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Review article

Cognitive effects of repetitive transcranial magnetic stimulation in patients with neurodegenerative diseases — Clinician's perspective

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) represents a promising tool for studying and influencing cognition in people with neurodegenerative diseases. This procedure is noninvasive and painless, and it does not require the use of anesthesia or pharmacological substances. In this systematic critical review we report outcomes from research focused on behavioral cognitive effects induced by rTMS in patients with Alzheimer's disease (AD), Parkinson's disease (PD), and mild cognitive impairment (MCI) preceding AD. There are still major limitations to rTMS use, such as a poor understanding of its after-effects and inter-individual variability in their magnitude, discrepancies in stimulation protocols and study designs, varied selection of the specific stimulated areas and control procedures, and neuropsychological methods for assessment of after-effects; hence, the results of the present research can only be considered preliminary. The future directions are discussed.

Contents

1. Introduction

A number of studies have investigated repetitive transcranial magnetic stimulation (rTMS) as a potential therapeutic tool. rTMS is a noninvasive method that is able to modulate brain function. Lasting effects on brain plasticity can be observed after application of rTMS [1]. Two common neurodegenerative diseases, Alzheimer's disease and Parkinson's disease, are diagnosed in millions of people worldwide [2]. The diseases share several characteristics: they target predominantly the aging population and show gradual progression, individual disease-specific histopathological brain changes, and molecular mechanisms of pathogenesis. An increasing number of people are diagnosed as a result of population growth and prolonged life expectancies. Alzheimer's disease (AD) and Parkinson's disease (PD) are associated with impaired cognitive functions, reduced independent functioning, and psychological and behavioral problems. The increasing cumulative prevalence of these diseases has a huge economic impact in developed countries throughout the entire world.

Mild Cognitive Impairment (MCI) is a term used for people with impaired memory and/or other cognitive functions beyond the expected

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outcomes for the age and education but not yet within the diagnostic criteria for dementia [3]. MCI patients do not show signs of significant functional impairment but they are at high risk for dementia conversion [2].

The key principle of rTMS is based on regularly repeated stimulation of the focal cortical area by a train of magnetic pulses. Stimulating coils of different shapes induce electric currents in neurons (secondary conducting material). The effect of stimulation decreases with the distance from the stimulating coil. There is an immediate effect on underlying brain tissue to a depth of approx. 2 cm beneath the scalp as well as possible changes in distant interconnected regions. Generally, low-frequency rTMS ($\leq$1Hz) reduces cortical excitability when applied over the motor cortex, and high-frequency rTMS increases it [1,4]. Online stimulation refers to the condition in which a person is executing a task (motor, cognitive, etc.) while receiving rTMS. The offline approach is when stimulation occurs before a task but some rTMS after-effects may interrelate with the final results [5]. There is no universal agreement on the rTMS parameters to be used or on the overall effect of therapeutic rTMS, mainly due to a lack of understanding of the mechanisms responsible for the lasting modifications of cortical excitability induced by stimulation and due to within-subject and between-subject variability of rTMS-induced effects. There is evidence that rTMS induces some after-effects that outlast the period of stimulation and depend on the number of pulses applied, the rate of application, and the intensity of each stimulus [6].

Several neurotransmitter systems can be modulated by rTMS with effects that are measurable for longer periods of time. Application of rTMS to the motor cortex or dorsolateral prefrontal cortex may increase or decrease the release of monoamines (particularly dopamine) in different cortical and subcortical areas of the brain interconnected with the stimulated area [7–9]. In addition, high-frequency rTMS applied over the prefrontal cortex may act via the stimulation of the glutamatergic prefrontal neurons [10] and may increase neurotrophic factors in the brain [11].

Other mechanisms of action have also been proposed, including changes in the effectiveness of synapses between cortical neurons (long-term potentiation and long-term depression). Positive changes can also be measured in behavior [1,5,6].

Since the first introduction in the late 1980s, rTMS has been used as a potential treatment for a variety of neurological and psychiatric disorders [1]. Studies and meta-analyses have included the therapeutic use of rTMS in depression (FDA approved since 2008) [12–14], schizophrenia [15–17], stroke [18,19], tinnitus [20–22], addiction [23,24], obsessive–compulsive disorder [25], Tourette's syndrome [26] and many other diseases.

