

DOES TMS HAVE A PLACE IN THE TREATMENT OF PATIENTS WITH AD?

Babek Tousi

USA

Our knowledge about Alzheimer's dementia (AD) has increased dramatically over past few years. Unfortunately these findings have not been successfully translated into new treatment options for AD. Most current efforts to find new therapies for AD are directed at identifying new compounds that affect the underlying disease process and produce a drug-placebo difference in outcomes. These attempts by the pharmaceutical industry have not been successful over past decade, with an overall failure rate of 99.6%, in the United States. (Cummings 2014)

The pharmaceutical industry has scaled down the search for new Alzheimer's treatments after the failure of several high profile expensive trials. Therefore, alternative or complementary adjuvant therapeutic strategies have gained increasing attention. The development of noninvasive methods of brain stimulation has increased the interest in neuromodulatory techniques as potential therapy for cognitive rehabilitation in AD. In particular, repetitive transcranial magnetic stimulation (rTMS) is a noninvasive approach that may induce prolonged functional changes in the cortex.

The use of rTMS involves the discharge of a transient electromagnetic field through the skull. Repetitive TMS (rTMS) can induce lasting modulation of brain activity in the targeted brain region and across brain networks through transcranial induction of electric currents in the brain (Wagner 2007).

It is not completely understood how TMS induces these lasting effects on the brain. There is evidence to suggest that the physiologic impact of this technique involves synaptic plasticity, specifically long-term potentiation (LTP) and long-term depression (LTD). (Freitas 2011)

TMS has been FDA cleared for use in adults with treatment-resistant depression in the United States. Several studies have used rTMS to improve cognitive performances in patients with AD. The rTMS applied bilaterally on the dorsolateral prefrontal cortices (DLPFC) improved naming of actions in both mild and moderate to severe AD patients (Cotelli 2006, 2008). They later showed that improvement in sentence comprehension continues after the end of the rTMS protocol, providing support on long-lasting cognitive effect of rTMS in AD (Cotelli 2011).

High frequency rTMS over the left and subsequently over the right DLPFC in patients with mild to moderate AD, produced an improvement in all rating scales, MMSE, instrumental ADL scale and geriatric depression scale for 3 months (Ahmed 2012).

There have been promising results from novel protocols of high frequency rTMS, in combination with cognitive training, as therapy for AD patients.

Bentwich and his colleagues showed in a proof of concept study that a combination of rTMS and Cognitive training, improved ADAS-cog by approximately 4 points after both 6 weeks and 4.5 months of treatment and CGIC by 1.0 and 1.6 points. (Bentwich et al., 2012)

Fifteen AD patients received rTMS+ cognitive training or sham treatment for five sessions/week for 6 weeks, followed by biweekly sessions for 3 months. There was an improvement in their primary outcome, ADAS-cog score and also secondary outcome, CGIC score in the treatment group compared to the placebo group. (Rabey 2012)

In another study, Patients with mild AD received 6 weeks of either daily active or sham treatment. Active treatment combined computerized cognitive training with rTMS. In each session, 3 of 6 different brain regions were stimulated: right or left DLPFC, right or left parietal cortex, Broca's area, or Wernicke's area. Simultaneously, a Cognitive function associated with each brain site was treated. Patients undergoing real treatment improved significantly in ADAS-Cog as compared to sham treatment within the first month after treatment. They were not able to show significant improvement in CGIC as previously reported. (Brem 2014)

The hypothesis of impaired synaptic plasticity in the pathophysiology of dementia suggests a role for rTMS as a neurorehabilitative tool. The rTMS protocols could improve cognitive performance in other types of neurodegenerative diseases such as PPA (Cotelli 2012). A semi-systematic review of 18 studies is recently done in patients with AD(13), DLB (1) and MCI (4). A total of 16 of the 18 studies showed improvements in at least one neuropsychiatric outcome measure. There was also report of neuropsychiatric improvements in 12 of the 14 studies conducted in patients with Parkinson's. (Elder 2014).

Most of these studies induced short-duration benefits or not adequately powered. There was a general trend for improvements across a wide range of cognitive measures following TMS. These results of rTMS studies to enhance cognitive function in AD are promising but preliminary.

Many factors impact effectiveness of this technique, such as frequency or location of stimulation. Combining TMS and cognitive training in placebo controlled studies has shown promising results, based on the findings that rTMS influence learning, with consequent changes to synaptic function. The heterogeneity of these studies and more importantly small size of these studies encourage larger double blind studies in the future.

I believe rTMS has a place for the future studies in the treatment of patients with Alzheimer's dementia.

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