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Review Article

Non-invasive Brain Stimulation Therapy in Multiple Sclerosis: A Review of tDCS, rTMS and ECT Results

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ABSTRACT

Background: Multiple sclerosis (MS) is a disabling neurological disorder presenting a variety of symptoms which are hard to control by actual drug regimens. Non-invasive brain stimulation (NIBS) techniques have been investigated in the past years for the improvement of several neurologic and psychiatric disorders.
Objective: Here, we review the application of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (rTMS, iTBS) and electroconvulsive therapy (ECT) in MS patients.
Methods: Articles were searched in common literature databases. Crosslinks were reviewed.
Results: ECT was shown to be efficacious for the treatment of severe psychiatric disorders in 21 case reports. The results of tDCS and TMS for the treatment of depressive symptoms, fatigue, tactile sensory deficit, pain, motor performance, and spasticity were assessed in several studies and showed mixed results.
Conclusions: Overall, data for the treatment of MS with NIBS is sparse regarding TMS and tDCS. Treatment of severe psychiatric disorders with ECT is only reported in single cases. More studies are needed to elucidate the potential role of NIBS in MS treatment.

Introduction

Multiple sclerosis (MS) is a very frequent neurological disorder and the most common cause of disability in young subjects [1]. MS affects adults during their most productive years, influencing several crucial decisions of their life, like academic studies, careers, marriage and others [2]. It decreases their physical ability and raises serious financial concerns, resulting in a significant economic burden on subjects, families, society and health care systems [3]. MS course is characterized by a progressive neurological deterioration due to the accumulation of several neurological dysfunctions including motor deficit, sensory dysfunction, and sphincter disorders [2]. Furthermore, several comorbidities, like tremor, spasticity, fatigue, pain, affective and cognitive disorders can appear and worsen the course of illness [4–11]. Although fatigue has been widely studied in the literature, pain and psychiatric symptoms remain poorly evaluated in this disease. Recently, special attention has been paid on the diagnosis and management of these symptoms. Painful syndromes encountered in MS patients have been well described and divided in four major categories: trigeminal neuralgia, spasticity, neuropathic and musculoskeletal pain syndromes [12]. In addition, depression and anxiety usually associated with chronic health problems have been investigated over the last few years. For instance, it was found that up to 50% of MS patients suffer from depressive symptoms or depressive disorders [13–15]. Emergence of depressive and anxiety symptoms was attributed to the incertitude of illness progress [16]. Furthermore, the loss of social functioning seems to play a greater role on the onset of depressive disorders than the loss of physical function [17]. Although several pharmacological solutions exist, neuropathic pain, spasticity as well as depression and anxiety remain difficult to be fully controlled. Therefore, new approaches are needed in MS population.

Non-invasive brain stimulation (NIBS) techniques are relatively new therapeutic options that proved to be beneficial in several neurological and psychiatric disorders, like chronic neuropathic pain syndrome, major depressive and general anxiety disorders. The potential mechanisms of action of transcranial direct current

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Table 1
tDCS and TMS/TBS results in multiple sclerosis.

