & Rudroff, T. (2020). Different effects of transcranial direct current stimulation on leg muscle glucose uptake asymmetry in two women with multiple sclerosis. *Brain sciences*, *10*(8), 549.

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends in neurosciences*, *37*(12), 742–753.

Friese, M. A., Schattling, B., & Fugger, L. (2014). Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. *Nature Reviews Neurology*, *10*(4), 225–238.

Gellner, A.-K., Reis, J., & Fritsch, B. (2016). Glia: a neglected player in non-invasive direct current brain stimulation. *Frontiers in cellular neuroscience*, *10*, 188.

Goldfarb, S., Fainstein, N., & Ben-Hur, T. (2020). Electroconvulsive stimulation attenuates chronic neuroinflammation. *JCI insight*, *5*(17), e137028.

Hanken, K., Bosse, M., Möhrke, K., Eling, P., Kastrup, A., Antal, A., & Hildebrandt, H. (2016). Counteracting fatigue in multiple sclerosis with right parietal anodal transcranial direct current stimulation. *Frontiers in Neurology*, *7*, 154.

Hess, C. W., Mills, K. R., Murray, N. M., & Schriefer, T. N. (1987). Magnetic brain stimulation: central motor conduction studies in multiple sclerosis. *Annals of neurology*, *22*(6), 744–752.

Hiew, S., Nguemeni, C., & Zeller, D. (2022). Efficacy of transcranial direct current stimulation in people with multiple sclerosis: a review. *European Journal of Neurology*, *29*(2), 648–664.

Hsu, W. Y., Cheng, C. H., Zanto, T. P., Gazzaley, A., & Bove, R. M. (2021). Effects of transcranial direct current stimulation on cognition, mood, pain, and fatigue in multiple sclerosis: a systematic review and meta-analysis. *Frontiers in Neurology*, *12*, 626113.

Huang, J., Zhao, K., Zhao, Z., & Qu, Y. (2021). Neuroprotection by Transcranial Direct Current Stimulation in Rodent Models of Focal Ischemic Stroke: A Meta-Analysis. *Front Neurosci*, *15*, 761971. https://doi.org/10.3389/fnins.2021.761971

Iodice, R., Dubbioso, R., Ruggiero, L., Santoro, L., & Manganelli, F. (2015). Anodal transcranial direct current stimulation of motor cortex does not ameliorate spasticity in multiple sclerosis. *Restorative Neurology and Neuroscience*, *33*(4), 487–492.

Iodice, R., Manganelli, F., & Dubbioso, R. (2017). The therapeutic use of non-invasive brain stimulation in multiple sclerosis–a review. *Restorative Neurology and Neuroscience*, *35*(5), 497–509.

Javanbakht, P., Taghizadeh, F., Takabi, F. S., Tajik, M., Iranshahi, S., Pasbakhsh, P., Kashani, I. R., & Mojaverrostami, S. (2023). Effects of calorie restriction on multiple sclerosis: A review of the preclinical and clinical studies. *Neurochemical research*, *48*(6), 1597–1610.

Kasahara, Y., Nakashima, H., & Nakashima, K. (2023). Seizure-induced hilar ectopic granule cells in the adult dentate gyrus. *Frontiers in Neuroscience*, *17*, 1150283.

Kaviannejad, R., Karimian, S. M., Riahi, E., & Ashabi, G. (2022). A single immediate use of the cathodal transcranial direct current stimulation induces neuroprotection of hippocampal region against global cerebral ischemia. *Journal of Stroke and Cerebrovascular Diseases*, *31*(3), 106241.

Kuo, M. F., Paulus, W., & Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage*, *85*, 948–960.

Langdon, D. W. (2011). Cognition in multiple sclerosis. *Current opinion in neurology*, *24*(3), 244–249.

Lazzaro, V. D., Oliviero, A., Profice, P., Pennisi, M., Pilato, F., Zito, G., Dileone, M., Nicoletti, R., Pasqualetti, P., & Tonali, P. (2003). Ketamine increases human motor cortex excitability to transcranial magnetic stimulation. *The Journal of physiology*, *547*(2), 485–496.

