Deep Transcranial Magnetic Stimulation

A Food and Drug Administration (FDA)–approved, noninvasive, medication-free treatment option for major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and smoking cessation.

In this unique technology transfer transaction, the National Institutes of Health (NIH) Office of Technology Transfer (OTT) licensed Deep Transcranial Magnetic Stimulation (Deep TMS), an NIH-developed technology, to a company co-founded by one of the inventors, and helped facilitate continued collaboration between the licensee and NIH to establish efficacy of the device in humans.

Context/Background

An estimated 21 million American adults had at least one major depressive episode in 2020,[1] making it the leading cause of disability worldwide.[2] Depression and other mental health conditions are typically treated with antidepressants. Although antidepressants are efficacious for treating moderate through severe depression, [3] they have been reported to have a range of undesirable side effects ranging from weight gain to suicidality. For patients who are unsuccessfully treated with antidepressants, some receive electroconvulsive therapy (ECT), which can improve depression in 70%–90% of patients.[4] Despite the high success rate, ECT is an invasive treatment involving general anesthesia and can cause many side effects, including nausea, headaches, and even memory problems.[5] Alternatively, TMS is a non-invasive method of brain stimulation that relies on electromagnetic induction using an insulated coil placed over the scalp.

Repetitive TMS (rTMS) relies on a figure-8 coil design that induces supra-threshold fields at a depth of 0.27" (0.7cm).[6] Deep TMS (dTMS) uses the "H-coil," a novel rTMS tool invented by a team of NIH researchers, which enables stimulation of deeper neuronal structures and simultaneous stimulation of several brain regions "without a significant increase in the electric field induced in superficial cortical layers." [7,8] The H-coil induces supra-threshold fields at a depth of 0.7" (1.8 cm).[9] The H-coil was exclusively licensed by BrainsWay and then was FDA cleared to treat not only MDD, but also OCD, smoking addiction, and anxious depression.

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[1] National Institute of Mental Health. "Major Depression." (January 2022). https://www.nimh.nih.gov/health/statistics/major-depression

[2] World Health Organization. "Depression." (September 2021). https://www.who.int/news-room/fact-sheets/detail/depression

[3] InformedHealth.org. "Depression: How effective are antidepressants?" Cologne, Germany: Institute for Quality and Efficiency in Health Care. (June 2020). https://www.ncbi.nlm.nih.gov/books/NBK361016/

[4] Johns Hopkins Medicine. "Brain Stimulation Services". (n.d.). https://www.hopkinsmedicine.org/psychiatry/specialty_areas/brain_stimulation/services.html

[5] Johns Hopkins Medicine. "Brain Stimulation Services". (n.d.). https://www.hopkinsmedicine.org/psychiatry/specialty_areas/brain_stimulation/services.html

[6] Ginou, A., Roth, Y., & Zangen, A. "Comparison of Superficial TMS and Deep TMS for Major Depression." *Brain Stimulation*, *7*(5), e19. https://doi.org/10.1016/j.brs.2014.07.008

[7] Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. "Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils". *Journal of Clinical Neurophysiology*, *24*(1), 31–38 (2007). https://doi.org/10.1097/WNP.0b013e31802fa393

[8] Levkovitz, Y., et al. "Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Major Depression: A Prospective Multicenter Randomized Controlled Trial". *World Psychiatry*, 14: 64-73 (2015). https://doi.org/10.1002/wps.20199

[9] Ginou, A., Roth, Y., & Zangen, A. "Comparison of Superficial TMS and Deep TMS for Major Depression." *Brain Stimulation*, *7*(5), e19. https://doi.org/10.1016/j.brs.2014.07.008

The Discovery of the Technology (inventor story)

