Video Article

Treating Clinical Depression with Repetitive Deep Transcranial Magnetic Stimulation Using the Brainsway H1-coil

David Feifel[1], Katherine Pappas[1]

[1]Department of Psychiatry, University of California, San Diego

Correspondence to: David Feifel at dfeifel@mail.ucsd.edu

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is an emerging non-pharmacological approach to treating many brain-based disorders. rTMS uses electromagnetic coils to stimulate areas of the brain non-invasively. Deep transcranial magnetic stimulation (dTMS) with the Brainsway H1-coil system specifically is a type of rTMS indicated for treating patients with major depressive disorder (MDD) who are resistant to medication. The unique H1-coil design of this device is able to stimulate neuronal pathways that lie deeper in the targeted brain areas than those reached by conventional rTMS coils. dTMS is considered to be low-risk and well tolerated, making it a viable treatment option for people who have not responded to medication or psychotherapy trials for their depression.

Randomized, sham-control studies have demonstrated that dTMS produces significantly greater improvement in depressive symptoms than sham dTMS treatment in patients with major depression that has not responded to antidepressant medication. In this paper, we will review the methodology for treating major depression with dTMS using an H1-coil.

Video Link

The video component of this article can be found at https://www.jove.com/video/53858/

Introduction

Major depressive disorder (MDD) is a prevalent and debilitating condition that is marked by significant levels of morbidity and mortality[1,2]. Antidepressant medication and psychotherapy are considered the first line of treatment for MDD; however a large portion of patients diagnosed with MDD do not respond to serial trials of medication or therapy, and are classified as having treatment resistant depression (TRD)[3,4]. Electroconvulsive therapy (ECT) is the traditional intervention for TRD patients, but many TRD patients reluctant to undergo ECT due to a significant side effect burden, including occasional long-term cognitive deficits, as well as the necessity for anesthesia administration for every ECT treatment visit, which carries the additional difficulty of the patient obtaining transportation to and from every ECT treatment. Alternatively, TMS is non-invasive and does not require anesthesia, making it a valuable alternative to ECT for many TRD patients.

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a novel alternative approach to treating TRD, as well as a number of other psychiatric and neurological disorders. rTMS utilizes devices containing electro-magnetic coils that create magnetic pulses in close proximity to a patient's skull. The magnetic pulses travel unimpeded through the scalp and skull and activate neurons. Pulses delivered with a high frequency rate (*e.g.,* 10-20 Hz) are thought to increase neural excitability and produce long-term potentiation (LTP), a state of persistent increased firing rates, in neuronal circuits activated by the pulses; whereas pulses delivered with a low frequency (*e.g.*, <5 Hz) are thought to reduce neural excitability, producing long term depression (LTD), or reduced firing rates[5]. Thus, by selectively targeting certain brain regions, rTMS can increase or decrease baseline activity in that area. High frequency rTMS aimed at the left dorsolateral prefrontal cortex (DLPFC), an area associated with reduced activity in MDD, has been successfully used to improve symptoms of MDD[6].

Conventional rTMS devices target specific brain regions by positioning a figure-8 electro-magnetic coil next to the skull directly over the targeted brain area. This approach typically can safely deliver a magnetic field to a maximal depth of approximately 2 cm below the cortical surface. This produces direct activation of a limited volume of the targeted brain region. Recently a device with a novel coil design, the H-coil, was cleared by the FDA for treating TRD. The H-coil employs a unique coil configuration, which is designed to directly activate brain tissue to greater depths than conventional coils such as the figure-of-eight design[7,8,9]. As a result, treatment using the H-coil is referred to as "deep" TMS (dTMS) to distinguish it from conventional surface rTMS approaches. However, among the research into the depth that the H-coil penetrates relative to the conventional figure-of-eight coil, there have been controversial findings. One such study published in 2009 by Fadini and colleagues reports that there was no significant difference between the two coils with regards to penetration depth[10] (for further discussion, please see also references[11,12]).

