*Research Article*

# DEEP TMS IN A RESISTANT MAJOR DEPRESSIVE DISORDER: A BRIEF REPORT

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**Introduction:** *Repetitive transcranial magnetic stimulation (rTMS) has proven effective. Recently, a greater intracranial penetration coil has been developed. We tested the efficacy of the coil in the treatment of resistant major depression.* **Methods:** *Our sample included seven patients suffering from major depression who were treated using Brainsway's H1-coil connected to a Magstim rapid 2 stimulator. Deep TMS treatment was given to each patient in five sessions per week over a period of 4 weeks. Patients were treated with 120% intensity of the motor threshold and a frequency of 20 HZ with a total of 1,680 pulses per session.* **Results:** *Five patients completed 20 sessions: one attained remission (Hamilton Depression Rating Scale (HDRS) = 9); three patients reached a reduction of more than 50% in their pre-treatment HDRS; and one patient achieved a partial response (i.e., the HDRS score dropped from 21 to 12). Average HDRS score dropped to 12.6 and average Hamilton Anxiety Rating Scale score dropped to 9.Two patients dropped out: one due to insomnia and the second due to a lack of response.* **Discussion:** *Compared to the pooled response and remission rates when treating major depression with rTMS, deep TMS as used in this study is at least similarly effective. Still, a severe limitation of this study is its small sample size, which makes the comparison of the two methods in terms of their effectiveness or side effects impossible. Greater numbers of subjects should be studied to achieve this aim.* **Conclusions:** *An H1 deep TMS coil could be used as an alternative treatment for major depressive disorder. Depression and Anxiety 27:465–469, 2010.* © 2010 Wiley-Liss, Inc.

**Key words:** *deep transcranial magnetic stimulation; rTMS; major depressive disorder; treatment resistant patients*

## INTRODUCTION

Major depressive disorder is a chronic and recurrent disorder. Brain stimulation techniques, in general, are considered a relevant treatments for this disorder, and particularly transcranial magnetic stimulation (TMS) has been proven to be both effective and safe. Traditionally, studies had used a "figure-eight" shaped coil capable of penetrating about 2 cm into the brain.[1]

Deep TMS is currently being evaluated as a possible treatment for major depression and has been demonstrated as a safe and effective procedure.[1–3] The deep TMS coil maximizes the electrical field deep in the brain via summation of separate fields projected into the skull from several points around its periph-

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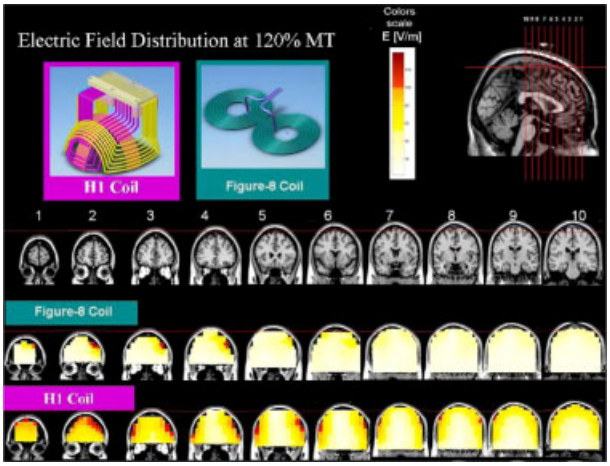


**Figure 1. Magnetic field distribution of figure-eight coil and H1-coil during anti-depressant treatment. The images are based on mathematical calculations in phantom model.**

ery.[4] The motor cortex can be activated by the H-coil at a distance of 5.5 cm compared with centimeter penetration depth of the figure-eight coil.[1]

With stimulator output set at 120% of the hand motor threshold, the H1-coil induces a supra-threshold field in the lateral and medial frontal regions at depths of up to 4 cm compared to the 1.5 cm depth of supra-threshold field under the central segment of the coil induced by the figure-eight coil. The H-coils' ability to effectively stimulate deeper neuronal structures is obtained at the cost of a wider electrical field distribution in the brain. However, the H-coils enable simultaneous stimulation of several brain regions, and the depth penetration in each region can be controlled by either adjusting the stimulator output and/or by varying the distance between the coil elements and the skull.[5]

The ability of the H-coil to stimulate deep brain regions was demonstrated using mathematical simulations and measurements via phantom brain model.[5] At a depth of 4.5 cm, the field intensity induced by the figure-eight coil is only 12% of the maximal field induced just below the coil compared to the H1-coil for which at a depth of 4.5 cm the field intensity is 66% of the maximal field just below the coil.[5]

Figure 1 presents maps of the electric field achieved by the treatment position of both the figure-eight coil and the H-coil. As shown in this phantom simulation, the H-coil field is deeper, covers larger brain tissue, and stimulates both right and left sides even though the left is preferentially stimulated.