Dr. Abraham "Boomy" Zangen joined the NIH National Institute on Drug Abuse (NIDA) in 1999 as part of his postdoctoral fellowship. While at NIDA, his research focused on treating drug abuse via electrostimulation on animals. Dr. Zangen wanted to translate his work on animals to humans, so he connected with TMS pioneer, Dr. Mark Hallett, at the National Institute of Neurological Disorders and Stroke (NINDS). During this time, rTMS over the prefrontal cortex had been shown to be effective as a treatment for MDD.[10] Because a standard figure-8 coil could only stimulate cortical regions (regions close to the scalp), research on the efficacy of TMS during this time focused on its effect on superficial regions of the prefrontal cortex. Combining his background in physics and biology, Dr. Zangen hypothesized that a new coil design could penetrate deeper, reaching the nucleus accumbens, the area of the brain associated with reward and motivation.[11] For the early prototype of a new coil, Dr. Zangen reached out to his physicist brother-in-law, Dr. Yiftach Roth, to help him refine the concept. Dr. Zangen and Dr. Roth, in collaboration with Dr. Hallett and NINDS visiting scholar Pedro Miranda, worked to design a new coil. They developed a coil that stimulates deep brain regions, including the nucleus accumbens and the nerve fibers connecting the prefrontal cortex with the nucleus accumbens, because this region plays a key role in mediating dopamine (motivation and reward) and dependent depressive behavior.[12] Over several years, the team developed a first-of-its-kind nonstandard TMS coil design termed the H-coil. The novel H-coil could induce neuronal activation in deeper areas of the brain without increasing stimulation intensity to unsafe or painful levels.[13]

Role of OTT (tech transfer story)

In June 2000, NIDA submitted an invention report to OTT for the coil. Recognizing the potential and uniqueness of the H-coil design, OTT filed a patent application to protect the intellectual property covering the invention. In October 2000, NIH filed U.S. Provisional Patent Application 60/242,297, titled "Coil for Magnetic Stimulation." This technology could induce neuronal activation in deeper areas of the brain without increasing stimulation intensity to unsafe or painful levels. This was later proven by Dr. Zangen, Dr. Roth, and Dr. Hallet's 2002 seminal study using mathematical simulations and measurements in a realistic phantom brain model.[14]

At the conclusion of his postdoctoral fellowship, Dr. Zangen joined the Weizmann Institute of Science in Israel, a world-renowned science institution founded in 1934, and established a laboratory there in 2003. Shortly thereafter, Uzi Sofer, a well-known entrepreneur, contacted Dr. Zangen after seeing the technology advertised by NIH. Mr. Sofer wanted to start a company focused on advancing brain health. The two of them, along with Dr. Roth, founded BrainsWay, developed a plan for commercial development, and attracted investors. Later the same year, BrainsWay applied for an exclusive license from NIH to the patent estate covering the H-coil invention. When an exclusive license is requested, NIH OTT must determine whether licensing the technology to a sole entity will serve the best interest of the public. NIH OTT personnel had to assess BrainWay's commercial development plan and determine whether they made a cogent case to predicate the granting of an exclusive license. After making this

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[10] Overstreet, D H. "The Flinders Sensitive Line Rats: A Genetic Animal Model of Depression." *Neuroscience and Biobehavioral Reviews* vol. 17,1 (1993): 51-68. https://doi.org/10.1016/s0149-7634(05)80230-1

[11] Zangen, A., Nakash, R., Overstreet, D.H. *et al.* "Association Between Depressive Behavior and Absence of Serotonin–Dopamine Interaction in the Nucleus Accumbens". *Psychopharmacology* **155**, 434–439 (2001). https://doi.org/10.1007/s002130100746

[12] Zangen, A., Nakash, R., Overstreet, D.H. *et al.* "Association Between Depressive Behavior and Absence of Serotonin–Dopamine Interaction in the Nucleus Accumbens". *Psychopharmacology* **155**, 434–439 (2001). https://doi.org/10.1007/s002130100746

[13] Roth, Y., Zangen, A., & Hallett, M. "A Coil Design for Transcranial Magnetic Stimulation of Deep Brain Regions". *Journal of linical neurophysiology*, *19*(4), 361–370 (2002). https://doi.org/10.1097/00004691-200208000-00008

[14] Roth, Y., Zangen, A., & Hallett, M. "A Coil Design for Transcranial Magnetic Stimulation of Deep Brain Regions". *Journal of clinical neurophysiology*, *19*(4), 361–370 (2002). https://doi.org/10.1097/00004691-200208000-00008

assessment, NIH OTT invited objections by publishing notice in the Federal Register indicating a prospective grant of an exclusive license. With no objections, NIH OTT crafted and negotiated the license agreement with BrainsWay, allowing them an exclusive license that opened the door to future commercialization of the technology.

Even after Dr. Zangen left NIH, the continued collaboration between him and Dr. Hallett at NIH supported further development of Deep TMS. Following the finalization of the licensing deal, Dr. Zangen flew back to the United States to work with Dr. Hallett in his lab to conduct the first study using the H-coil on humans. OTT facilitated access to the technology for Dr. Hallett's lab to perform the study. This study ultimately demonstrated that the H-coil had significantly improved depth penetration and a slower rate of decay of the electric field with distance, as compared to the standard figure-8 coil,[15] enabling BrainsWay to move forward with clinical trials.

