Deep TMS in Peer-Reviewed Literature

Brainsway
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Deep transcranial magnetic stimulation (Deep TMS) using the Brainsway H-Coils is a non-invasive neurostimulatory technique based on the principle of electromagnetic induction of an electric field in the brain. There follows a compilation of highlights from selected peer-reviewed publications relating to Deep TMS. For further details please refer to the full articles.
The Deep TMS H1-Coil
The Deep TMS H-Coils are a novel development in transcranial magnetic stimulation (TMS) designed to achieve effective stimulation of deep neuronal regions.

Standard TMS is generally applied with a figure-8 coil, which targets superficial brain regions and is sensitive to the coil orientation. Other TMS coils with claims of depth penetration achieve it at the cost of stronger activation of superficial regions, which may be intolerable.

The H-Coils are a novel alternative to these coils, representing the state of the art in TMS coil technology. Their unique structure offers a good compromise between depth and focality, allowing deeper electric field penetration at safe and tolerable stimulation levels.
A Coil Design for Transcranial Magnetic Stimulation of Deep Brain Regions
Roth Y, Zangen A, Hallett M.

This seminal study authored by Yiftach Roth and Abraham Zangen, the two key inventors of the Deep TMS technology, under the supervision of TMS pioneer Prof. Mark Hallett, describes the construction principles of a first-of-its-kind nonstandard TMS coil design, termed the H-Coil. The study was performed at the National Institutes of Health (NIH) and was followed by the filing of a provisional patent application, which served as the basis for the intellectual property rights held by Brainsway over the Deep TMS technology.

The H-Coil was designed for TMS of deep brain regions. This ability was demonstrated using mathematical simulations and measurements in a realistic phantom brain model.

This paper describes the theoretical considerations of coil designs allowing deeper penetration. The basic concept of the H-Coil is to obtain summation in depth of several electric fields produced across the cranial surface, while minimizing the current components that only cause accumulation of surface charge. The dissipation of the electric field with distance from the coil was compared between the H-Coil and circular and double-cone coils, and found to be the markedly slower with the H-Coil. The upshot of this is that neuronal activation may be induced in deeper areas using the H-Coil without increasing stimulation intensity to levels that would render it unsafe and intolerably painful.

The following figure from the study depicts the decay of the electric field induced by different coils as a function of distance, illustrating The slower decay of the electric field induced by the H-Coil:
Induced electrical field plotted as a function of distance for the double-cone coil and the H-Coil. Although the double-cone coil produces a much larger induced field, the rate of decay of the field with distance is much smaller for the H-Coil. This allows the H-Coil to stimulate deeper brain areas without inducing an intolerable electric field in more superficial brain areas.
The H-Coil was designed based on numeric calculations and optimized using measurements in a phantom brain model. The current study sought to test the actual biological efficacy of the H-Coil, using motor threshold as a measure of biological effect.

Depth penetration of the field induced by the H-Coil and the standard figure-8 TMS coil was compared by measuring thresholds for activation of the abductor pollicis brevis (APB) representation in the motor cortex as a function of distance from each coil in 6 healthy subjects. The results confirmed the theoretical calculations and measurements of the previous study, demonstrating significantly improved depth penetration and a slower rate of decay of the electric field with distance, when using the H-Coil.

This is the first study in which the H-Coil was used in humans, and it provided proof of the until-then theoretical concept of Deep TMS. This study also provided initial safety data concerning the technology, with subjects reporting no significant side effects as a result of administration of single TMS pulses at intensities greater than the motor threshold intensity.
The percentage of stimulator output required for APB activation by figure-8 coil and the H-coil as a function of distance from the 'hot spot' on the scalp. The higher efficiency of stimulation using the H-Coil is demonstrated by the lower stimulator output required to reach threshold at each distance.

The graph shows that as the distance from the 'hot spot' increases, the stimulator power setting required to reach threshold also increases. The H-coil (△) requires a lower setting compared to the figure-8 coil (●) across all distances.
Roth et al. employed two types of H-Coils on a model human head filled with a physiological solution in order to provide a quantitative measure of the strength of the electromagnetic field these coils generate. Three-dimensional electrical field distributions of the H1 and H2-coils, designed for effective stimulation of prefrontal regions, and of a standard figure-8 coil, were measured.

With stimulator output at 120% of the hand motor threshold (MT), a suprathreshold field was induced by the H1-Coil at lateral and medial frontal regions at depths of up to 4 to 5 cm (when depth is measured as distance from the skull upper edge), and by the H2-coil at medial prefrontal regions up to 2 to 3 cm, and at lateral frontal regions up to 5 to 6 cm. The figure-8 coil induced suprathreshold field focally under the coil's central segment, at depths of up to 1.5 cm.

The ability of the H-Coils to stimulate effectively 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.