## HYPOTHESIS

We presume deep TMS to be an effective treatment for major depression in terms of remission and response rates.

## MATERIALS AND METHODS

Patients signed an informed consent form approved by the local ethics committee and the Ministry of Health. In addition, patients completed a psychiatric interview and a Structural Clinical Interview for DSM Disorders (SCID (WMH SCID 2000-1 (revised) structured clinical interview for DSM-IV axis I disorders modified for use in the World Mental Health 2000 Project); version 2, 2000). Patients were also evaluated using the Hamilton Depression Rating Scale (HDRS) with 24 items, the Hamilton Anxiety Rating Scale, and the Beck Depression Inventory at the onset of the trial to establish a baseline. Participants were evaluated with the aforementioned scales after 5, 10, 15, and 20 treatments.

We used Brainsway's H1-coil made of seven Shelamid 200 copper wires that are insulated by two polyester layers. We connected the windings to a Magstim cable and a connector, which we then connected to a Magstim Rapid 2 stimulator. The most effective electric field produced by the H1-coil is oriented in the anterior–posterior axis with hemispheric preference for the left hemisphere.[5]

The first step of the treatment procedure was locating the exact point at which a minimum electric field will cause a motor response, i.e., twitching of the contra lateral finger muscles in the hand. Specifically, as the H1-coil preferentially stimulates the left motor cortex, the muscles of the right hand twitch. After locating this point, we moved the coil 5.5 cm parallel to the Sagital suture of the skull.[2] Patients were treated with 120% of the motor threshold at a frequency of 20 HZ. Each train of pulses included 40 pulses within 2 sec. The inter-train interval was 20 sec. Forty-two such trains of pulses were administered for a total of 1,680 pulses per treatment.

A positive treatment response was considered a reduction in the HDRS-24 score by at least 50%, and remission was considered a reduction of the HDRS-24 score to below 10 points.

### DATA ANALYSES

The repeated measures ANOVA results for rating outcomes after 10, 15, and 20 treatments include three, four, and five time-points, respectively.

### SUBJECTS

One female patient and six male patients diagnosed as suffering from major depression according to DSM-IV-TR criteria were enrolled in the trial. Their current depressive episode was considered to be treatment-resistant after they failed to respond to at least two trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance).[6]

Before enrollment in the study, all patients were drug-free, for at least 3 weeks. One patient had previously undergone inpatient electroconvulsive therapy (ECT) twice with a good response. After being discharged from our hospital and the reoccurrence of the depressive episode, he was offered deep TMS as a treatment option and agreed to participate in our study.

## CLINICAL EVALUATION AND RESULTS

All patients completed 10 treatments. Detailed results are given in Tables 1 and 2 and statistical calculations are given in Table 3. One patient dropped out due to insomnia. This patient had no other symptoms or side effects yet needed to receive stronger medications than sleeping pills to treat his insomnia.

**TABLE 1. Demographics**

| Patient number | Gender | Age (years) | Years of education | Age MDD onset | Current episode (months) | No. lifetime episodes | Past psychotherapy/ cognitive therapy | Family history MDD | No. failed pharmacological trails in current episode |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Female | 54 | 16 | 24 | 12 | >10 | Yes | Brother, mother | 5 |
| 2 | Male | 24 | 15 | 17 | 12 | 3 | Yes | No | 3 |
| 3 | Male | 55 | 12 | 48 | 24 | 2 | Yes | Father | 4 |
| 4 | Male | 53 | 17 | 10 | 7 | 4 | Yes | Mother | 2 |
| 5 | Male | 59 | 12 | 58 | 1 | 3 | | No | 3 |
| 6 | Male | 40 | 12 | 33 | 2 | 10 | Yes | No | 5 |
| 7 | Male | 47 | 15 | 43 | 2 | 20 | Yes | No | 4 |

