Rewiring the Brain

WILL TRANSCRANIAL MAGNETIC STIMULATION WORK FOR ALZHEIMER'S DISEASE?

Best-selling author Jenny Lawson, also known as "The Bloggess" to her online followers, struggled with a year-long episode of deep depression that medication couldn't budge. She decided to try transcranial magnetic stimulation and had 40-minute treatments on weekdays for seven weeks.

By day seven, she thought they might be working, and after day 20, she was sure they were making a difference. After day 36, Lawson told her husband and daughter she wanted to go on a family vacation.

Transcranial magnetic stimulation (TMS) is a non-invasive treatment that applies pulses of magnetic energy to the brain.

It is an approved and proven effective therapy in Canada and the United States for treating major depressive disorder that does not respond to medications.

For more than a decade, scientists have been exploring the potential of TMS for treating Alzheimer's disease (AD). Research findings to date are encouraging, but more work lies ahead to answer outstanding questions before determining if TMS could be an effective treatment for warding off AD or slowing its progression.

This article provides an overview of how TMS works for depression and the rationale, emerging clinical trial

evidence, and outstanding questions under investigation for its use as a potential treatment for AD.

HOW TMS WORKS FOR DEPRESSION

TMS passes repetitive, focused magnetic pulses through the skull to stimulate electrical activity in targeted brain regions.

CONDITIONS APPROVED FOR TMS VARY BY COUNTRY

HEALTH CANADA APPROVAL:

2002 – major depressive disorder that does not respond to medication

U.S. FDA CLEARANCES:

2008 – major depressive disorder that does not respond to medication
2013 – migraine with aura
2017 – obsessive compulsive disorder
2020 – smoking cessation
2021 – anxiety together with major depressive disorder

Since the original approvals of TMS for major depressive disorder, manufacturers have created a variety of different TMS devices.

EUROPEAN APPROVALS:

The BrainsWay Deep TMS™ device is approved for use in Europe to treat AD, Parkinson's disease, post-stroke rehabilitation, post-traumatic stress disorder, and symptoms of schizophrenia. The device uses an H-coil, which delivers a deeper and broader stimulation pattern compared to the standard figure-8 coil.

ALZHEIMER'S DISEASE APPROVAL HISTORY:

2012 – approved in the European Union and Israel for mild to moderate AD
2017 – approved in Australia for mild to moderate AD
2019 – The U.S. FDA turned down the first request for a TMS application for AD*

*** The U.S. FDA denied clearance for the neuroAD™ Therapy System made by Neuronix, stating that while the device met safety standards, clinical trial results did not demonstrate effectiveness. The device, intended for treating individuals with mild to moderate AD, consists of a chair fitted with a TMS coil and a computer screen to present cognitive training exercises during neurostimulation treatments. The neuroAD™ Therapy System has been approved and in clinical use in the European Union, Australia, and Israel since 2017.**

A hand-held device or helmet containing a magnetic coil is placed on the scalp and delivers the pulses.

A typical treatment course of repetitive TMS (rTMS) involves 20 to 30 sessions delivered once daily on weekdays over four to six weeks at a clinic.

High-frequency pulses of 5 to 20 Hz are directed to the dorsolateral prefrontal cortex (DLPFC), an area of the brain located at the top front of your head, where you might wear a hair band. The DLPFC plays a role in working memory, task planning and switching, goal-driven attention, problem-solving, and novelty seeking.

A single TMS pulse is strong enough to stimulate cells in the target area. Repeated pulses cause changes in connections between neurons – a concept called neuroplasticity.

Lawson told *People Magazine* the pulses felt like an invisible chisel drilling holes into her head while having an ice cream headache. While sensory experiences are personal, most people describe the treatment as feeling like a woodpecker tapping or someone poking their head with a finger. "I've never had a patient living with depression who couldn't tolerate it," said Dr. Mark George, the psychiatrist and neurologist who pioneered rTMS. "They all say it's not pleasant, but they're willing to undergo it to treat their depression."

About 50 to 60% of people with medication-resistant depression experience a clinically meaningful benefit from TMS, and symptoms disappear entirely for about one-third of those individuals, according to a 2020 Harvard Health Blog post authored by Dr. Adam Stern, director of psychiatry at Beth Israel Deaconess Medical Center's Berenson-Allen Center for Noninvasive Brain Stimulation.

