

The use of transcranial magnetic stimulation in preserving cognitive function: A literature review

Chelsea Alana Foster

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A literature review

Chelsea Alana Foster

The University of Toledo

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Introduction

Mild cognitive impairment (MCI) is a diagnosis that describes a transitional period between healthy cognitive aging and clinical dementia (Morris et al., 2001; Petersen et al., 2014). Morris et al. suggest that most cases of MCI are actually unrecognized cases of very mild Alzheimer disease (AD) based on data that included a progression of MCI to AD at a rate of 10% to 15% per year (Morris et al., 2001). Among other risk factors, age is the strongest risk factor in the development of dementia (American Psychiatric Association, 2013). The population in the United States is growing and the number of individuals with dementia is also increasing. In 2010, an estimated 4.7 million people over age 65 in the United States had AD dementia, a number projected to grow to 13.8 million by the year 2050 (Hebert, Weuve, Scherr, & Evans, 2013). According to Hebert et al., the identification and utilization of an intervention to delay the onset of AD dementia would substantially decrease the overall prevalence of the condition (2013).

Despite extensive research, there is currently no curative treatment or effective prevention for AD dementia and the current therapeutic drugs have very limited value with significant adverse side effects. Various diets and alternative treatments have been proposed to be neuroprotective, however, there is currently no established diet recommended for individuals with cognitive impairment (Solfrizzi et al., 2011). Marketed alternative treatments that are not approved by the United States Food and Drug Administration (FDA) include herbal remedies, dietary supplements, and “medical foods.” Pharmacologic approaches approved by the FDA to treat the cognitive symptoms of AD include cholinesterase inhibitors and memantine, and these medications seem to have some benefit in relieving symptoms, however, they are unable to stop

the disease from progressing (Alzheimer's Association, 2016; Rutherford, Lithgow, & Moussavi, 2015).

A newer non-pharmacologic approach in the area of preserving cognitive function involves non-invasive brain stimulation, specifically transcranial magnetic stimulation (TMS). TMS has been studied as a therapeutic modality in a wide range of patients with neurodegenerative and neuropsychiatric disorders with the overall rationale for its use being the ability of the beneficial effects to last longer than the period of stimulation (Anderkova & Rektorova, 2014). The purpose of this project was to review existing evidence for whether TMS can preserve or improve cognitive functions and help in treatment of MCI, AD, and other degenerative brain diseases that lead to loss of cognitive functions.

Methodology

Search terms

Search terms included the following: transcranial magnetic stimulation; repetitive transcranial magnetic stimulation; Alzheimer disease; dementia; mild cognitive impairment; cognition; cognitive disorders; cognitive performance; executive function; brain stimulation; non-invasive brain stimulation; treatment; dorsolateral prefrontal cortex; memory circuit; working memory; memory.

Databases

The following databases were used: PubMed; Web of Science; Embase.

Inclusion and exclusion criteria for articles

Articles were only included if they were written in English. Articles written in any language other than English, and unavailable in English translation, were excluded from this review.

Problem statement: Due to the growing population and subsequent increase in neurodegenerative diseases in the older population, new therapies are needed to help improve patient health and quality of life. Utilizing a non-invasive therapy to modulate and improve cognitive functioning would ideally be superior to the alternatives, including medications with known and possibly unknown side effects.

Literature Review

Overview and Background of TMS

Since its conception in the 1980s, transcranial magnetic stimulation has been studied for a variety of purposes ranging from motor system physiology to cognitive neuroscience (Sliwinska, Vitello, & Devlin, 2014). Hallett (1996) describes how TMS has been used to study and map the motor cortex by measuring the motor evoked potential (MEP) at exact locations. In other studies, TMS has been used for investigating brain-behavior relationships as a refined way of analyzing behavioral changes and deficits associated with specific brain lesions (Sliwinska et al.). In addition to its usefulness in mapping and improving understanding of the brain's architecture, TMS has been used to modulate activity of neurons, perhaps by altering functional connectivity and influencing morphological changes within neural structures (Lan, Chhetry, Liston, Mann, & Dubin, 2016). Parkin et al. (2015) note two overall uses of TMS, the first being suprathreshold stimulation to disrupt undesirable ongoing activity, and the second as a neuromodulatory approach to inducing plasticity.