In 2015, Levkovitz and colleagues published a double-blind, multicenter, randomized, sham-controlled trial to investigate the safety and efficacy of dTMS using H1-coil (designed to target the left prefrontal cortex) for treatment of MDD[13]. Patients with MDD who had failed one to four adequate trials of antidepressant medication, or failed to tolerate two antidepressant treatments in the current depressive episode, were

randomized to either: receive 20 daily dTMS (M-F) treatments over four weeks, followed by biweekly treatments up until twelve weeks; or to receive an inactive sham treatment of otherwise identical treatment parameters. 181 participants were included in the final analysis.

Significantly more patients receiving active dTMS as opposed to inactive sham dTMS treatment experienced a remission of their depression (Hamilton Depression Rating Scale score <10; p = 0.0051). This result indicates that the technique used in that study, which is the same that we describe below, was effective at targeting circuits underlying depression. In this paper, we will review the treatment methodology for dTMS using the H1-coil, which is only to be performed by a trained licensed medical professional.

Protocol

The protocol presented here follows the guidelines of our institution's human research ethics committee.

Note: The operator who is administering treatment should always wear earplugs.

1. Preparation before the Initial Visit

1. Have the patient complete a TMS safety questionnaire[14] to ensure he or she is appropriate for treatment.
2. Review the patient's medical history to be aware of any relevant information, including notes to file.
3. Have a consultation with the patient, where they can ask all questions they may have about the treatment, and sign an Informed Consent document in preparation for the procedure.
4. Prepare the materials needed for the patient's personal cap: cap, chin strap, one red and one black measuring tape.

2. Preparing the Patient upon Arrival

1. Have the patient sit in the chair positioned in front of the TMS machine's cart, ensuring the patient is at an appropriate angle for the coil to be positioned comfortably on their head.
2. Have the patient remove any eye glasses, hair clips or pins, as well as any earrings.
3. Give the patient earplugs, and ensure they are properly and stably positioned.
4. Position the TMS machine's arm at 45° relative to the cart holding the stimulator.

3. Placement of the Personal Cap

1. Slide the cap onto the patient's head, with the front over their forehead just above the eyebrows. The cap's red-stitched midline should be along the midline of the patient's head.
2. Pull the cap's ear covers down stretching the cap firmly around their head and attach the chin strap from one ear cover to the other.
3. Pull the cap down snugly onto their head and stretch the back peripheral straps up and across the back of their head, fastening the straps onto the back of the cap.
4. Attach the black, anterior-posterior, flexible ruler along the midline of the cap, with the cap's red midline positioned directly to the left of the ruler. Position the "0" point on the ruler at the patient's nasion, which is the junction of their nasal bone to forehead.
5. Locate the patient's inion (the most prominent projection at the lower rear part of the head), and record the location on the black midline ruler.
6. Calculate 40% of the distance between the nasion and the inion and place the red, lateral-medial, flexible ruler so that its 25 cm mark lines up with this location on the black midline ruler (the two rulers are now perpendicular).

4. Finding the Individual's Motor Threshold (MT)

1. For the entire MT procedure, line up the "0" point on the lateral ruler of the helmet at the cap's midline.
2. Position the front end of the helmet coil cover at 7 cm on the black midline ruler. Adjust the helmet so entire front edge of the helmet is level and perpendicular to the midline ruler on the cap. Record the location at which the helmet coil cover meets the red, lateral-medial ruler on the left side of the patient's head.
3. Shift the coil cover on left side of the helmet two cm medially along the red lateral-medial ruler. Ensure the coil cover at the front of the helmet still meets the black midline ruler at 7 cm, and the "0" mark on the helmet remains positioned at the cap's midline. This will position the maximal magnetic output of the coil approximately over the upper left motor cortex region associated with contralateral hand control.
4. Turn on the stimulator and press "Single Pulse (MEP)" then set the "Stimulator Output" to 50%. Arm the machine by pressing the green button.
5. Position the patient with the right hand resting over a pillow on their lap, palm facing up, so that any finger movement is more easily seen.
6. Location of the motor cortex:
    1. Begin at the location found in Step 4.3. Stand to the left of the patient. Press down on the helmet with one hand while supporting the patient's neck with the other, and apply a single pulse by depressing the stimulus foot-pedal.
    2. Rate any involuntary finger movement on the patient's right hand from 0-5, with 0 being no movement detected, and 5 being a very vigorous involuntary movement (**Table 1**).
    3. Wait five seconds, then perform this again at the same location. If there is no motor response after 5 single pulses, increase the stimulator output by increments of 5%.
7. Repeat Step 4.6 at several more locations in a grid pattern, first finding the most consistently active location along the midline, and then while staying at that midline location, move one centimeter at a time along the lateral-medial ruler to again find the most consistently active location. Manually document this process using a pen and paper (or digitally on a tablet device) to find the location that has the most consistently robust motor response.

