

Repetitive Transcranial Magnetic Stimulation in the Treatment of Alzheimer's Disease

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Key highlights:

- Repetitive transcranial magnetic stimulation (rTMS) alone or with concurrent cognitive training may improve cognitive function in dementia patients with Alzheimer's disease.
- In addition to dorsolateral prefrontal cortex and corresponding cortical regions for cognitive training, precuneus emerges as a promising neuromodulation target for Alzheimer's disease.
- A recent phase II trial found two weeks of intensive high frequency rTMS over precuneus followed by once a week rTMS maintenance treatment can slow down cognitive and functional decline, maintain cortical excitability and enhance local gamma oscillations over a period of 24 weeks in patients with mild to moderate Alzheimer's disease.

Alzheimer's disease (AD) is the most common type of dementia and is characterized by progressive memory and cognitive declination leading to incapacitation. For a long time, cholinesterase inhibitors and NMDA receptor antagonist memantine have been the only approved pharmacological treatments with modest efficacy. The new potentially disease-modifying amyloid- β targeting monoclonal antibodies aducanumab and lecanemab were approved by the US Food and Drug Administration (FDA) via an accelerated approval pathway in 2021 and 2023. Still, more data are needed to evaluate their efficacy and safety carefully. The development of effective non-pharmacological treatments is important.

Noninvasive brain stimulation (NIBS) has become an important biological intervention for mental disorders, especially in treatment-resistant cases. Of the many NIBS techniques, transcranial magnetic stimulation (TMS) is probably the most widely used neuromodulatory method in clinical practice nowadays. A TMS machine works by generating a vital, rapidly changing magnetic field nearby its probe in which time-varying high-intensity electrical currents pass through. As a TMS probe is placed beside the scalp, the magnetic field can penetrate the skull

and induce small local electric currents in superficial layers of the cerebral cortex. In addition to stimulating regional cortical regions acutely through neuronal depolarization, prolonged effects on neuroplasticity can be produced when TMS pulses are given repeatedly (repetitive TMS, rTMS). In general, high-frequency (≥ 5 Hz) rTMS enhances and low-frequency rTMS (≤ 1 Hz) reduces cortical excitability, probably through mechanisms of long-term potentiation and long-term depression, respectively. In addition to the local effects, other interconnected brain regions within the same network can also be modulated (Valero-Cabre, Amengual et al. 2017). Therapeutic effects of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC), low-frequency rTMS over the right DLPFC, and sequential bilateral rTMS on treatment-resistant major depressive disorder have been well established. The US FDA first approved TMS for treating depression in 2008, and since 2018 FDA has approved TMS for the treatment of obsessive-compulsive disorder (OCD) (Cohen, Bikson, Badran, and George, 2022).

Several clinical trials have investigated Therapeutic rTMS in AD in the past decade. A substantial of them applied rTMS over DLPFC, similar to the protocols of rTMS for treating depression, and found rTMS superior to sham stimulation to enhance cognitive function in patients with AD (Chou et al. 2022). Another strategy was to use high-frequency rTMS in conjunction of concurrent cognitive training (rTMS-COG). A meta-analysis of 15 trials involving 240 patients indicated rTMS was more effective than a sham in improving cognition, and subgroup analysis found protocols of multiple stimulation sites or with concurrent cognitive training were more effective (Wang et al. 2020). A phase III randomized, double-blinded, sham-controlled trial comparing neuro^{AD}TM Therapy System (rTMS-COG over six cortical regions, left and right DLPFC, Broca area, Wernicke area, and left and right somatosensory association cortex) with sham stimulation recruited 131 subjects with mild to moderate AD, a fairly large sample size among rTMS trials. This trial found rTMS better than sham in improving cognitive function of patients with better baseline cognitive function (ADAS-Cog ≤ 30), and the improvements were maintained at 12-week follow-up only in rTMS group (Sabbagh et al. 2020).

Exciting results of a phase II, randomized, double-blinded, sham-controlled trial comparing high-frequency rTMS and sham over precuneus were published in 2022 (Koch et al., 2022). Their pilot study demonstrated high frequency over precuneus selectively improved episodic memory in patients with early AD (Koch et al., 2018). The activity of precuneus is known to be involved in episodic memory retrieval and is affected by AD neuropathology. Precuneus is also an important hub of the default mode network which is altered in AD. The

intervention in this phase II study was composed of a 2-week acute treatment phase (daily session, 5 days/week) and a 22-week maintenance phase (once weekly session). In addition to cognition and function assessment, outcome measures included local cortical excitability and oscillatory activity measured by the TMS-evoked potentials (TEP) through online EEG recordings of brain response to single TMS pulses. Patients who received rTMS over precuneus had stable performance of the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) and their cortical excitability didn't change, while performance of CDR-SB worsened and cortical excitability reduced in patients receiving sham stimulation. Comparing with sham group, patients in the rTMS group also performed better in several other cognitive measures and their gamma oscillations were enhanced after 24 weeks.

Although pharmacotherapy remains the main stream of biological treatments for mental disorders, there are still a substantial proportion of patients who respond unsatisfactorily to or cannot tolerate the side effects of psychotropic medications. The success of TMS in treating treatment-resistant MDD and OCD and the rapid development of NIBS techniques have brought hope to patients suffering from other mental disorders, such as AD. Clinicians should provide evidence-based information about the off-label use of TMS. In addition to acute effects, patients also care about maintaining the efficacy and preventing future relapses. When it comes to neurodegenerative diseases such as Alzheimer's disease (AD), the question is how to use TMS to maintain cognitive function and to slow down the degeneration process. Another issue patients usually inquire about is whether objective quantitative methods to monitor brain function change during the rTMS treatment are available since the organ brain is "treated" by the stimulation. The aforementioned trial by Koch et al. demonstrated that the maintenance of weekly rTMS at precuneus can slow down cognitive decline during a 6-month follow-up, and the benefits were corroborated by cortical excitability and oscillations measured by TEP. rTMS can be expected as a viable intervention for Alzheimer's disease.

For further reading:

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