The technique has been published as a non-invasive intervention in relief of chronic neuropathic pain (Pommier et al., 2016) and as a therapeutic tool for treatment-resistant depression (Lan et al., 2016). Luber and Lisanby (2014) reviewed sixty-one reports of TMS-related performance enhancement across a wide range of tasks including motor function and higher cognitive functioning such as tasks involving attention, memory, and language. While there are differences, TMS has become a more popular tool for research and clinical use than transcranial electrical stimulation (TES), which is an older method of brain stimulation that inflicts more pain in patients (Reid, 2003).

Overview of Dementia

Dementia can be defined as a disorder of cognition involving impairment in learning and memory, impairment in executive cognitive functions such as handling complex tasks and ability to reason, and impaired visuospatial ability and language functions (Cecil, Goldman, & Schafer, 2012). Cognitive impairment may be due to a variety of causes, and is often multifactorial in the older population. A diagnosis of mild cognitive impairment requires ruling out a multitude of factors that may lead to cognitive decline. Alzheimer's disease is the most common cause of dementia, however, the diagnosis may remain unclear in patients with other health considerations such as vascular disease, due to the effects of vascular pathology on cognition (Albert et al., 2011; Cecil et al.). Individuals with dementia may exhibit a range of clinical manifestations in addition to what has been described above; irritability, depression, and anxiety are common. People may also experience symptoms of psychotic disorders, which include paranoia, delusions, and hallucinations. Additionally, it is common for affected individuals to have anosognosia, or lack of insight regarding their condition (Cecil et al.).

While dementia is a clinical diagnosis, further attempts can be made to determine the etiology in order to help guide treatment. Pathologic biomarkers may be present in patients with dementia, some of which are specific to Alzheimer's disease, such as the beta-amyloid and tau proteins, which are deposited in aggregated plaques and intracellular neurofibrillary tangles, respectively (Albert et al., 2011). Decreased metabolism of specific brain regions is also characteristic of AD, particularly of the frontal lobe, medial temporal lobe, and parietal lobes, along with degeneration of other brain regions involved in memory formation and retrieval, including the hippocampus and basal forebrain cholinergic nucleus basalis of Meynert (Bick & Eskandar, 2016).

Overview of the Memory Circuit

Memory is a complex phenomenon that has been studied for many years. It is currently understood that there are different types of memory that operate within unique systems. Long term memory can be divided into explicit, or declarative, and implicit, or non-declarative memory (Bick & Eskandar, 2016). Explicit memory involves conscious recall of facts and events, while implicit memory involves unconscious recall, such as skills and habits, and associations between environment and behavior. Multiple structures and circuits can be associated with memory formation, storage, and retrieval. The hippocampus is an allocortex area located within the medial temporal lobe and is known to play a major role in memory formation. Two structures that are associated with the hippocampus and that have established functions in memory are the entorhinal cortex and the dentate gyrus. Input to the hippocampus is first received by the entorhinal cortex from the cingulate gyrus and is then projected to the dentate gyrus (Hescham, Lim, Jahanshahi, Blokland, & Temel, 2013). According to Bick and Eskandar, stimulation of the entorhinal cortex may yield improved memory encoding and long-term memory capacity by inducing neurogenesis along the hippocampal memory circuit. This finding supports the theory that hippocampal neuron degeneration may be involved in the pathogenesis of Alzheimer dementia. Interestingly, the entorhinal cortex does not appear to be affected by healthy aging (Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016).

Working memory involves a unique circuit, with top-down control beginning at the level of the dorsolateral pre-frontal cortex (DLPFC) (Bagherzadeh, Khorrami, Zarrindast, Shariat, & Pantazis, 2016). Since dementia is characterized by problems in working memory and adaptive

decision making, it can be concluded that abnormal function of the DLPFC is related to dementia (Rutherford et al., 2015).

Brain Aging

The impact of the aging process on memory and cognition is variable among individuals, however, there are distinct age-related changes within the hippocampus and frontal lobe that are associated with cognitive changes. Spatial cognition and navigation, or “place learning,” require involvement of the hippocampus, as indicated in multiple animal and human studies of aging (Samson & Barnes, 2013). There are both age-related structural and functional changes associated with changes in cognition and memory. Reduced metabolism in the dentate gyrus of aged mice, monkeys, and humans on functional MRI is associated with memory impairment (Small, Schobel, Buxton, Witter, & Barnes, 2011; Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002). More significant anatomic and metabolic changes are correlated with more severe clinical outcomes.