8. Minimum motor threshold:
   1. Using the location found in Step 4.7, and the intensity found in Step 4.6, administer up to 6 single pulses and count the number of elicited involuntary finger motor responses.
   2. Adjust the stimulus intensity up or down by 1-2% until the number of elicited motor responses from the 6 single pulses is no less than 2 and no more than 3. This intensity is the motor threshold (MT) for activating the patient's motor neurons. Document the motor threshold minimum found by this process.

5. Treatment

1. Position the coil to deliver the maximal magnetic output over left lateral prefrontal cortex (PFC), the targeted treatment region, by moving the front edge of the helmet down 6 cm on the midline ruler, or the level of the patient's eyebrow, whichever is higher (*i.e.,* do not position the front of helmet below the patient's eyebrow).
2. After positioning the coil at the treatment location, secure the helmet coil cover to the patient's head by pulling down on the pad at the back of the helmet, tightening the knob and adjustment cords, and fastening the helmet's chin strap.
3. Turn on the cooling system and wait for the temperature gauge to read below 14 °C before starting treatment.
4. Press the "Single Pulse" button on the stimulator touchscreen to return to Single Pulse mode.
5. Set the "Stimulator Output" to the patient's established MT, which was determined in step 4.8. Set the "%MT" to 100%, which refers to 100% of the patient's established MT.
6. Press "Repetitive Mode" on the stimulator touchscreen and enter the following treatment parameters: Frequency of 18 Hz (18 pulses per sec); duration of 2.0 sec; wait time of 20 sec; 55 trains. The number of pulses (36) will auto-populate based on the duration and frequency, and "power" will auto-populate based on the values entered for the Stimulator Output and %MT on the previous screen. Press "Run Session."
7. Arm the machine by pressing the green button.
8. Describe to the patient what they will experience (*i.e.,* 2-sec trains of 36 pulses, separated by 20 sec stimulus-free intervals), and verify that they are ready to begin treatment.
9. Count down loudly and clearly "3-2-1," using fingers in front of the patient so that they are ready for the first train. Press the yellow start button on the panel to administer the first train at the end of the countdown.
10. Observe patient's face and limbs, then after the first pulse ask how it felt. If the patient experiences anything more than mild discomfort or mild facial contractions, then the treatment may be stopped by pressing the red button on the panel, and the location may be adjusted (up to 2 cm in any direction) to eliminate discomfort and contractions.
11. Begin the first treatment session by administering at 100% power relative to the patient's MT response value (found in step 4.8). In the second treatment session, titrate the patient up to 110%, and the full 120% in the third treatment session. If any increase in power produces significant discomfort, return to the previous power setting and allow the patient to further acclimate to the sensation at the lower power before attempting to increase power again.
12. During the treatment session, continue to monitor the patient for any signs of facial contractions, limb movement, or inadvertent repositioning of the helmet.
13. Once the treatment is completed: remove the coil, remove the patient's personal cap, and assist them out of the treatment chair if necessary.

Representative Results

dTMS represents an important non-pharmacological treatment modality with established efficacy for clinical depression that has not responded to antidepressant medication trials, and it also shows promise for treating many other neuropsychiatric disorders. Technical advances that allow improvements in the targeting of perturbed circuits in the brain represent an important means by which dTMS therapy will progress as a treatment. The H1-coil is a novel design that was developed to activate tissue in the targeted brain areas that lie deeper than the depth safely activated by conventional TMS coils.