Lefaucheur, J. P., Antal, A., Ahdab, R., de Andrade, D. C., Fregni, F., Khedr, E. M., Nitsche, M., & Paulus, W. (2008). The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain stimulation*, *1*(4), 337–344.

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M. A., Padberg, F., Palm, U., Poulet, E.,

Priori, A., Rossi, S., Schecklmann, M., Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*, *128*(1), 56–92. https://doi.org/10.1016/j.clinph.2016.10.087

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*(Pt 10), 2238–2247. https://doi.org/10.1093/brain/awf238

Linnhoff, S., Haghikia, A., & Zaehle, T. (2023). Effects of repetitive twice-weekly transcranial direct current stimulations on fatigue and fatigability in people with multiple sclerosis. *Scientific Reports*, *13*(1), 5878.

Liu, M., Fan, S., Xu, Y., & Cui, L. (2019). Non-invasive brain stimulation for fatigue in multiple sclerosis patients: A systematic review and meta-analysis. *Multiple sclerosis and related disorders*, *36*, 101375.

Lopez-Diego, R. S., & Weiner, H. L. (2008). Novel therapeutic strategies for multiple sclerosis—a multifaceted adversary. *Nature Reviews Drug Discovery*, *7*(11), 909–925.

Magyari, M., & Sorensen, P. S. (2019). The changing course of multiple sclerosis: rising incidence, change in geographic distribution, disease course, and prognosis. *Current opinion in neurology*, *32*(3), 320–326.

Marenna, S., Huang, S. C., Rossi, E., Castoldi, V., Comi, G., & Leocani, L. (2022). Transcranial direct current stimulation as a preventive treatment in multiple sclerosis? Preclinical evidence. *Experimental Neurology*, *357*, 114201.

Márquez-Ruiz, J., Leal-Campanario, R., Sánchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P. C., Ruffini, G., Gruart, A., & Delgado-García, J. M. (2012). Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proceedings of the National Academy of Sciences*, *109*(17), 6710–6715.

Mattioli, F., Bellomi, F., Stampatori, C., Capra, R., & Miniussi, C. (2016). Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. *Multiple Sclerosis Journal*, *22*(2), 222–230.

Mojaverrostami, S., Khadivi, F., Zarini, D., & Mohammadi, A. (2022). Combination effects of mesenchymal stem cells transplantation and anodal transcranial direct current stimulation on a cuprizone-induced mouse model of multiple sclerosis. *Journal of Molecular Histology*, *53*(5), 817–831.

Monai, H., Ohkura, M., Tanaka, M., Oe, Y., Konno, A., Hirai, H., Mikoshiba, K., Itohara, S., Nakai, J., & Iwai, Y. (2016). Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. *Nature communications*, *7*(1), 11100.

Monte-Silva, K., Kuo, M.-F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation*, *6*(3), 424–432.

Mori, F., Codecà, C., Kusayanagi, H., Monteleone, F., Buttari, F., Fiore, S., Bernardi, G., Koch, G., & Centonze, D. (2010). Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. *J Pain*, *11*(5), 436–442. https://doi.org/10.1016/j.jpain.2009.08.011

Mori, F., Nicoletti, C. G., Kusayanagi, H., Foti, C., Restivo, D. A., Marciani, M. G., & Centonze, D. (2013). Transcranial direct current stimulation ameliorates tactile sensory deficit in multiple sclerosis. *Brain stimulation*, *6*(4), 654–659.

Muccio, M., Pilloni, G., Walton Masters, L., He, P., Krupp, L., Datta, A., Bikson, M., Charvet, L., & Ge, Y. (2024). Simultaneous and cumulative effects of tDCS on cerebral metabolic rate of oxygen in multiple sclerosis. *Frontiers in Human Neuroscience*, *18*, 1418647.

Muñoz-Paredes, I., Herrero, A. J., & Seco-Calvo, J. (2023). Influence of Transcranial Direct Current Stimulation and Exercise on Physical Capacity and Gait in Multiple Sclerosis: A Cross-Over Pilot Study. *Healthcare (Basel, Switzerland), 11*(10), 1384. https://doi.org/10.3390/healthcare11101384.