Age-related changes of the frontal and pre-frontal cortex have also been shown to influence cognition and memory, specifically in tasks that require working memory, behavioral flexibility, and attention processes. In general, slower learning and poorer performance in memory tasks is associated with the aging process (Samson & Barnes, 2013). There appears to be a loss of frontal lobe volume, with general preservation of neurons but some neurodegeneration may also occur. This decrease in volume seems to correlate with poorer accuracy in recognition memory tasks (Samson & Barnes). In addition, a decline in executive functioning, working memory, and information processing have been correlated with alterations in prefrontal white matter and shrinking of grey matter (Gunning-Dixon & Raz, 2003).

Cortical plasticity is reduced in Alzheimer disease as a result of amyloid-beta and tau protein formation which disrupt long-term potentiation (LTP) within the hippocampal region (Di Lorenzo et al., 2016). Long-term potentiation underlies long-lasting enhancements in synaptic transmission between two neurons as result of concurrent pre- and post-synaptic activation and is thought to be one of the major cellular mechanisms of learning and memory (Bentwich et al., 2011). Disruption of LTP is correlated with undesirable changes in learning and memory. An increase in long-term depression (LTD) is also seen with buildup of the tau and amyloid proteins, and this has been linked to impaired synaptic transmission between neurons, as well as increased apoptosis and degeneration (Di Lorenzo et al.). In a trial evaluating alterations in cortical plasticity, Di Lorenzo et al found that patients with AD showed altered cortical plasticity with a shift from long-term potentiation to long-term depression, compared to healthy subjects without dementia. Continued cognitive decline in the AD patients was reflected in follow-up as decreased Mini Mental Status Exam (MMSE) scores over an 18 month follow up period. Di Lorenzo et al. propose abnormalities in LTP-like cortical plasticity with a shift toward increased LTD is a hallmark of AD, and that a more pathological level of tau in CSF analysis is correlated with an increase in LTD, together leading to a more aggressive clinical outcome.

Use of TMS in Individuals With and Without Dementia

Using TMS to modulate the process of neurocognitive decline in older adults is an emerging topic that is relevant to the aging population as life expectancy increases. The prefrontal cortex is known to be a critical structure in memory encoding and retrieval. External activation of the dorsolateral prefrontal cortex (DLPFC) may improve verbal memory encoding and retrieval (Bick & Eskandar, 2016). In healthy individuals without evidence of cognitive

impairment or dementia, TMS applied to the DLPFC enhanced working memory performance in a variety of tasks including memory and recall, attention, reasoning and more. On brain imaging studies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), there is increased activation of the DLPFC during tasks related to working memory. Additionally, the DLPFC is thought to have an executive role over other brain structures involved in the working memory pathway (Bagherzadeh et al., 2016).

Mechanism and Parameters of TMS

Repetitive TMS (rTMS) involves applying a rapidly changing magnetic field to the outer surface of the skull, which is produced by running a strong electrical current through a conducting wire in a circular or figure eight shaped coil. The coil is then used to induct electrical fields in the brain tissue, resulting in movement of ions and leading to depolarization or hyperpolarization of targeted neurons (Rutherford et al., 2015). The pulse protocol for delivery of TMS is critically important in order to achieve desirable outcomes. Different pulse protocols may have varying or even opposite effects, including the duration of effects after the stimulation takes place. TMS can cause immediate disruption to cortical activity, with the level of disruption correlating to the frequency and intensity of stimulation, or it may also modulate cortical excitability in a longer-term fashion with inhibitory or excitatory effects (Bagherzadeh et al., 2016). Repetitive TMS induces synaptic plasticity and reorganization of the cortex, resulting in longer lasting effects. In elderly subjects, it is also noted that higher frequencies and intensities yield better responses which may be related to the increased distance between the cortex and the skull with age-related atrophic changes in the brain (Drumond Marra et al., 2015).

Parameters of stimulation frequency include single pulse, double pulse, on-line or off-line repetitive pulse; each one with unique physiological and behavioral effects. Low intensity pulses, or low frequencies, tend to yield inhibition of neuronal activity while high intensity leads to facilitation of activity. The mechanism for high-frequency rTMS effects can be likened to the mechanism of long-term potentiation, in that it increases efficacy of synaptic transmission (Bentwich et al., 2011; Kimbrell et al., 1999). Furthermore, the state of excitation of brain tissue at the time of stimulation will influence the overall effect for that given session. This creates a challenge as it is difficult to define or quantify a state of excitation, and so it is difficult to calibrate as well (Parkin et al., 2015). It is, however, known that a higher level of activity or excitation before stimulation produces an overall greater response to the stimulation (Pasley, Allen, & Freeman, 2009).

