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Is Brain Stimulation in Multiple Sclerosis and Amyotrophic Lateral Sclerosis Worth Doing? A Mini-Review

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Abstract

Multiple sclerosis and amyotrophic lateral sclerosis are a public health priority with significant medical, psychological and economic repercussions. As no effective pharmacological treatments for their motor and cognitive symptoms are currently available, researchers have started to investigate the potential contribution of neuromodulation techniques in contrasting patients' decay. While these techniques may represent an interesting therapeutic option, to date the evidence available cannot be considered strong enough to suggest their standard use in clinical practice. Further and more robust studies are urgently needed to clarify neuromodulation techniques' efficacy in these invalidating neurodegenerative conditions.

Keywords: Amyotrophic lateral sclerosis; Cognitive impairment; Motor deficits; Multiple sclerosis; Neuromodulation; Transcranial direct current stimulation; Transcranial magnetic stimulation

Abbreviations: ALS: Amyotrophic lateral sclerosis; DLPFC: Dorsolateral prefrontal cortex; MS: Multiple sclerosis; NIBS: Non-Invasive Brain Stimulation Techniques; tDCS = transcranial Direct Current Stimulation; TMS: Transcranial Magnetic Stimulation

Introduction

Neurodegenerative diseases such as Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) are a public health priority with significant medical, psychological and economic repercussions. They are not homogeneous in their clinical profiles and underlying pathophysiology, and time and accuracy of diagnosis are crucial factors in order to plan timely and appropriate clinical management. As no effective pharmacological treatments for their motor and cognitive symptoms are currently available, in recent years various studies had started to investigate the potential contribution of neuromodulation techniques (such as non-invasive brain stimulation techniques, NIBS) in contrasting patients' decay [1]. These techniques can stimulate the brain by providing magnetic stimulation or direct current from outside the skull, and they have been used within the neurological field with promising results.

The present mini-review reports evidence of some neuromodulation studies targeting motor and cognitive impairment in MS and ALS. The aim of the present brief paper is to show some preliminary evidence available in the field in order to stimulate further and more robust studies about the strengths and weaknesses of these promising therapeutic options.

NIBS in MS

MS is a chronic neurodegenerative disease typically characterized by white matter lesions, axonal damage and cerebral atrophy [2,3] that affects both the neurological and the psychological domains [4-8].

A series of studies over the last years have investigated motor and cognitive effects of transcranial Direct Current Stimulation (tDCS) in patients with MS. In the motor domain, anodal stimulation of the primary motor cortex (at 1 mA intensity for 20 min in a single session) contralateral to the impaired hand produced increased corticospinal excitability, as compared to "sham" stimulation [9]. However, in another study using the same stimulation parameters these effects were not observed [10]. Notably, the anodal stimulation of primary motor cortex contralateral to somatic painful arm also produced a significant decrease in pain, measured with standardized pain scales [11]. More recently, similar results have been also observed with the anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) [12]. In the domain of sensory processing, anodal stimulation (at 2 mA intensity for 20 min over 5 consecutive day) of primary somatosensory cortex led to diminished sensory deficits in spatial discrimination with effects lasting for a 2-3 weeks' period [13].

Regarding the cognitive domain, Mattioli and colleagues showed that the combination of a cognitive training focused on attentional abilities with an anodal tDCS over the left DLPFC (25 cm2, current density: 0.08 mA/cm2), as compared to sham, led to a significant higher improvement in the scores of Symbol Digit Modality Test, Wisconsin Card Sorting Test and in the Paced Auditory Serial Addition Test. These effects were maintained also at a six-months follow up [14]. In another study, Charvet et al. tested the efficacy of a remotely-supervised transcranial direct current stimulation combined with cognitive training. The protocol consisted in ten sessions of 20-min stimulation (1.5 mA) over the DLPFC and the cognitive outcomes were tested by composite scores measuring change in performance on 1) standard tests (Brief International Cognitive Assessment in MS); 2) basic attention (ANT-I Orienting and Attention Networks, Cogstate Detection); 3) complex attention (ANT-I Executive Network, Cogstate Identification and One-Back); and 4) intra-individual response variability (ANT-I and Cogstate identification; sensitive markers of disease status) in the experimental group and in a control group in which participants only executed cognitive training without the concurrent electrical stimulation. Results showed that, after ten sessions, the experimental group had significantly greater improvement in complex attention and response variability while the two groups did not differ in measures of basic attention or standard cognitive measures [15]. The efficiency of remotely supervised home delivery of tDCS was also supported by another study by Kasschau and colleagues in which feasibility and protocol adherence of RS-tDCS was tested across 10 sessions taking place in 2 weeks. The authors reported that with the only exception of one participant, all other 19 participants completed at least eight of the ten sessions. Across a total of 192 supervised treatment sessions, no session required discontinuation and no adverse events were reported. The results of these RS-tDCS study are particularly relevant as they allow to expands patient access to tDCS and the positive effects reported in previous investigations [16].

The use of a different stimulation technique (Transcranial Magnetic Stimulation, TMS) in MS has been proven to elicit statistically significant improvements in: a) hand dexterity during a 9-hole pegboard task in patients with cerebellar dysfunction [17]; b) lower limb spasticity [18-19]; c) gait [20]; d) lower urinary tract dysfunction [21]. However, the effectiveness of NIBS with this clinical target has not been proved definitely yet, as preliminary evidence has not been replicated in a sufficient number of methodologically robust studies.

NIBS in ALS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that primarily involves voluntary motor functions, due to the degeneration of upper and lower motor neurons [22]. It is typically characterized by a focal onset in limbs or bulbar muscles, where upper and lower motor signs are maximal [23] and cognitive impairment play a significant role as well in a significant proportion of patients [24-25].

Up to date, few studies have investigated the effects of tDCS and TMS in ALS. These showed no significant modulation of cortical excitability after primary motor cortex cathodical stimulation [26-27] and small effects for anodal stimulation [28]. These negative results were probably due to less responsive corticospinal pathways to the inhibitory ctDCS effects in patients with ALS [29]. However, such an interpretation seems at odd with a series of findings obtained with TMS and particularly using continuous theta burst stimulation (cTBS) which showed, successively to stimulation, a statistically significant reduction in the Revised ALS Functional Rating Score [30] and a reduction in maximal expiratory pressure in both control group and participants with ALS. However, in this latter study, more sessions of stimulation were required to reach the same effect size of controls in the ALS group [31]. Furthermore, other TMS protocol of stimulations were applied for purposes other than inducing persistent neuromodulation, such as a tool for early diagnosis [32-33]. However, as previously mentioned for MS, also for ALS the effectiveness of NIBS has not been proved definitely yet, as preliminary evidence has not been replicated in a sufficient number of methodologically robust studies [34-35].

Conclusion

NIBS techniques such as TMS and tDCS have been shown to be safe and effective methods for improving motor, cognitive and affective functions in various neurological and neuropsychiatric disorders. As briefly presented in this mini review, neuromodulation techniques may represent an interesting tool for treating the motor and cognitive symptoms in MS and ALS as well, even if current research in the field has not reached already an appropriate level of maturity, and thus its results should be considered necessarily as preliminary. A more precise identification of treatments' targets, more robust experimental design and a better definition of relevant clinical outcomes would allow researchers and clinicians to clarify neuromodulation techniques' efficacy in these invalidating neurodegenerative conditions.

Conflict of interest

The author declares the absence of conflict of interest.

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