**TABLE 2. Rating results**

| | Before study | Session 5 | Session 10 | Session 15 | Session 20 |
|---|---|---|---|---|---|
| *Patient no.1* | | | | | |
| HDRS | 27 | 28 | 25 | 27 | |
| HARS | 17 | 21 | 15 | 12 | |
| BDI | 42 | 42 | 40 | 39 | |
| *Patient no. 2* | | | | | |
| HDRS | 30 | 25 | 17 | 17 | 15 |
| HARS | 28 | 19 | 11 | 17 | 11 |
| BDI | 27 | 29 | 22 | 22 | 22 |
| *Patient no. 3* | | | | | |
| HDRS | 26 | 26 | 26 | | |
| HARS | 20 | 22 | 20 | | |
| BDI | 44 | 37 | 49 | | |
| *Patient no. 4* | | | | | |
| HDRS | 26 | 24 | 16 | 25 | 9 |
| HARS | 20 | 18 | 16 | 18 | 9 |
| BDI | 38 | 34 | 28 | 36 | 21 |
| *Patient no. 5* | | | | | |
| HDRS | 35 | 22 | 16 | 16 | 17 |
| HARS | 24 | 17 | 11 | 9 | 11 |
| BDI | 31 | 25 | 19 | 23 | 22 |
| *Patient no. 6* | | | | | |
| HDRS | 21 | 10 | 15 | 17 | 12 |
| HARS | 23 | 11 | 14 | 14 | 10 |
| BDI | 22 | 15 | 26 | 20 | 17 |
| *Patient no. 7* | | | | | |
| HDRS | 26 | 17 | 10 | 8 | 10 |
| HARS | 21 | 9 | 6 | 5 | 4 |
| BDI | 23 | 9 | 5 | 2 | 4 |

Six patients completed 15 treatments. One patient dropped out after 18 sessions due to a lack of response. Five patients completed 20 sessions.

Five patients positively responded to the treatment. Specifically, one attained remission (HDRS = 9); three patients reached a reduction of more than 50% in their pre-treatment HDRS; and one patient achieved a partial response (i.e., the HDRS score dropped from 21 to 12) (Fig. 2).

Another patient developed insomnia after the seventh session, i.e., a maximum of 3 hr of sleep per night. His insomnia subsequently deteriorated into a total inability to sleep after the 12th session. He was reluctant to continue the study after the 14th session. One patient developed dizziness accompanied by mild nausea after the second treatment. The nausea disappeared after 3 days of further treatment, but the dizziness continued for two additional days. He expressed no desire to leave the study. A third patient reported numbness in the right temporal and right cervical zone after the seventh session. This side effect continued for an additional day and then disappeared. Another side effect accompanying the treatment of this particular patient was trembling of the lower limbs. We lowered the treatment intensity to 100% of the motor threshold for this patient. The average treatment intensity of this patient in 20 sessions was 113.7% of his motor threshold.

# DISCUSSION

Two patients dropped out from this study, and five patients positively responded to the treatment. Specifically, one attained remission, three patients reached a reduction of more than 50% of their pre-treatment HDRS-24 scores, and one patient achieved a partial response.

Regarding the efficacy of repetitive TMS (rTMS) in the treatment of depression, several of the studies compare TMS and sham TMS. Among treatment possibilities of rTMS are different frequencies [generally between 1 and 20 Hz] and different locations of treatment [i.e., right versus left prefrontal cortex].

To compare our results with the results of rTMS, we explored the literature for open-label studies that involved 20-Hz frequency to the left dorsolateral prefrontal cortex. The studies we encountered used treatment intensity far below the intensity used in this study [80% motor threshold versus 120% in this study]. Taken together, a comparison between deep and traditional rTMS would be virtually impossible. Still, in a systematic review and meta-analysis of 24 studies involving rTMS, the pooled response and remission rates for the treatment of resistant depression were 25% and 17%, respectively for active rTMS and 9% and 6%, respectively, for sham conditions.[7] In the aforementioned, pooled rates of a systematic review and meta-analysis were roughly one of the six patients (17%) achieved remission and one of every four (25%)