"One out of 10 American psychiatrists uses TMS to treat individuals with treatment-resistant depression," said Dr. George, distinguished university professor of psychiatry, radiology, and neuroscience, and Layton McCurdy Endowed Chair in Pyschiatry and director of the Brain Stimulation Laboratory at the Medical University of South Carolina.

> **"IT WORKS FOR A MAJORITY OF PEOPLE WITH DEPRESSION, NO MATTER THE CAUSE OR WHETHER IT'S A FIRST INSTANCE OR RESULTS FROM OTHER CONDITIONS, SUCH AS A STROKE. I LIKE TO SAY WE'VE GOT A NAIL CALLED DEPRESSION AND A HAMMER CALLED TMS. THE TYPE OF NAIL DOESN'T MATTER – TMS WORKS.**

THE RATIONALE FOR USING TMS FOR ALZHEIMER'S

"Progress in treating Alzheimer's with rTMS has not been the same home run we have seen in depression," said Dr. George. "Alzheimer's is a neurodegenerative disease that involves damage to neurons that, at a certain point, can't be restored. With depression, the neurons are not damaged and only need retraining."

Dr. George recalled treating a colleague's wife who struggled throughout her life with recurrent depression and later developed AD. The colleague noticed she was depressed and not looking after herself as well as she had been doing, so he asked Dr. George to treat her with rTMS.

The treatment did not change her underlying AD. However, it lifted her depression enough that she returned to mostly taking care of herself, allowing her to live at home longer until she needed the next level of care.

Up to 40% of individuals living with AD suffer from significant depression, according to the Alzheimer's Association.

"In each square millimetre of the brain, there are millions of neurons, and each neuron is hypothetically connected to others by synapses. Given that the brain has about 80 to 100 billion neurons in total, theoretically there are at least two to the power of 80 to 100 billion synapses, an astronomically high number," explained Dr. Zahra Moussavi, professor in the Department of Electrical and Computer Engineering and Biomedical Engineering Program at the University of Manitoba, and Canada Research Chair in Biomedical Engineering, Tier 1.

"The hope with rTMS as a treatment for Alzheimer's is that it will encourage the generation of new synapses as workarounds for those that are no longer functioning properly."

LATEST EVIDENCE FOR TREATING ALZHEIMER'S

An 82-year-old woman named Brigit was the first participant in a groundbreaking clinical trial of rTMS as a treatment for individuals living with AD. Led by Dr. Moussavi at the University of Manitoba, the trial was the first study of rTMS as a potential treatment for AD in Canada.

Brigit would usually say she was in her 20s and had no children. After seven days of rTMS, she was frustrated with the treatments and said they were uncomfortable. Her husband reminded her she'd agreed to participate in the study because she wanted to remember her three children. She then named two of her children and one grandchild.

Even if it was not entirely correct, Brigit's recaptured memory was a breakthrough. The next day, she returned to saying she was in her 20s and had no children. Still, Dr. Moussavi was encouraged to continue her work in collaboration with colleagues at McGill University, in Montreal, and Monash University, in Australia.

Throughout the five-year trial, more than 150 patients with mild to moderate AD randomly received either rTMS or a sham treatment to the DLPFC. The study results were remarkable and, at the same time, raised additional questions: 68% of participants showed a significant improvement in cognition that lasted more than two months post-treatment – including those who received the sham treatment. These results were published online in the journal *Neurotherapeutics* in February 2024.

On further investigation, Dr. Moussavi and colleagues discovered that while the sham coil they used produced sensations and sounds identical to the actual coil, it still induced a low current in the brain.

"Another group confirmed this brand of sham coil produced up to 25% of the magnetic field intensity of a real coil," said Dr. Moussavi. "While we can't say rTMS made a difference compared to the sham treatment in our study, our results still demonstrated rTMS is worth investigating further as a potential treatment for Alzheimer's."

One of the outstanding questions about applying rTMS to AD has been determining the best area of the brain to target.

Researchers in Italy recently reported the first results for applying rTMS to the precuneus, an area at the top back part of the brain.

The precuneus is a vital node of the default mode network, an essential network that plays a role in the brain's resting state and abstract thoughts, such as reminiscing and future planning. It is also the earliest brain region affected by amyloid deposition, gray matter loss, and disconnection between essential regions and brain networks in AD development.

The study included 50 study participants, with an average age of 74, and 52% were women. They randomly received rTMS or a sham treatment to the precuneus for five days per week for two weeks, followed by 22 weeks of once-weekly maintenance treatments.