With clinical evidence demonstrating the effectiveness of the Deep TMS coil, BrainsWay began their clinical trials at Tel Aviv University's Shalvata Mental-Health Center in 2005. Results of the clinical trials found that H-coils were well tolerated with few physical or neurological adverse events, and that participants both with and without depression showed improvement of behavioral patterns and mood associated with depression. BrainsWay went on to gain regulatory approval in Europe in 2009 for treatment of depression. Subsequently, they received their first FDA clearance in 2013 for the treatment of patients with MDD who fail to respond to medication.[16]

In this unique technology transfer transaction, OTT licensed an NIH-developed technology to one of the inventors and helped facilitate continued collaboration between the licensee and NIH to establish efficacy of the device in humans. These transactions paved the way for BrainsWay to market a device that received FDA clearance for several indications.

Role of Licensee (commercialization story)

BrainsWay developed several variations of the H-coil using the technology licensed from NIH. The different coils use the same underlying technology but have varied shapes and target different regions of the brain.

- **The H1-coil** is designated for activation of deep neuronal targets in lateral and medial prefrontal regions[17] and was FDA cleared in 2013 for the treatment of patients with MDD who fail to respond to medication.
- **The H7-coil** is designed to target the medial prefrontal cortex and the anterior cingulate cortex.[18] It was FDA cleared in 2018 for the treatment of patients with OCD who have not responded to traditional treatments; in 2022, the H7 was FDA cleared for its use in treating adults with MDD and depression, including those with comorbid anxiety symptoms commonly known as anxious depression.

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[15] Zangen, A., Roth, Y., Voller, B., & Hallett, M. "Transcranial Magnetic Stimulation of Deep Brain Regions: Evidence for Efficacy of the H-coil". *Clinical neurophysiology*, *116*(4), 775–779 (2005). https://doi.org/10.1016/j.clinph.2004.11.008

[16] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=k122288

[17] Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. "Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils". *Journal of Clinical Neurophysiology*, *24*(1), 31–38 (2007). https://doi.org/10.1097/WNP.0b013e31802fa393

[18] Harmelech, Tal et al. "Deep TMS H7 Coil: Features, Applications & Future." *Expert review of medical devices* vol. 18,12 (2021): 1133-1144. doi:10.1080/17434440.2021.2013803

- **The H4-coil** targets cortical and subcortical structures involved in food craving–related disorders[19] and was FDA cleared in 2020 as an aid in short-term smoking cessation for adults.

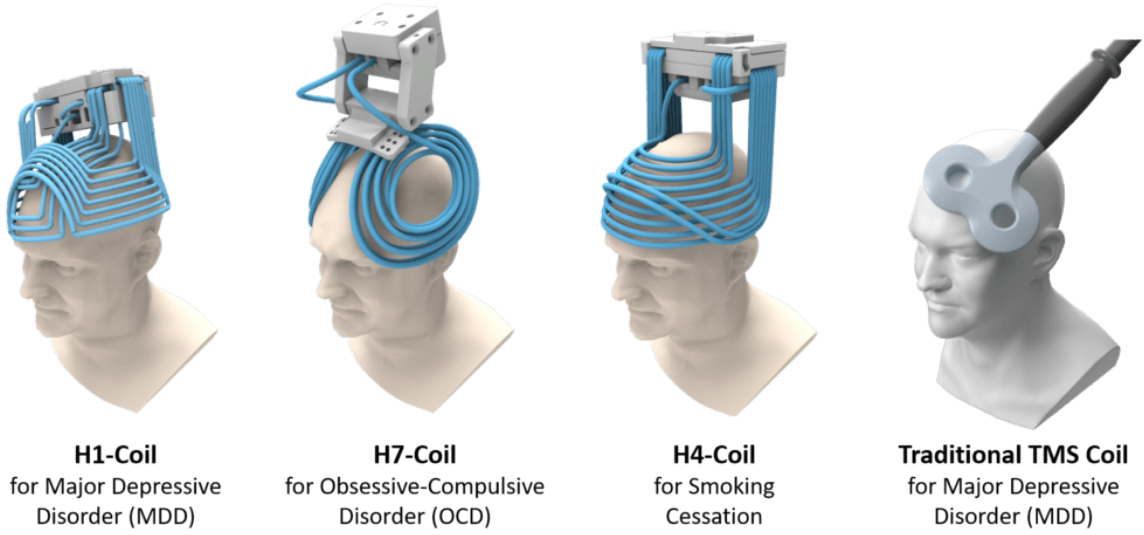

Image Source: https://brainsway.co.il/how-does-it-work/rtms-vs-deep-tms/

Impact

The invention of the H-coil by NIH scientists enabled the development of an FDA-cleared device that has demonstrated significant clinical success. An independent study published in 2019 found that a treatment regimen of Deep TMS combined with standard pharmacotherapy was significantly more effective than standard pharmacotherapy alone at reducing depression levels among patients with MDD.[20]

