
A REVIEW OF TRANSCRANIAL MAGNETIC STIMULATION AND ALZHEIMER'S DISEASE

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ABSTRACT

Since four decades ago, that the transcranial magnetic stimulation (TMS) technique was introduced, the increasing attention of neuroscience researchers and medical engineers has been focused on the development of this technique and its use to manage the treatment of a wide range of neurological conditions, including Alzheimer's disease. The ability of TMS, specifically a substantial type known as repetitive transcranial magnetic stimulation (rTMS) in changing the plasticity of the cortex, has been the most important feature that has created the hopes of controlling Alzheimer's disease with this technique more than ever.

Keywords Alzheimer's disease · Repetitive transcranial magnetic stimulation · Neuroplasticity · rTMS

1 Introduction

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a powerful tool for non-invasively inducing plasticity in the human cortex and has opened a new perspective for its therapeutic use in a wide range of neurological disorders. Despite its growing popularity in basic and clinical research, we still know little about how rTMS affects the human brain. Most of the researches use the amplitude changes of motor evoked potentials (MEPs), which are used by single-pulse transcranial magnetic stimulation as a neurophysiological index of neuroplasticity induction after rTMS.

TMS is a non-invasive method to stimulate the brain by passing a temporary magnetic field through the skull and causes an electric current in the underlying cortical tissue. There is evidence that TMS techniques, specially rTMS, can be used to modulate the activity of the human brain. It has been almost three decades since the early studies of rTMS as a non-invasive method in patients with focal epilepsy [7]. Other studies have shown that rTMS can be used to improve motor performance in patients with Parkinson's disease [9]. Furthermore, when rTMS apply to the prefrontal cortex (DLPFC) for several days, it can be a beneficial treatment option that has fewer adverse effects than electrical stimulation treatment for patients with drug-resistant depression.

Several studies used MEPs measured from rTMS to explore the electrophysiological effects of different stimulation parameters. It appears that rTMS tends to cause a change in cerebral cortex excitability that decreases with low-frequency rTMS (<1 Hz) and increases with high-frequency rTMS (>10 Hz). Recently, in an effort to use stimulation protocols to induce synaptic plasticity in animal models [14], various studies have conducted using high-frequency repetitive stimulation, known as theta burst stimulation (TBS). Huang et al. (15) adapted the TBS technique for use in humans, and reported that MEP amplitudes increased during sequential stimulation (eg, continuous theta stimulation, cTBS).

The expectation that facilitatory and inhibitory protocols can restore normal brain function by increasing and decreasing cortical excitability, respectively, has created a basis for the use of rTMS in various neurological and psychological conditions [1.] Using neuroimaging approaches like fMRI and EEG to measure rTMS-induced neuroplasticity has ad-

vanced our understanding of the mechanisms of rTMS effects on the human brain; It also promises us to provide new ways to target the therapeutic use of rTMS in clinical disorders. The problem of individual response variability in rTMS research has received considerable attention in the past decade, with a number of MEP studies failing to replicate the results of the previous studies. In many ways, it should not be surprising that the changes in neural activity caused by rTMS are highly variable. Compared to the protocols used to induce long-term potentiation (LTP) and long-term depression (LTD) in animal models, rTMS applied through the human scalp is much more precise and activates a diffuse cortical network of different cell types. The evidence from various experiments shows that the boundary between LTP and LTD is not clear. Similarly, it is now well recognized that the level of the effects of rTMS is susceptible to many experimental and biological factors, that not only depends on inter-individual variability (e.g., age, gender, genetics, physical activity levels, etc.) but also it depends on session-related factors (e.g., duration of session, history of synaptic activity, etc.) [20].

It is worth considering an alternative possibility: whether rTMS has no lasting effect on human neural activity, and whether our response variability is only a random noise. While we do not believe that this is true for all rTMS protocols, it cannot be simply dismissed with the available evidence. Further research involving larger sample sizes, sham control conditions, and repeated assessments in the same subject under the same test conditions to maximize transparency as well as minimize bias [21], can determine the type of rTMS required. Finally, in regard to conducted studies, it appears rTMS significantly alter neural activity in humans.

Nevertheless, while the variable effects of rTMS are a significant challenge for the field, there are still good reasons to be optimistic about its future in basic and clinical research. Alzheimer's disease (AD) is one of the most common neurological disorders, which is characterized by a decrease in cognition, and interruption of daily routine activities. AD severity can range from a very early preclinical stage to late-stage dementia with multi-domain cognitive and functional impairments along a biological and clinical continuum. The syndrome of mild cognitive impairment (MCI) occurs between these stages and represents a landmark from the stage without symptoms to the onset of dementia [22]. Among several clinical subtypes of MCI [23], it is assumed that amnestic MCI (aMCI) has a destructive cause and is more likely to turn into AD dementia [24, 23]. Considering the limited effectiveness of existing drugs to restore brain function, AD is known as one of the main foci in the field of non-pharmacological interventions. Cognitive training (CT) is a non-pharmacological intervention that is usually recommended in AD and is known as an important adjunctive treatment or even an alternative to pharmacological intervention [26, 25] during the late stage [33-27] with promising results. Failure to remember names is one of the first distinguishing symptoms of episodic memory impairment in AD patients.

