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Is there a therapeutic potential for repetitive Transcranial Magnetic Stimulation (rTMS) in the management of cognitive impairment in Multiple Sclerosis?

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Abstract

Multiple sclerosis (MS) is an autoimmune central nervous system disease, with inflammatory and degenerative components, affecting mostly young individuals, and resulting in accumulation of motor and cognitive dysfunction. Even from its insidious, subclinical phase, and through the entire course, cognitive impairment is frequently present, although often undiagnosed, and almost always untreated. Cognitive impairment is important, due to its impact on patients' quality of life and everyday functioning capacacity as current pharmaceutical interventions have not provided sufficient therapeutic efficacy. One reason why cognitive impairment remains hidden for long periods is the brains functional reorganization, in other words its capacity to recruiting reserve networks in order to compensate for damaged ones, retaining "normal" functioning. In the era of neuromodulation, techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) can serve as a non-pharmacological therapeutic option, enhancing neuroplasticity changes, and maintaining or improving cognitive functioning. In this short review we discuss the therapeutic potential of rTMS in the management of cognitive impairment in MS patients.

Key-words: multiple sclerosis, cognitive impairment, transcranial magnetic stimulation

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Transcranial magnetic stimulation and neuroplasticity

Multiple sclerosis (MS) is considered the most common non traumatic neurological disorder. Although the etiology of the disease is still unknown, MS is considered an autoimmune, chronic, central nervous system disease. Its major neuropathological characteristics are an ongoing demyelinating, inflammatory and degenerative process, that affects both the white and grey matter of the brain and the spinal cord. As a result there is an accumulation of disabling motor and cognitive dysfunction over time. These symptoms have a significant impact on functional capacity, psychosocial and professional status and overall quality of life [1, 2, 3].

Although Charcot firstly described the cognitive and mood aspects of MS almost 150 years ago, it was only more recently that these symptoms were considered an important aspect of the disease. Evidence now exists that deterioration of cognitive performance can be detected many years before formal diagnosis [4,5]. Of significant interest is that even in the so-called "benign" form of the disease, where the disability status (EDDS) score remains up to 3, at least 15 years after the diagnosis, cognitive impairment can be diagnosed in at least 50 % of these patients [6].

The therapeutic impact of disease modifying medications on patients' cognitive capacity, has not reached the desired outcomes [7], although they do provide protection by delaying the accumulation of brain tissue damage and brain volume loss. Even in the small proportion of patients achieving the desired NEDA status (no evidence of disease activity) over time, cognitive dysfunction was not precluded [8]. The lack of sufficient evidence from the pharmacological arena to treat cognitive deficits in MS has provided the ground for non pharmacological neurobehavioral treatments to emerge with relatively positive outcomes [9, 10]. Various other non pharmaceutical interventions have also been introduced in ameliorating the physical and cognitive aspects of the disease [11]. Among these interventions repetitive transcranial magnetic stimulation (rTMS) appears to have both the scientific-theoretical support and evidence from experimental models of the disease and trials in MS patients. [12,13,14,15]

Transcranial magnetic stimulation (TMS) is a neurostimulatory and neuromodulatory technique, based on the principle of electromagnetic induction of an electric field in the brain [12]. This technology has become a method of choice for noninvasive stimulation of the brain in conscious human subjects in the last two decades in order to study the excitability of different cortical areas and to map the connectivity of neuronal pathways [16,17]. When TMS pulses are applied repetitively they can modulate cortical excitability, either decreasing or increasing it, depending on the parameters of stimulation. Repetitive Transcranial Magnetic Stimulation (rTMS) has local and remote effects on neural function either of an excitatory or inhibitory nature [18]. The direction, magnitude, and duration of conditioning rTMS effects depends on the stimulation site, frequency, intensity, and the duration of the rTMS training. Evidence from experimental animal models of MS (experimental autoimmune encephalomyelitis) has shown that rTMS modifies astrocytosis, cell density and lipopolysaccharide levels, implying that it could be a promising treatment for neuroinflammatory conditions such as multiple sclerosis [19].

Of significant interest supported by accumulating evidence towards this is that we can impact cognitive functioning in healthy humans by utilizing rTMS. In an interesting systematic review, Guse et al., reported that high-frequency rTMS (10–20 Hz) is most likely to cause significant cognitive improvement when applied over the left (dorsolateral) prefrontal cortex, within a range of 10–15 successive sessions and an individual motor threshold between 80 and 110% [14]. In another study, Li et al., noted that high-frequency rTMS over the left DLPFC not only recruits more neural resources from the prefrontal cortex by inducing an electrophysiologic excitatory effect but also enhances efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing in healthy young people [15]. Moreover, Wan-Yu Hsu et al., in a systematic review and meta-analysis of the literature involving the period from (1990 to 2014) evaluating the effects of non-invasive brain stimulation (rTMS and tDCS) on cognitive function in healthy older adults and patients with Alzheimer's disease (AD), concluded that non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging [20].