The efficacy and safety of dTMS has not been directly compared to conventional TMS coils in a head-to-head study; however, comparable research has been performed between the two systems. Research that is representative of the efficacy demonstrated in a pivotal multicenter study of the first conventional rTMS device (which uses the figure-of-eight coil) was relegated to subjects who failed a single antidepressant[15]; whereas the pivotal study performed for dTMS demonstrated efficacy for patients with 1-4 failed medication trials[13].

At the target treatment stimulation strength described above (120% of the established hand MT), the H1-coil produces an electrical field distribution that penetrates deeper into the targeted brain area than that of a traditional surface figure-of-eight coil. The electrical field distribution maps in **Figure 1** were created using a phantom brain model and measuring the electrical field strength at various points in the phantom head. This was done using coils placed at a treatment position relative to the phantom head, and at a treatment intensity of 120% of the hand MT. The electric field above the neural activation level extended 1.5 cm below the brain surface for the figure-8 coil and 4.5 cm below the brain surface for the H1-coil[15].

The time it takes from beginning daily dTMS treatment to when a patient experiences a significant clinical improvement in their symptoms varies across patients; some people begin to show an early response to treatment, with depression rating scale scores dropping after approximately three to four weeks of daily treatment. That being said, it is common for true full remission of depressive symptoms to not occur until after about five weeks of daily treatments. For this reason, a typical course of dTMS treatment involves six weeks of daily treatments prior to beginning the taper period, which maximizes and prolongs the response to treatment.

Presented here is data from two recent patients who were treated using the above dTMS protocol, and both experienced remission of their severe treatment resistant major depression, as measured by the Beck Depression Inventory II (BDI-II). On the BDI-II, full remission is considered to be a score of 10 or lower, and the maximum score one can obtain on the BDI-II is 63. Because different patients respond to the treatment at different time points, it is important to continue treatment through the full 30 daily sessions, as some people do not respond until near the end; early termination of treatment may write off dTMS as ineffective for a patient who may have still had a positive response, if given a full course of treatment. This is particularly detrimental due to this patient population having already tried several treatment modalities unsuccessfully, leading to the categorization of being "treatment resistant."

Patient D first experienced a decrease in depressive symptoms during the fifth week of treatment, which was pushed into a full and sustained remission during the sixth week of treatment, which sustained through the one month post-treatment follow-up (**Figure 2**). Patient S first showed a decrease in symptoms during the end of the second week of treatment, but did not reach a full and sustained remission of symptoms until the end of week 4 — which sustained through the three-month post-treatment follow-up (**Figure 3**). It is common for patients (like S, depicted in **Figure 3**) to experience an initial dip in their symptoms, which may be due to an increase in hopefulness, or even placebo effect; typically, this effect will dissipate, leading to an increase in their depressive symptoms (or a return to their baseline symptoms), and true sustained remission of the patient's depressive symptoms will present further on in the course of treatment.
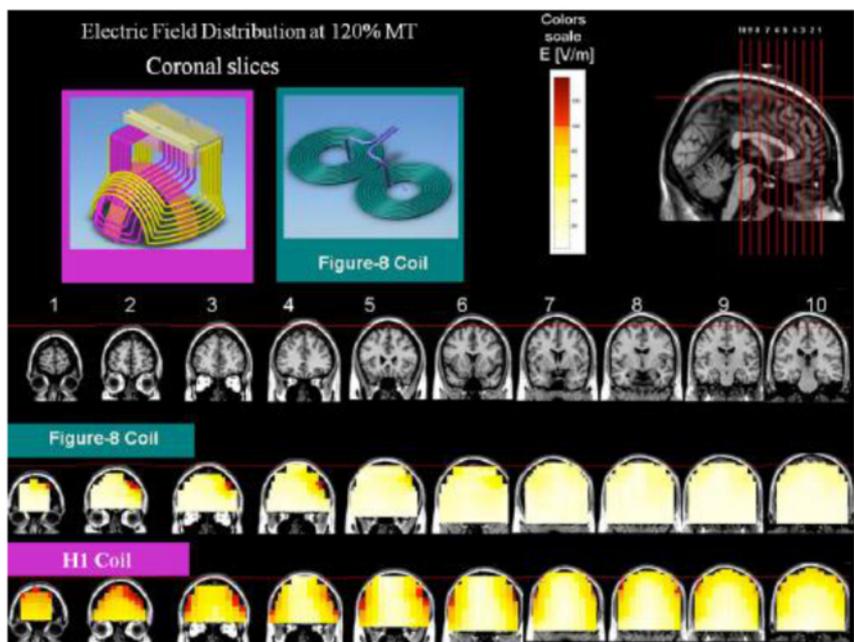