This issue increases with the progression of the disease throughout the spectrum of AD, from the early stages to dementia [34]. Several neuroimaging studies have shown that the memory of face-name association consists of a complex network. In addition to playing an essential role in episodic memory, specialized visual areas in the occipitotemporal cortex and other cortical areas related to higher cognitive functions, like the prefrontal cortex (DLPFC) [35] are a central pole for integrating networks, that mediate organizational functions and may function in different types of tasks. Cognitive changes and DLPFC dysfunction are prominent features of AD in its early stages [36-38] DLPFC is a key region that contributes to several large-scale brain networks, like default mode network (DMN), fronto-parietal network (FPN) and central executive network (CEN) [19, 18], that its changes are related to clinical manifestations of AD. Along with cognitive interventions, repetitive transcranial magnetic stimulation (rTMS) is an emerging and promising therapeutic option in the field of non-pharmacological treatments for AD [41-46].

In the last two decades, rTMS has received increasing attention as a potential therapeutic tool for the treatment of several neurological and neuropsychiatric disorders [47]. rTMS is a non-invasive technique capable of stimulating a magnetic pulse through a coil placed on the head. The created magnetic field induces a transient electric field on the subsurface that can depolarize cortical neurons [49, 48]. Interestingly, rTMS not only acts locally on interneuronal circuits, but also induced activation across cortical connections to functional brain regions [50]. In addition, rTMS is able to produce long-term changes in cortical excitability, that may indicate mechanisms similar to long-term potentiation. [51.] This evidence has aroused great interest in the therapeutic use of rTMS in various clinical fields [53,52]. Existing studies of rTMS in AD suffer from several shortcomings including small sample size, changes in stimulation parameters, target areas, number of sessions and outcome measures, heterogeneity of patients' disease severity, and lack of control groups.

Recent evidence-based guidelines have not confirmed left DLPFC rTMS as an effective treatment option for AD treatment, while it shows the possible effect of rTMS combined with CT in improving cognitive functions in AD patients [54].

The rationale for promoting rTMS as an adjunctive therapy relies on the results of several studies showing that the most effective way to increase neural plasticity (i.e., our brain's ability to change functions and structure by modulating synaptic connections) is a combination of exogenous and endogenous stimulation. In this sense, rTMS may be used

as a preparation tool that can pre-activate the initial state of the system so that the neural impact of any subsequent intervention depends on the interaction of ongoing brain activity [52]. This mechanism have a central role in cognitive intervention, where adding rTMS to CT protocol may be a key role to enhance its efficacy [53].

Padullés et al. [59] first showed the beneficial effect of high-frequency rTMS on the left frontal cortex using memory-name association among MCI patients. Since then, the DLPFC has been the target of most rTMS interventions in different stages of AD pathology [66-58]. A recent meta-analysis showed the effects of rTMS in the DLPFC in MCI and AD patients, with high-frequency rTMS protocols in the left DLPFC significantly improve memory performance [42] (as well as low-frequency protocols in the right DLPFC). In the present study, our aim is to review the effect of high-frequency rTMS of the left DLPFC in patients with memory deficits.

2 rTMS Effect on Neural Diversity for Clinical Research

Deactivating the lateral magnocellular nucleus of the anterior neostriatum located directly in motor pathways, prevents the normal modulation of changes and reduces learning capacity [68-71]. Similarly, in people, behavioral diversity increases during the initial learning of new tasks, and it is thought that this process is done by the release of dopamine in the cortico-basal ganglia circuit [73,72].

To support this idea, it is notable that Parkinson's disease characterized by a decrease in dopamine, is associated with movement stiffness and impaired learning ability [75,74]. Additional evidence that movement variability can be beneficial for learning in subjects was shown in a study by Wu et al. [76] They found that the structure of movement-to-movement variability in motor output can predict individual differences in motor learning ability in two different tasks, one reward-based and the other error-based.

Similar to variation and vocal learning in songbirds, task-related variation in motor control circuits can facilitate learning in humans. This concept is naturally extended to neurorehabilitation, where, as a result, increasing movement variety during exercise, it can potentially help restore movement functions lost due to injury. The present results provide evidence that rTMS is used as an adjunctive tool to increase the effects of name-related memory training and generalization to spatial reasoning in Alzheimer's disease. Future studies combining rTMS with CT protocols and focusing on different cognitive domains (e.g., executive functions) are needed to further investigate the beneficial effect of adjunctive rTMS. In addition, the present findings showed that the level of rTMS additive effect depends on the severity of the disease as well as the level of education of the patients. This finding is important for maximizing treatment effects, as patients with different degrees of cognitive impairment may benefit differently from rTMS. Studies on patients in the early stage of AD, as well as the long-lasting follow-up may address the key question of whether rTMS treatments can delay development of the disease or even stop it.

3 References

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