An important characteristic of the brain that modulates the potential of cognitive therapeutic interventions is neuroplasticity, which is studied as altered brain functional connectivity both at rest (resting state functional connectivity, rs-FC) and during tasks. Hyper-connectivity or hypo-connectivity can be detected, depending on the severity and extension of structural brain damage, the nature of disease process and its time course. These alterations may be adaptive, or maladaptive. A far as multiple sclerosis is concerned, several reports have noted that early stage patients activate additional brain areas adjacent to those primarily involved during task performance, allowing them to perform normally prior to cognitive deficits being detectable on formal neuropsychological assessment [21]. This additional activation serves as a compensatory mechanism through which the patient is able to maintain relatively intact cognitive capacity for a period of time, functionally compensating for damage related to disease progression, thus masking the defects [22,23]. In one such study, Mainero et al., found that RRMS patients exhibit altered patterns of activation during tasks exploring sustained attention, information processing and episodic memory. Specifically, fMRI activity was greater in MS patients with better cognitive function. The authors concluded that functional changes in specific brain areas increase with increasing tissue damage suggesting that they may also represent adaptive mechanisms that reflect underlying neural disorganization or disinhibition, possibly associated with MS [24]. In contrast to task-based fMRI, resting state functional connectivity (rs-FC) examines the communication between different brain regions within neural networks at "rest." Increased connectivity during rs-FC is thought to serve as a compensatory mechanism for cognitive deficits early in the MS disease process [9,25,26], but later in the disease process, extra connections are associated with worse cognitive performance [9,27].

Is there a therapeutic potential for utilizing rTMS in MS?

Owing to the absence of effective pharmacological treatments, the combination of rTMS with medications has been used with efficacy mainly for the improvement of spasticity [28,29,30], fatigue and depression [11], lower urinary tract dysfunction [31], gait [32] and hand dexterity [33] in MS. The majority of these studies, however, have methodological limitations, including small number of participants, and low to moderate level of efficacy, indicating the emerging need for more studies in the future. Considering the management of cognition in MS, we are of the opinion that a therapeutic potential may exist for utilizing rTMS, for several reasons that we will expand on. First of all, pharmaceutical interventions have not provided sufficient evidence regarding their efficacy in treating cognitive dysfunction in MS. Perhaps, as we stated above, they have an indirect positive influence on cognitive performance by delaying the accumulation of brain tissue damage and brain volume loss, but they failed to show effectiveness directly on cognition. Secondly, accumulating empirical research has provided evidence that MS patients' brains undergo functional reorganization even from the initial disease phases, by altering functional connectivity in various regions, therefore acting as a compensatory mechanism. A third important point is that no major safety or adverse event considerations have been raised in a large and fast growing number of MS patients which are exposed to rTMS protocols for various symptoms. Finally, and more importantly, rTMS has shown beneficial effects on cognitive performance in healthy persons and in patients with other neurological diseases, by enhancing the brain's functional capacity (evoking neuroplasticity changes). We have further evidence that cognitive performance in MS patients can be positively influenced by higher cognitive reserve [34] and cognitive rehabilitation interventions [35,36], and this is possible through neuroplasticity changes [9,34,37].

Despite this favorable theoretical background, clinical trials using rTMS to target cognitive deficits in patients with MS are absent. To our knowledge, only Hulst and colleagues investigated the therapeutic use of rTMS on cognition in MS patients [38]. In their recent study, they studied the effects of high-frequency rTMS of the right dorsolateral prefrontal cortex (DLPFC) on working memory performance in patients with MS, while measuring task-related brain activation and task-related brain connectivity. They reported improvement in task accuracy only in patients and interpreted these results as an rTMS-induced change in network efficiency in MS patients, implicating the potential role for rTMS in cognitive rehabilitation in MS. With the limitation of the small sample of participants (17 MS patients and 11 HCs), the results of this study are very promising, and undoubtedly call for more trials, in order to provide robust evidence of r-TMS therapeutic effects in cognitively impaired MS patients.

One could, therefore, consider using, and even combining, the available non-pharmacological, non-invasive interventions to enhance functional reorganization in MS patients' brains in order to compensate for continuous brain damage. Ideally these interventions should be utilized early in the disease course, in order to maximize benefits, by maintaining patient activity in all aspects of their lives.

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