Although traditional rTMS has been around for decades, it is only FDA cleared to treat MDD. The development of the H-coil has catalyzed the use of Deep TMS for treating various mental health disorders. Deep TMS is FDA cleared to treat MDD, OCD, and smoking cessation. Deep TMS has also received the European Union's Conformitè Europëenne (CE) certification mark for its treatment of several additional mental health and neurological conditions, confirming that Deep TMS meets the European health, safety, and environmental protection standards. As a result, Deep TMS has received CE market certification to treat MDD, OCD, Alzheimer's disease, autism, bipolar disorder, chronic pain, multiple sclerosis, Parkinson's disease, post-stroke rehabilitation, posttraumatic stress disorder, negative symptoms of schizophrenia, and smoking cessation. BrainsWay continues to work to expand Deep TMS' FDA clearance status to treat other mental health conditions.

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[19] S. Fiocchi *et al*., "Deep Transcranial Magnetic Stimulation for the Addiction Treatment: Electric Field Distribution Modeling," in *IEEE Journal of Electromagnetics, RF and Microwaves in Medicine and Biology*, vol. 2, no. 4, pp. 242-248, (Dec. 2018). https://doi.org/10.1109/JERM.2018.2874528

[20] Filipčić, Igor et al. "Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-Coil in treatment of major depressive disorder; A randomized clinical trial." *Journal of psychiatric research* vol. 114 (2019): 113-119. https://doi.org10.1016/j.jpsychires.2019.04.020

TMS Timeline

From Invention to Commercialization

Invention

Technology transfer

Commercialization

1999 — Dr. Zangen, Dr. Roth, Dr. Hallett, and Dr. Miranda collaborate to develop a new coil that can be used to stimulate deep brain regions without increasing stimulation intensity to unsafe or painful levels.

2000 — NIDA submits an invention report to OTT for the coil.

2001 — OTT files a provisional patent application titled "Coil for Magnetic Stimulation."

2002 — Dr. Zangen, Dr. Roth, and Dr. Hallet's publish a seminal study that showed that the coil could induce neuronal activation in deeper areas of the brain without increasing stimulation intensity to unsafe or painful levels using mathematical simulations and measurements in a realistic phantom brain model.

2003 — Dr. Zangen, Dr. Roth, and Uzi Sofer founded BrainsWay.

2004 — BrainsWay signs an exclusive license from NIH for the technology.

OTT facilitated the acquisition of the licensed technology back from BrainsWay so that Dr. Zangen and Dr. Hallet could collaborate on the first study using the H-coil on humans, which took place in Dr. Hallett's lab at NIH.

2005 — The study is published and demonstrates the H-coil significantly better depth penetration and a slower rate of decay of the electric field with distance than the standard figure-8 coil.

BrainsWay begins clinical trials at Shalvata Mental Health Center.

2007 — Results from the first clinical trial are published, showing that H-coils were well tolerated with no adverse physical or neurological outcomes, and that participants both with and without depression showed improvements of behavioral patterns and mood associated with depression.

2009 — BrainsWay Deep TMS receives European regulatory approval for treatment of depression.

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011

PRE-FDA CLEARANCE TIMELINE

2013 — BrainsWay Deep TMS H1 coil receives FDA clearance to treat patients with major depressive disorder who fail to respond to medication.

2018 — BrainsWay Deep TMS H7 coil receives FDA 510(k) Clearance for Use of its device for patients with obsessive-compulsive disorder who have not responded to traditional treatments.

2020 — BrainsWay Deep TMS H4 coil receives FDA clearance as an aid in short-term smoking cessation for adults.

2022 — BrainsWay Deep TMS H7 coil receives FDA 510(k) clearance for the H7 coil for its use in treating adults suffering from major depressive disorder and depression, including those with comorbid anxiety symptoms commonly known as anxious depression.

2013 2014 2015 2016 2017 2018 2019 2020 2021 2022

FDA CLEARANCE TIMELINE