Nitsche, M., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of physiology*, *553*(1), 293–301.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., & Fregni, F. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain stimulation*, *1*(3), 206–223.

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., Lang, N., Henning, S., Paulus, W., & Tergau, F. (2004). GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. *European Journal of Neuroscience*, *19*(10), 2720–2726.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology*, *527*(Pt 3), 633.

Pagliari, C., Di Tella, S., Bonanno, C., Cacciante, L., Cioeta, M., De Icco, R., Jonsdottir, J., Federico, S., Franceschini, M., & Goffredo, M. (2025). Enhancing the effect of rehabilitation on multiple sclerosis: A randomized clinical trial investigating the impact of remotely-supervised transcranial direct current stimulation and virtual reality telerehabilitation training. *Multiple Sclerosis and Related Disorders*, *94*, 106256.

Pikhovych, A., Stolberg, N. P., Jessica Flitsch, L., Walter, H. L., Graf, R., Fink, G. R., Schroeter, M., & Rueger, M. A. (2016). Transcranial direct current stimulation modulates neurogenesis and microglia activation in the mouse brain. *Stem cells international*, *2016*(1), 2715196.

Pilloni, G., Choi, C., Shaw, M. T., Coghe, G., Krupp, L., Moffat, M., Cocco E., Pau, M., & Charvet, L. (2020). Walking in multiple sclerosis improves with tDCS: a randomized, double-blind, sham-controlled study. *Annals of Clinical and Translational Neurology*, *7*(11), 2310–2319.

Pilloni, G., Lustberg, M., Malik, M., Feinberg, C., Datta, A., Bikson, M., Gutman, J., Krupp, L., & Charvet, L. (2024). Hand functioning in progressive multiple sclerosis improves with tDCS added to daily exercises: A home-based randomized, double-blinded, sham-controlled clinical trial. *Multiple Sclerosis, 30*(11–12), 1490–1502. https://doi.org/10.1177/13524585241275013.

Quartarone, A., Morgante, F., Bagnato, S., Rizzo, V., Sant'Angelo, A., Aiello, E., Reggio, E., Battaglia, F., Messina, C., & Girlanda, P. (2004). Long lasting effects of transcranial direct current stimulation on motor imagery. *Neuroreport*, *15*(8), 1287–1291.

Ramezani, M., Ehsani, F., Delkhosh, C. T., Masoudian, N., & Jaberzadeh, S. (2023). Concurrent multi-session anodal trans-cranial direct current stimulation enhances pelvic floor muscle training effectiveness for female patients with multiple sclerosis suffering from urinary incontinence and pelvic floor dysfunction: a randomized clinical trial study. *International Urogynecology Journal*, *34*(8), 1771–1779.

Ran, D., Luo, Y., Gan, Z., Liu, J., & Yang, J. (2019). Neural mechanisms underlying the deficit of learning and memory by exposure to Di (2-ethylhexyl) phthalate in rats. *Ecotoxicology and Environmental Safety*, *174*, 58–65.

Rehab, N. I., Emira, S., Badr, M. Y., Shendy, W. S., & Tawfik, R. M. (2024). Effect of transcranial direct current stimulation on sleep disorders in patients with multiple sclerosis. *NILES journal for Geriatric and Gerontology*, *7*(2), 340–353.

Rossi, E., Marenna, S., Castoldi, V., Comi, G., & Leocani, L. (2024). Transcranial direct current stimulation as a potential remyelinating therapy: Visual evoked potentials recovery in cuprizone demyelination. *Experimental neurology*, *382*, 114972.

Rossi, E., Marenna, S., Castoldi, V., Criscuolo, E., Giuliani, B., Malacrida, C., Clementi, N., Comi, G., & Leocani, L. (2025). Tracking remyelination in a model of multiple sclerosis: Visual evoked potentials reveal therapeutic effect from brain stimulation and exercise. *Experimental neurology, 397*, 115565. https://doi.org/10.1016/j.expneurol.2025.115565.

Rossi, S., Studer, V., Motta, C., Polidoro, S., Perugini, J., Macchiarulo, G., Giovannetti, A. M., Pareja-Gutierrez, L., Calò, A., & Colonna, I. (2017).

Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. *Neurology*, *89*(13), 1338–1347.

Rumpf, J.-J., Dietrich, S., Stoppe, M., Fricke, C., Weise, D., Then Bergh, F., & Classen, J. (2018). Compromised tDCS-induced facilitation of motor consolidation in patients with multiple sclerosis. *Journal of neurology*, *265*, 2302–2311.

Saiote, C., Goldschmidt, T., Timaeus, C., Steenwijk, M. D., Opitz, A., Antal, A., Paulus, W., & Nitsche, M. A. (2014). Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. *Restorative Neurology and Neuroscience*, *32*(3), 423–436.

Shibuya, R., Ishikuro, K., Hattori, N., Takasawa, S., Hirosawa, H., Yamamoto, M., Konishi, H., Nakane, S., Noguchi, K., & Nakatsuji, Y. (2025). Effects of transcranial direct current stimulation on multiple sclerosis and neuromyelitis optica spectrum disorder: A double-blind, randomized, crossover trial. *Clinical and Experimental* N*euroimmunology, 16(4): 348–356.* https://doi.org/10.1111/cen3.70002.

Solaro, C., Trabucco, E., & Messmer Uccelli, M. (2013). Pain and multiple sclerosis: pathophysiology and treatment. *Current neurology and neuroscience reports*, *13*(1), 320.

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of transcranial direct current stimulation. *The journal of ECT*, *34*(3), 144–152. https://doi.org/10.1097/YCT.0000000000000510

Tecchio, F., Bertoli, M., Sbragia, E., Stara, S., Pasqualetti, P., L'Abbate, T., Croce, P., Pizzichino, A., Cancelli, A., & Armonaite, K. (2025). Fatigue relief in multiple sclerosis by personalized neuromodulation: A multicenter pilot study [FaremusGE]. *Multiple Sclerosis and Related Disorders*, *94*, 106276. https://doi.org/10.1016/j.msard.2025.106276

Tecchio, F., Cancelli, A., Cottone, C., Zito, G., Pasqualetti, P., Ghazaryan, A., Rossini, P. M., & Filippi, M. M. (2014). Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. *Journal of neurology*, *261*, 1552–1558.

Thompson, A. J., Baranzini, S. E., Geurts, J., Hemmer, B., & Ciccarelli, O. (2018). Multiple sclerosis. Lancet (London, England), 391(10130), 1622–1636. https://doi.org/10.1016/S0140-6736(18)30481-1

Wang, K. L., Meng, F., Chen, S., Ramirez-Zamora, A., & Zhang, Y. Q. (2024). Editorial: Advances in neuromodulation treatment of Parkinson's disease and aging-related movement disorders. Frontiers in aging neuroscience, 16, 1407216. https://doi.org/10.3389/fnagi.2024.1407216

Workman, C., Kamholz, J., & Rudroff, T. (2020). Transcranial direct current stimulation (tDCS) for the treatment of a Multiple Sclerosis symptom cluster. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *13*(1), 263–264.

Zakibakhsh, N., Basharpoor, S., Ghalyanchi Langroodi, H., Narimani, M., Nitsche, M. A., & Salehinejad, M. A. (2024). Repeated prefrontal tDCS for improving mental health and cognitive deficits in multiple sclerosis: A randomized, double-blind, parallel-group study. *Journal of Translational Medicine*, *22*(1), 843.

Zhang, K.-Y., Rui, G., Zhang, J.-P., Guo, L., An, G.-Z., Lin, J.-J., He, W., & Ding, G.-R. (2020). Cathodal tDCS exerts neuroprotective effect in rat brain after acute ischemic stroke. *BMC neuroscience*, *21*, 1–13.

Zhang, L., Sun, Y., Diao, Z., Jiang, Y., Hu, Y., & Ma, Y. (2025). Effects of non-invasive brain stimulation on balance control in patients with multiple sclerosis: a systematic review and meta-analysis. *Frontiers in Neurology*, *16*, 1696343.

Zoghi, M., & Jaberzadeh, S. (2023). A step toward restoring hand functions in patients with multiple sclerosis—a study protocol. *Frontiers in Rehabilitation Sciences*, *4*, 1053577.