Resting motor threshold (RMT) can be defined as the lowest intensity of stimulation required to produce a visible muscle contraction with single pulses of TMS applied to a region of the motor cortex. Rutherford et al (2015) measured the RMT using EEG pulses over the motor cortex to induce three consecutive finger movements. The RMT is used to determine the intensity of the stimulation.

Cognitive and Behavioral Outcomes of TMS Studies

In a meta-analysis, it was concluded that high-frequency rTMS at 80-110% of RMT applied to the left DLPFC for numerous consecutive sessions would be most likely to result in significant cognitive improvement in patients with neuropsychiatric disorders (Guse, Falkai, & Wobrock, 2010). Much of the TMS/rTMS cognitive research has been dedicated to

neuropsychiatric disorders such as depression and schizophrenia; this review will focus on studies dedicated to mild cognitive impairment and dementia.

In animal studies, a single pulse of TMS increased spontaneous neuronal activity. Mueller et al recorded action potentials within 1 millisecond of delivering TMS pulses to a group of awake primates and then observed changes in activity as compared to a control group. They found that an increased level of activation is seen with greater stimulus intensity (Mueller et al., 2014).

There is evidence of improvement in working memory among healthy subjects without cognitive impairment who were treated with rTMS (Bagherzadeh et al., 2016). When the left DLPFC was stimulated using high-frequency rTMS, healthy individuals were found to have an enhancement in working memory performance among various tasks (Bagherzadeh et al.). The tasks measured different domains of working memory, including verbal and visual short-term memory, storage capacity, executive function, spatial recognition and maintenance, abstract visual pattern recognition, and strategic planning abilities. Results of the treatment group's performance were compared with a placebo (sham) group, and the post-TMS results were compared with individual baseline scores. Improvement in accuracy and reduction in latency were seen from baseline to follow up in most tasks. Significant improvement was seen in the digit span task, which measured the capacity of verbal short-term memory, and the spatial 2-back task, which evaluated storage and executive processes including manipulation and maintenance of spatial information in working memory. These results are consistent with expectations and current understanding of left versus right hemisphere control over specific domains. Stimulation of the left DLPFC would be expected to improve skills related to verbal memory and attention, whereas stimulation of the right DLPFC may be expected to have effects on visual memory

(Bagherzadeh et al.). Additionally, these two tasks were considered as having a higher cognitive load, potentially allowing more room for improvement. Bagherzadeh et al. therefore propose that tasks requiring a higher cognitive demand may have more room for improvement and thus may be more responsive to rTMS-induced effects.

Rutherford et al. also compared results of a TMS treatment group with results of a sham group. Instead of applying TMS only to the left DLPFC, Rutherford et al. applied high-frequency rTMS to the right and left DLPFC bilaterally. They used the Montreal Cognitive Assessment (MOCA) and Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) to determine whether a trial of rTMS would be effective as a tool for improving cognitive abilities in patients with early to moderate AD. Cognitive abilities including memory, language, and attention were evaluated by the ADAS-cog, which was administered by a trained clinical psychologist who was blinded to the randomized groups. The MOCA test was used more frequently throughout the study to measure visual, language, memory, and cognitive skills.

They found an overall statistically significant change in MOCA scores, especially in subjects identified to be in earlier stages of the disease. In long term analysis, trends also showed less decline in cognitive function than would be expected otherwise. Rutherford et al. concluded rTMS can be an effective tool for improving cognitive abilities in this population, with the caveat that positive results may only persist up to a few weeks following discontinuation of treatment. While there was a clear improvement in ADAS-cog scores, there was no statistical significance in this assessment (Rutherford et al., 2015). Though not statistical evidence, and perhaps a result of the placebo effect, it is important to note the caregivers and patients receiving treatment noticed and expressed improvements in cognition during the course of treatment (Rutherford et al.).

Another study showed that when combining rTMS treatment with cognitive training tasks in patients with mild to moderate AD, significant improvement in ADAS-cog scores were seen after 6 weeks of intensive daily treatments and at 4.5 months after biweekly maintenance treatments (Bentwich et al., 2011). More than half of these patients were undergoing maintenance treatment with cholinesterase inhibitors for at least two months prior to enrolling in the rTMS trial. Therefore, it is suggested that a combination of rTMS, cognitive training, and pharmacologic therapy may have synergistic effects in preserving cognitive function in this patient population.