Author (year)	Stimulation method/ study design	Number of participants/ MS type	Targeted brain region	Targeted symptom/ measurement	Results
tDCS					
Mori et al. (2010) [29]	Anodal/sham tDCS 2 mA, 20 min, 5 sessions/double blind, placebo-controlled	19/RRMS	C3/C4 contralateral to painful somatic area	Pain, anxiety/visual analog scales, questionnaire	Significant pain relief in the active group compared to sham, no differences in anxiety
Mori et al. (2013) [30]	Anodal/sham tDCS 2 mA, 20 min, 5 sessions/double blind, placebo-controlled	20 (10 active, 10 sham)/RRMS	S1 contralateral to hypesthetic upper limb	Tactile perception/grating orientation task, questionnaire	Active tDCS reduced sensory threshold compared to sham
Ferrucci et al. (2014) [31]	Anodal/sham tDCS 1.5 mA, 15 min, 5 sessions/double blind, placebo-controlled	25/RRMS, SPMS	C3/C4	Fatigue/questionnaire	1/3 non-responders and 2/3 responders after active tDCS, no change after sham
Saiote et al. (2014) [32]	Anodal/sham tDCS 1 mA, 20 min, 5 sessions/double blind, placebo-controlled	13/RRMS	Left DLPFC	Fatigue, depression/ questionnaires, correlation to magnet resonance imaging	No difference of active and sham tDCS in fatigue and depression outcome. Correlation of lesion load and response to tDCS
Cuypers et al. (2013) [33]	Anodal/sham tDCS 1 mA, 20 min, single session/double blind, placebo-controlled	10/N.A.	M1 (FDI muscle region) contralateral to impaired hand	Corticospinal excitability/ TMS-EMG montage, MEP measures	Increased corticospinal output and projections strength after active tDCS
Meesen et al. (2014) [34]	Anodal/sham tDCS 1 mA, 20 min, single session/double blind, placebo-controlled	31/RRMS, SPMS	M1 (FDI muscle region) contralateral to exercised hand	Motor performance/ finger tapping test	No difference between active and sham group
TMS/TBS					
Koch et al. (2008) [43]	Real/sham 5 Hz rTMS, single session, 900 pulses, 15 min, placebo-controlled	8/RRMS	M1 (arm region), contralateral to the most affected hand	Hand dexterity/nine-hole pegboard task	Active rTMS improved hand dexterity in MS patients and not in healthy subjects
Centonze et al. (2007) [44]	5 Hz active rTMS, 10 sessions (2 week protocol), 1000 pulses, 16 min.	10/N.A.	M1 (leg region), contralateral to the most affected spastic leg	Lower Urinary tract symptoms/urodynamic measures	Active rTMS ameliorates voiding phase of micturation cycle
Centonze et al. (2007) [45]	Real/sham 5 Hz rTMS, 10 sessions (2 week protocol), (900 pulses, 15 min), placebo-controlled	19/RRMS	M1 (Leg region)	Lower limb spasticity/ H/M amplitude of soleus H reflex, MAS	Active rTMS reduced spasticity compared to sham. Effects lasted for at least 7 days after the end of stimulation protocol
Mori et al. (2010) [46]	Real/sham iTBS, 10 sessions (2-week protocol), ten bursts (600 pulses), placebo-controlled	20/RRMS	M1 (leg region) contralateral to the most affected limb	Lower limb spasticity/H/M amplitude ratio of the Soleus H reflex, MAS	Reduction of H/M amplitude ratio and MAS scores following active stimulation. Effects persisted 2 weeks after the end of stimulation protocol
Mori et al. (2011) [47]	Real/sham iTBS ± ET, 10 sessions (2-week protocol), ten bursts (600 pulses), placebo-controlled	30/RRMS	M1 (leg region) contralateral to the most affected limb	Spasticity, fatigue and daily life activity/MAS, MSSS-88, FSS,Barthel index and MSQoL-54 questionnaires	iTBS associated with ET could significantly reduce spasticity and fatigue, and ameliorate quality of life iTBS alone could decrease spasticity, without any effect on fatigue No significant changes were observed after sham iTMS plus ET

N.A. = Not Available; RRMS = Relapsing Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; M1 = primary motor cortex; S1 = primary somatosensory cortex; FDI = First Dorsal Interosseous, MEP = Motor Evoked Potential; ET = Exercise Therapy; MAS = Modified Ashworth Scale; MSSS-88 = 88 items Multiple Sclerosis Spasticity Score, FSS = Fatigue Severity Scale; MSQoL-54 = 54 items Multiple Sclerosis Quality of life inventory.

stimulation (tDCS) or transcranial magnetic stimulation (TMS) in MS are related to processes of neuronal plasticity, such as long term potentiation (LTP) or depression (LTD) of synaptic transmission, and focal changes in brain network activities. These effects can be measured, for example after tDCS application, by functional magnetic resonance imaging (MRI) [18] or electroencephalography (EEG) [19]. The modulation of neuronal activities by NIBS techniques supports their use in the treatment of cognitive and mood symptoms in depression [20–22], or for motor rehabilitation after stroke [23], for examples. The same concepts apply to MS patients to ensure the treatment of various neurological symptoms and psychiatric comorbidities occurring in this disease. However, the stimulation settings and targeted cortical regions are heterogenous, according to the given neurological and psychiatric symptoms, thereby precluding the existence of a unique protocol in this clinical condition, in which, moreover, structural brain lesions could hamper the modulatory effects and outcome of NIBS therapy. The rationale for using ECT differs from that of tDCS and rTMS, mostly because its mechanism of action is based on a widespread seizure-induced release of a variety of neurotransmitters. This non-focality might be the most prominent reason for a lack of action in specific neurological symptoms, whereas ECT can act on severe psychiatric disorders due to a complex dysfunction of a combination of neuronal circuits.

Thus, the application of these techniques in MS patients could be of help for therapeutic purpose but needs to be studied carefully, according to the technique and the treated symptoms in this multi-aspect disease. In this paper, we review the potential benefits of NIBS treatment on various disabling symptoms encountered in MS patients, in either the neurological (e.g. pain, fatigue, or spasticity) or the psychiatric (e.g. anxiety or depression) domain. Our review focuses on transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), including its theta burst stimulation (TBS) variant, as well as the application of