The fundamental rationale for therapeutic use of rTMS is the fact that the effect of rTMS on cerebral cortex outlasts the duration of stimulation. Moreover, the changes induced by rTMS are not restricted to the stimulated region and possible effect may also occur in the distant functionally connected areas [8,9,27]. Another important issue is the fact that protocols using multiple sessions of stimulation may lead to long-lasting modulation of the brain plasticity [1,5,28]. It is probably not realistic to assume direct neuroprotective effects of rTMS on pathophysiological mechanisms involved in neurodegenerative diseases such as Alzheimer's disease (AD) or Parkinson's disease (PD). However, rTMS may interact with the normal processes of brain plasticity and induce or enhance compensatory mechanism leading to increase of the brain reserve; hence interfere with temporal evolution of clinically relevant cognitive symptoms of neurodegenerative diseases [29]. Postponing the clinical manifestation of fully blown dementia may be the major goal since we still do not have any causal treatment for neurodegenerative diseases.

It has been clearly shown that rTMS induces changes of cortical plasticity of motor cortices [28]. The positive effects of TMS on cognitive P300 event-related potential have also been well documented [27,30]. Although this may provide a rationale for using the rTMS as a therapeutic tool it is still not easy to estimate how and if the altered mechanism of brain plasticity can serve as a model for developing effective protocols [31]. Results of the studies employing functional MRI (fMRI), fluoro-deoxy-glucose PET (FDG PET), and EEG in different patient groups may help in formulating hypotheses to be tested by using rTMS. However, on the whole it is more difficult to induce clear behavioral and clinically relevant benefits of rTMS than to induce changes of cortical plasticity or brain activation/ network connectivity changes [28].

The limited effects of accessible pharmacological treatment for cognitive impairment in AD, PD, and MCI preceding AD has led to an increased interest in research on alternative therapeutic strategies and non-pharmacological interventions [32,33]. This review presents the results of current studies that have used rTMS in people with AD or PD and assessed its effect on cognitive functions. MCI preceding AD is included in the review because of the aim to treat impaired cognitive functions as early as possible.

2. Method

A systematic literature search of articles written in English before June 2013 was conducted in the Web of Science and PubMed databases. A wide range of keywords was used: “rTMS”, “TMS”, “magnetic stimulation”, “cognitive”, “cognition”, “Alzheimer”, “Parkinson”, “MCI”, “mild cognitive impairment”, and “neurodegenerative”. By combining the aforementioned keywords we identified 224 articles retrieved by the Web of Science and 67 papers collected from PubMed databases. We carefully reviewed all titles and abstracts and excluded the meeting abstracts, editorial material and non-english written articles. Then we focused on our predefined selection criteria: application of rTMS, involvement of human subjects, inclusion of patients with MCI, AD or PD, and evaluation of cognitive domains. Articles that did not meet these criteria were excluded. Our aim was to include original studies dealing with the therapeutic application of rTMS and assessing cognitive after-effects as one of the major outcomes. Having said that, we were able to identify 19 articles meeting our focus and field of interest.

Articles were divided into three groups according to the diagnosis (MCI preceding AD, AD, or PD). We found nine studies that included patients with PD, seven articles on patients with AD, and three articles that concern people with MCI. Articles were listed from the most recent to the oldest.

3. Results

We identified 19 studies published before June 2013. The mean clinical population was about 17 people per study (range of 1–45 participants). This review includes 315 people altogether, of which 48 were with MCI, 118 with AD, and 149 with PD. The publications consist of two case studies [34,35], three open studies [36–38] and 14 controlled studies [39–52]. In the text of this review, we focus only on the controlled studies, but information about all 19 studies is displayed in Tables 1–3.

As a sham condition in seven studies [39,40,42,44,45,48,52] active coils were tilted so that no magnetic stimulation reached the brain; in six studies [41,43,46,47,50,51] sham coils were used; and in one study, stimulation of the occipital cortex was used as a control site of stimulation [49].

There was certain uniformity in the selection of the targeted areas. The dorsolateral prefrontal cortex (DLPFC) was stimulated in nearly all of the studies. In 12 controlled studies, researchers stimulated this area either bilaterally [39,41,42,44–46], or unilaterally with a left-sided preponderance [43,48–51]; in one study solely the right DLPFC was stimulated [52]. Other cortical regions were stimulated less frequently, including the inferior frontal gyri [47], dorsal premotor cortex [49], supplementary motor area [52], parietal somatosensory association cortex, and Broca's and Wernicke's areas [41]. The high occurrence