Figure 1: Electrical field distribution of figure-8 and H1-coil. Colored field maps for the H1-coil and for the figure-8 coil, indicating the electric field absolute magnitude in each pixel over 10 coronal slices 1 cm apart. The red pixels indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output level required to obtain 120% of the hand motor threshold. This figure is from Rosenberg, Shoenfeld, Zangen, Kotler, and Dannon, 2010[13]. Please click here to view a larger version of this figure.
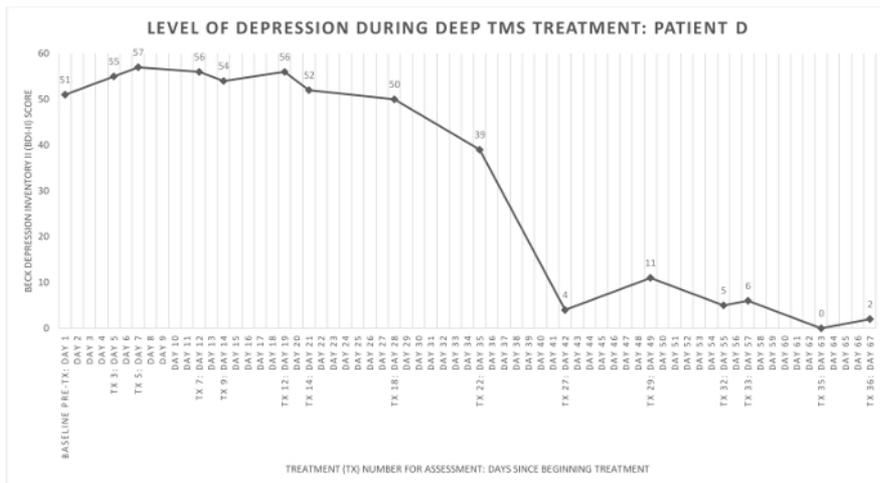
Figure 2: Patient D: BDI-II Scores Across Treatments. Patient D's response to dTMS treatment with this protocol is shown by BDI-II scores measured at various treatments/time points, with BDI-II score represented on the Y-axis, and treatment number/time point is shown on the X-axis. Patient D began to show a modest response to treatment during the fifth week of treatment (Day 28-35), but did not improve to the point of remission levels until the precipitous score drop seen from treatments 22 to 27 (Day 35-42), which was during the sixth week of treatment. The X-axis indicates the number of days since initiation of the first TMS treatment on Day 1. Treatments are administered daily (Monday-Friday), thus not every day on the X-axis is associated with administration of TMS to the patient. Please click here to view a larger version of this figure.
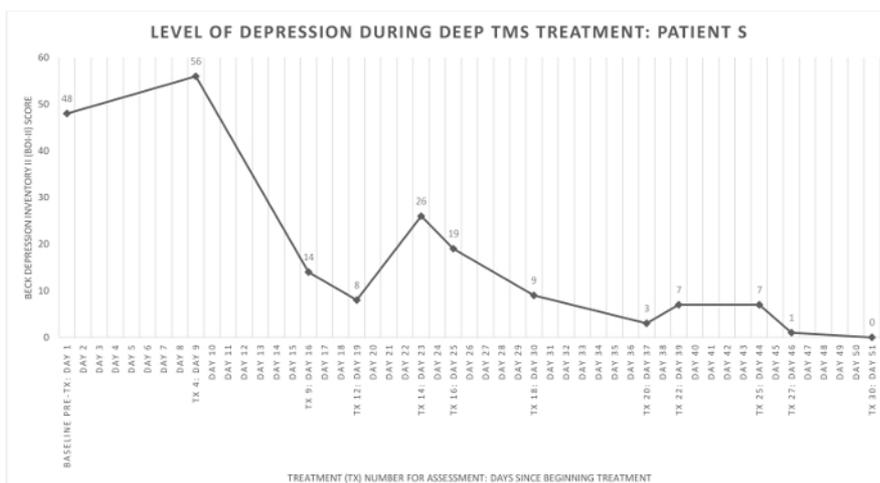