**TABLE 3. Statistics**

| | Baseline | After 5 | After 10 | After 15 | After 20 |
|---|---|---|---|---|---|
| *HDRS* | | | | | |
| Mean ± SD | 27.4 ± 4.3 | 21.7 ± 6.2 | 17.9 ± 5.7 | 18.3 ± 6.8 | 12.6 ± 3.36 |
| ANOVA *P*-value | | | .041 | .026 | .0002 |
| *F*-value | | | 8.9 | 7.5 | 10.5 |
| λ | | | 17.9 | 22.7 | 42.2 |
| *HARS* | | | | | |
| Mean ± SD | 21.9 ± 3.5 | 16.7 ± 4.9 | 13.3 ± 4.46 | 12.5 ± 4.9 | 9 ± 2.9 |
| ANOVA *P*-value | | | .007 | .0007 | < .0001 |
| *F*-value | | | 7.7 | 10 | 17.9 |
| λ | | | 15.4 | 30.15 | 71.6 |
| *BDI* | | | | | |
| Mean ± SD | Mean = 32 ± 9 | 27.3 ± 11.9 | 27 ± 14.3 | 23.66 ± 13.2 | 17.2 ± 7.6 |
| ANOVA *P*-alue | | | .13 | .05 | .02 |
| *F*-value | | | 2.3 | 3.2 | 3.9 |
| λ | | | 4.7 | 9.8 | 15.8 |

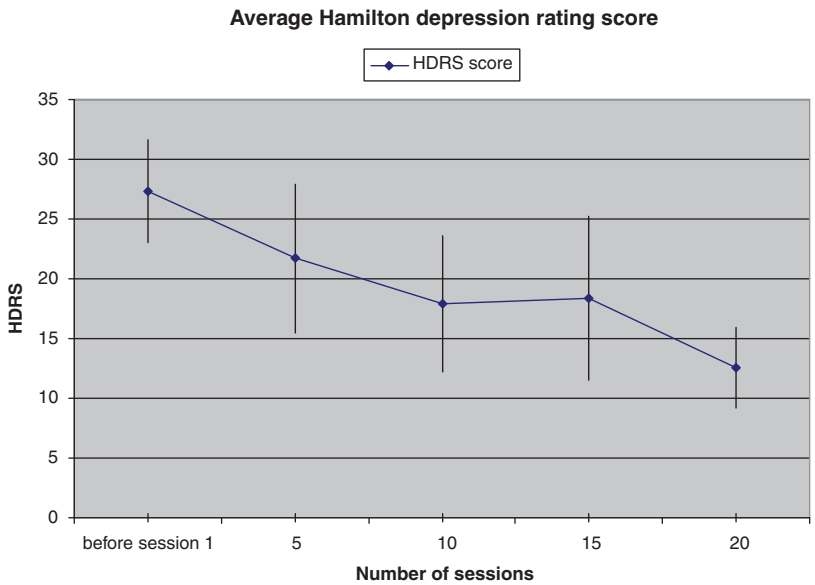


**Figure 2. HDRS average scores change according to number of sessions of Deep TMS.**

patients achieved response—while in the present small sample study the effect size is at least similar [14–57%].

The previously mentioned meta-analysis[7] stated that dropouts and withdrawals due to adverse events were very low. In our study, one dropout was due to an adverse event (i.e., insomnia), whereas the second dropout was due to a lack of response. Mayberg et al. reported that the chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with striking and sustained remission of depression.[8] Potentially, deep TMS, as opposed to conventional TMS, can stimulate fibers connecting the subgenual cingulate gyrus to the prefrontal cortex, thereby inducing an antidepressant action.

Insomnia after treatment with rTMS has been reported in the past.[9] One of the patients in this study developed severe insomnia with no other symptoms of mania.

In addition to insomnia, several of the side effects experienced by patients in this study have also been linked to rTMS; i.e., low rates of dizziness during rTMS treatments,[10] nausea after the end of low-frequency rTMS,[11] and numbness following a 10-Hz frequency rTMS[12] have all been reported.

ECT unresponsive patients may respond to deep TMS. We have previously reported,[3] six ECT non-responder patients who received deep TMS and responded well to the treatment.

In our current sample, one patient attained remission and three reached a clinical response [A reduction of more than 50% of their pre-treatment HDRS-24 scores]. The difference between the response rates in

patients resistant to ECT and patients who are not known to be resistant to ECT may insinuate that depression is more "deep TMS" resistant in patients resistant to ECT. Therefore, it would be less reasonable, although not entirely unfounded, to offer deep TMS to an ECT-resistant patient.

The major limitations of this study include the absence of a sham control group, the small sample size, and open-label treatment; therefore, its ability to predict deep TMS success in treating major depression is low but marks a direction for future research in the use of brain stimulation to treat depressive disorders.

## CONCLUSIONS

This preliminary study alludes to the efficacy of the H1-coil in treating major depression. The H1 deep TMS coil should be further studied using a greater number of patients as an alternative treatment of major depressive disorder.

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