At the end of the study, the rTMS group showed stable cognitive and functional performance according to various standard assessments, but those in the sham group continued to decline.

Patients in the rTMS group also showed increased activity in gamma brain waves, which play a role in working memory, whereas the sham group did not. The study results were published in *Brain* in November 2022 and presented at the Clinical Trials on Alzheimer's Disease (CTAD) conference in Boston in October 2023.

"Stabilizing cognitive decline is a promising finding from this study, one of the largest to date in patients with Alzheimer's," said Dr. Moussavi.

"MORE RESEARCH, HOWEVER, IS NEEDED TO DETERMINE WHETHER THIS TREATMENT APPROACH IS THE BEST STRATEGY FOR AD.

In another study presented at the CTAD 2023 conference, researchers from Korea reported results from their trial where they applied rTMS to the parietal lobe in a small number of individuals with early AD and evidence of amyloid deposits.

THE PARIETAL LOBE SITS ABOVE THE HIPPOCAMPUS, WHICH PLAYS A MAJOR ROLE IN LEARNING AND MEMORY AND IS ANOTHER AREA AFFECTED IN EARLY AD DEVELOPMENT.

After 20 sessions over eight weeks, the rTMS group of 18 patients showed higher cognitive and functional performance scores than the sham group of 12 patients. Brain imaging revealed increased working connections between the hippocampus and precuneus in the actual treatment group, which aligned with improved cognitive scores.

WHAT'S NEXT

Dr. Moussavi and Dr. George both agree many questions remain for applying rTMS as a treatment for AD, including the optimal brain area to target, the frequency and the total number of pulses used, the duration of treatment and whether maintenance sessions are required, and if it will be most helpful in people with mild cognitive impairment (MCI) or those who have been diagnosed with mild to moderate AD.

At the same time, manufacturers continue to develop newer types of TMS.

AT THE MEDICAL UNIVERSITY OF SOUTH CAROLINA, DR. GEORGE AND COLLEAGUES ARE NOW CONDUCTING A CLINICAL TRIAL TO DETERMINE THE OPTIMAL DOSE OF AN ACCELERATED FORM OF TMS, CALLED INTERMITTENT THETA BURST TMS, FOR PATIENTS WITH MCI.

Individuals with MCI are more likely to develop AD or other forms of dementia than people without MCI. Depression is also common among people living with MCI. The FDA recently approved intermittent theta burst TMS as a once-daily treatment for depression, so the effects of treatment are known.

In this innovative study, participants with MCI choose six treatment days within a two-week period. On each treatment day, they receive multiple treatments in sessions lasting about 2 1/2 hours. Pulses are administered in three-minute periods. Study participants randomly receive active or no stimulation in each session.

"THETA BURST STIMULATION IS MORE EFFICIENT AND MORE SIMILAR TO HOW THE BRAIN TALKS TO ITSELF, SO WE CAN USE FEWER, QUICKER PULSES THAN STANDARD RTMS.

"A shorter course of therapy would certainly be more convenient for patients." If this study can answer essential questions about the optimal dose for theta burst TMS in individuals with MCI, Dr. George and colleagues plan to conduct a larger, multisite trial to confirm their findings.

Dr. Moussavi is also designing more studies to find answers to outstanding questions about whether rTMS might help people with AD. For example, she has been investigating using a new diagnostic and monitoring technology called electrovestibulography (EVestG) to predict which patients will most likely respond to treatment.

EVestG measures electrical signal activity in the external ear canal. Clinicians are already using it to measure the severity of persistent post-concussion syndrome and major depressive disorder.

So far, the preliminary results have been encouraging: EVestG predicted which patients responded positively to rTMS with a high degree of accuracy. "I'm keen to add EVestG to future studies to ensure we are treating the patients most likely to benefit," Dr. Moussavi said.

Dr. Moussavi's mother's experience with AD continues to inspire her research. After establishing her lab in 2009 and securing research funding in 2013, Dr. Moussavi visited her mother in Iran. "I told her, 'Mom, I did it all for you.' She was not verbal at the time," Dr. Moussavi said. "She kissed me and smiled, and one week later, she passed away. Now, I hope that my work will be able to help others."

Are you interested in learning about clinical studies of TMS for AD? Search clinicaltrials.gov for studies in your area and discuss with your healthcare provider.