The same methodology was used by this group in a subsequent study (see study 2.3) to produce coronal field distribution maps for the H1-Coil and the standard TMS figure-8 coil. When depth is measured as distance along the direction perpendicular to the brain's surface, stimulation at 120% of MT using the H1-Coil induces suprathreshold fields at depths of up to 1.8 cm beneath the skull, and significant sub-threshold field at depths of up to 3.2 cm, compared to 0.7 cm and 0.7 cm for the figure-8 coil.*

Colored field maps for the H1-coil and figure-8 coil at the FDA-approved stimulation intensity for depression treatment (120% of motor threshold). Measurements were performed in a realistic head model. The absolute magnitude of the induced electric field is indicated in each pixel over 8 coronal slices 1 cm apart. Red pixels indicate field magnitudes above the threshold for neuronal activation.

* Figure adapted from Rosenberg et al. (2010) [Study 2.3].
Stimulator technology has not changed significantly since the early days of TMS. Stimulation of a single-element coil using the sole channel of a TMS stimulator is standard.

In this study, Roth et al. demonstrate the feasibility of a novel multi-channel stimulator device for which the stimulation parameters of each channel are independently controllable. A prototype of this device was assembled with 5 independent channels and a variety of multi-element coils were tested, including those based on deep H-coil design characteristics.

Significant improvements in stimulation efficiency and coil heating were demonstrated. For example, a 70% reduction of energy dissipated as heat for a 4-channel coil in comparison to a standard single-element (figure-8) coil.

Furthermore, the flexibility of the multi-channel stimulator enables novel combinations of pulse characteristics and timings. For example, inter-pulse intervals for the technique of paired pulse TMS were demonstrated in the range of 0-1ms, that is impossible to achieve with any other stimulator design known today. The use of this unique range of pulse intervals to exploit a well-known neurophysiological phenomenon indicated the exciting potential of a new approach for achieving enhanced depth penetration with reduced stimulation of intermediate tissues.
Section 2
Clinical Studies in MDD

The antidepressant effects of TMS have been investigated in clinical trials since the early 1990s.

Since 2009, an ever-expanding literature of research has provided an evidence base supporting the benefit of Deep TMS using the H-Coils as a treatment for resistant MDD.

The H-Coils may be expected to produce antidepressant effects of greater magnitude than those of standard TMS due to the stimulation of deeper and more widespread prefrontal reward-mediating neural pathways (to date, no head-to-head trials have compared standard TMS and Deep TMS directly).
2.1 A Randomized Controlled Feasibility and Safety Study of Deep Transcranial Magnetic Stimulation

This comprehensive safety study performed in healthy volunteers showed the safety of H-Coils used even in high frequencies and intensities. 32 healthy volunteers were randomly assigned to one of four groups: each of two H-Coil designs (H1, H2), standard figure-8 coil, and a sham-coil control. Subjects were tested in a pre-post design, during three increasing (single pulses, 10 Hz, and 20 Hz) stimulation sessions, as well as 24-36 hours after the last stimulation.

The major finding of this study is that stimulation with the novel H-Coils was well tolerated, with no adverse physical or neurological outcomes.

2.2 Deep Transcranial Magnetic Stimulation over the Prefrontal Cortex: Evaluation of Antidepressant and Cognitive Effects in Depressive Patients

This study by Levkovitz et al. was conducted in the Shalvata Mental Health Center, Israel, and is the first feasibility study of Deep TMS in pharmaco-resistant medication-free major depressive disorder (MDD) patients. In this study, 65 patients were treated with three different Deep TMS coil versions designed for prefrontal stimulation (H1, H1L, and H2). Three treatment groups differed in stimulation laterality (left preference, left side only, bilateral), while a fourth group differed only in stimulation intensity (110% of MT rather than 120%).

Patients received 20 daily treatment sessions at a frequency of 20 Hz. Each session consisted of 42 2-second trains, with a 20-second intertrain interval (for a total of 1,680 pulses over 15 minutes). Response was defined as a decrease of 50% or more from baseline in Hamilton Depression Rating Scale-24 (HDRS-24) scores and remission was defined as an absolute HDRS-24 score of 10 or less. 47% (9/19) of the patients treated with the H1-Coil, 30% (6/20) of the patients treated with the H2-coil, 60% (6/10) of the patients treated with the H1L-120%
coil, and none (0/8) of the patients treated with the H1L-110% coil reached the defined response criteria. Remission rates at 5 weeks for the H1, H2, and H1L-120% treatment groups were 42% (8/19), 10% (2/20), and 50% (5/10), whereas in the H1L-110% treatment group no patients remitted (0/8).