Turriziani et al. investigated the effects of transient inhibition and excitation via rTMS on verbal and non-verbal recognition memory and found that rTMS inhibition of the right DLPFC enhanced recognition among healthy controls and subjects with MCI (Turriziani et al., 2012). It was also revealed in their study that excitation of the right DLPFC induced by rTMS resulted in worsening memory performance. When investigating the differential involvement of the left and right DLPFC in verbal and non-verbal memory retrieval, Turriziani et al. found that rTMS-inhibition of the right DLPFC improved recognition memory performance in the healthy control subjects as well as subjects with MCI in both verbal and non-verbal recognition but that rTMS-inhibition of the left DLPFC had no impact on performance in either group. Further, rTMS-induced excitation of the right DLPFC actually impaired non-verbal recognition and had no effect when targeted at the left DLPFC. Turriziani et al. propose that inhibition of the right DLPFC therefore modulates a domain-general memory retrieval process due to the improvement in both verbal and non-verbal recognition tasks.

A study done by Drumond Marra et al. (2015) demonstrated improvement in basic everyday memory in elderly adults with mild cognitive impairment after only ten treatments with

rTMS to the left DLPFC. In their study, the Rivermead Behavioral Memory Test was used for efficacy assessment, and they continued to see improvement even at the one month follow up visit. According to Drumond Marra et al., the improvement noted at one month follow up suggests a sustained gain in episodic memory as a result of the rTMS treatment.

Other researchers have targeted different cortical areas with rTMS, including the right inferior frontal gyrus and right superior temporal gyrus (Eliasova, Anderkova, Marecek, & Rektorova, 2014). Eliasova et al. discovered significant improvement in attention and psychomotor speed in patients with MCI and AD after administration of high frequency rTMS to the right inferior frontal gyrus.

Physiology of TMS Effects

High frequency TMS leads to enhanced synaptic plasticity, induces upregulation of N-methyl-D-aspartate (NMDA) receptor activity and increases gamma-aminobutyric acid (GABA) mediated inhibition. It may also trigger changes in neural signaling by increasing activation of neuromodulators that are important in cognitive functions such as acetylcholine, dopamine, norepinephrine, and serotonin. Additionally, TMS may have effects due to increased blood flow to the targeted areas (Drumond Marra et al., 2015; Huerta & Volpe, 2009).

Conclusion

At this point, convincing evidence for any long-term benefits of TMS is still lacking in the domain of cognitive impairment. This is likely due to the current minimal level of understanding of the effects of TMS on brain activity and individual structures (Matheson, Shemmell, De Ridder, & Reynolds, 2016).

A large amount of TMS research in animals and humans has focused on primary motor and visual cortices due to the ease in measuring responses. The ability to translate these effects and extrapolate to other areas of the brain involved in different functions is difficult due to the differences in microstructure and surface curvature across the cortex (Matheson et al., 2016).

Based on results from Bagherzadeh et al. (2016), it may be possible that improvement via neuronal modulation of cortical networks may be best studied and identified in those with existing abnormal patterns, thus it is difficult to test efficacy on healthy subjects and extrapolate findings to fit those with deficits.

Other limitations noted in the discussed research studies include variations in mood and the question of whether the current assessments being used are a true measure of outcome. It would be expected that mood can play a role in outcome, considering the sensitive patient population. Subjective improvements have been reported by the patients and family members or caregivers, yet they are deemed not to be statistically significant. From more ethical considerations, should it matter if the results are statistically significant in a treatment that causes no harm but is subjectively improving a person's quality of life?

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Abstract

Objective: The goal of this literature review was to review existing evidence for whether transcranial magnetic stimulation can preserve or improve cognitive functions and help in treatment of mild cognitive impairment, Alzheimer disease, and other degenerative brain diseases that lead to loss of cognitive functions.

Methods: Scholarly articles were identified using databases including PubMed, Web of Science, and Embase. Search terms included “transcranial magnetic stimulation;” “repetitive transcranial magnetic stimulation;” “Alzheimer disease;” “dementia;” “mild cognitive impairment;” “cognition;” “cognitive disorders;” “cognitive performance;” “executive function;” “brain stimulation.”

Results: Research reviewed in this paper supports improvement in cognitive functions as a result of transcranial magnetic stimulation.

Conclusion: Evidence supporting any one given technique or protocol remains inconclusive in this population, however, research does show improvement in cognition with high-frequency transcranial magnetic stimulation both in the short term. It is less clear whether the effects are sustainable beyond the treatment period, thus, further research is needed.

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Name: Chelsea Foster

Signature: 

Department: Physician Assistant Studies College: Medicine and Life Sciences

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