Figure 3: Patient S: BDI-II Scores Across Treatments. Patient S's response to dTMS treatment with this protocol is shown by BDI-II scores measured at various treatments/time points, with BDI-II score represented on the Y-axis, and treatment number/time point is shown on the X-axis. Patient S showed a strong initial response to treatment, which did not sustain at that time, but did drop back down into remission at about treatment 18. The X-axis indicates the number of days since initiation of the first TMS treatment on Day 1. Treatments are administered daily (Monday-Friday), thus not every day on the X-axis is associated with administration of TMS to the patient. Please click here to view a larger version of this figure.

Discussion

This protocol covers the methodology for use of the dTMS H1-coil for treatment of MDD. This protocol explains the steps leading up to and during an initial treatment visit, wherein the motor threshold of the patient is first determined, and then treatment is administered. The parameters for a typical treatment session are also introduced. It is important throughout the course of the motor threshold determination and subsequent treatment sessions to take care that all steps of this protocol are being followed correctly, and that the patient is communicative with their TMS psychiatrist to ensure that the optimal treatment plan is being followed. The course of treatment is typically six weeks of daily treatment visits, Monday–Friday, followed by a taper period of a few weeks. This treatment plan varies across patients based on the TMS psychiatrist's best clinical judgment, and is dependent on how the individual responds to the treatment, which can be measured using validated depression rating scales.

Receiving verbal feedback from the patient is important when planning and modifying their treatment course, but rating scales for depressive symptoms, such as the BDI-II, Montgomery Asberg Rating Scale, Patient Health Questionnaire 9, or Hamilton Depression Rating Scale, are typically used as more objective measures to monitor the patient's response to treatment. These scales each have their own strengths, and may vary across patients for the most effective method of evaluating that particular patient's depressive symptoms.

A motor threshold recalibration, which involves re-assessing the intensity necessary to produce a reliable finger twitch (protocol step 4.8), should be performed regularly — ideally once per week — throughout the course of treatment in order to ensure that the patient's treatment is being administered at the optimal intensity.

After a motor threshold recalibration, if the motor threshold has increased, then the patient may need to ramp up to their new treatment dose (which is 120% of the established motor threshold) — this is at the best clinical judgment of the TMS psychiatrist, and may affect the total number of treatment sessions that the patient undergoes. For planning when to end daily treatments and begin the taper period, the TMS psychiatrist should take into account the patient's subjective account of their improvement in symptoms, as well as their ratings on the objective measures listed above. Each of the depression rating scales have accepted cut-off points for what is considered remission of the depressive episode, and if a patient has reached full remission they will then typically enter the taper phase of treatment. This treatment methodology is a reflection of the currently-established standard of care for TMS treatment, which has been shown to be effective in numerous trials, including the ones discussed above[7, 8, 13].

This treatment methodology is limited by its sole indication for treatment of severe, treatment resistant, major depressive disorder. The H1-coil used for this treatment is designed to specifically target the area of the brain associated with MDD, so using the H1-coil to treat other diagnoses, such as Obsessive Compulsive Disorder (OCD) or Post-Traumatic Stress Disorder (PTSD), is not currently a viable option. However, other coils have been developed that are designed to target the areas of the brain associated with these disorders, and research is currently underway to investigate the efficacy of dTMS for treatment of other diagnoses, such as OCD and PTSD, using different models of the H coil. As more research continues to come forward regarding the efficacy of dTMS for treatment of MDD and other disorders, it will be important for clinicians to keep abreast of any modifications to the established treatment methodology in order to ensure that patients are receiving the best possible treatment available to them.

Disclosures

The authors have nothing to disclose.

Acknowledgements

The authors have no acknowledgments to disclose.

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