These findings demonstrate again the safety of the H-Coils, as well as the higher efficacy of unilateral left stimulation relative to bilateral stimulation, and the advantage of 120% MT stimulation over the more superficial stimulation induced at 110% of MT.
2.3 Deep TMS in a Resistant Major Depressive Disorder: A Brief Report
Rosenberg O, Shoenfeld N, Zangen A, Kotler M, Dannon PN.  
*Depression and Anxiety, 27:465-9 (2010)*

Rosenberg et al. report on a case series of 7 pharmaco-resistant drug-free MDD patients who were treated with the H1-Coil. Patients were treated with the same parameters as the previous study. Of the 5 study completers, one reached remission, 3 met the criteria for response, and one achieved partial response. Despite the small sample of this study, it supports the previously established antidepressant action of Deep TMS.

2.4 Response to Deep TMS in Depressive Patients with Previous Electroconvulsive Treatment
Rosenberg O, Zangen A, Stryjer R, Kotler M, Dannon PN.  
*Brain Stimulation, 3:211-7 (2010)*

The research team that performed the previous study preliminarily explored the possible efficacy of the Deep TMS H1-Coil in a case series of 6 treatment-resistant MDD patients, who had previously undergone ECT. Patients were treated at 120% of the MT at a frequency of 20 Hz. Patients underwent five sessions per week, for as long as 4 weeks. 2/6 patients responded to the treatment, including one who achieved full remission (HDRS-24 score below 10 points). This study suggests that a subgroup of patients who do not respond to ECT may benefit from Deep TMS treatment.
Cognitive-Emotional Reactivation During Deep Transcranial Magnetic Stimulation over the Prefrontal Cortex of Depressive Patients Affects Antidepressant Outcome

Isserles et al. performed the second medium-sample feasibility study of Deep TMS for MDD at two additional centers in Israel (Hadassah Medical Center and Beer Yaakov Mental Health Center). The study assessed for the first time the safety and efficacy of the H1-Coil as an add-on in treating resistant unipolar depressive patients. In addition, the effect of cognitive-emotional reactivation on the outcome of Deep TMS treatment was evaluated.

Deep TMS was delivered at 20 Hz with the H1-Coil, designed to stimulate deep prefrontal brain regions, preferentially in the left hemisphere. Overall, of the 46 patients who completed at least 10 sessions, 21 (46%) achieved the response criteria (defined as an improvement of 50% or more in the HDRS-24 score) and 13 (28%) achieved remission. Negative cognitive-emotional activation was potentially disruptive to the therapeutic effects of Deep TMS.

This study shows that Deep TMS using the H1-Coil is effective not just as a monotherapy, but also as an add-on to medications, and not only in drug-free patients. Using Deep TMS as an add-on instead of monotherapy might be preferred when medications achieve a partial effect or when the clinical judgment is that taking the patient off medication might be unsafe. These results are especially important in the context of the finding that high dosages of psychoactive medications can increase convulsive vulnerability and the risk of TMS treatment.
In this open-label trial conducted at McGill University in Montreal, Canada, 17 outpatients with severe treatment-resistant MDD (at least 3 failed antidepressant drug trials) received 4 weeks of daily high frequency Deep TMS over the left dorsolateral prefrontal cortex. The primary outcome measures were rates of response and remission at week 5 using an intention-to-treat approach.

Each Deep TMS session consisted of 75 trains (2 s duration, 20-s inter-train interval) delivered at a frequency of 20 Hz (i.e., 3,000 pulses per session) and at an intensity of 120% of the resting MT. In order to minimize significant scalp discomfort and enhance initial tolerability, the intensity of Deep TMS treatment could be titrated to 120% of MT during the first two weeks.
Response and remission rates at week 5 were 70.6% and 41.2%, respectively. Also, depression, anxiety, and suicidality ratings were significantly improved by week 5.

This study confirms previous evidence of a positive therapeutic effect of Deep TMS in treatment-resistant depression (TRD), and suggests that when used as an augmenting strategy for antidepressants in severe TRD, Deep TMS is efficacious, safe and relatively well tolerated. The higher number of pulses administered (3,000 vs. 1,980 in other Deep TMS trials) may have improved clinical outcomes in these severe patients. Larger studies are warranted to confirm these results.
2.7 Effectiveness of a Second Deep TMS in Depression: A Brief Report
Rosenberg O, Isserles M, Levkovitz Y, Kotler M, Zangen A, Dannon PN.

Rosenberg et al. investigated the effectiveness of a second antidepressant course of Deep TMS in 8 depressive patients who relapsed after a previous successful Deep TMS course. In all patients, the second course of treatment (after first relapse) induced significant reductions in depression and anxiety scale scores. Although the magnitude of response in the second course was slightly smaller relative to that obtained in the first course of treatment, the results suggest that depressive patients who previously responded well to Deep TMS treatment are likely to respond again.

2.8 H-Coil Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Major Depressive Disorder: An 18-Week Continuation Safety and Feasibility Study
Harel EV, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y.

Harel et al. examined the safety and feasibility of Deep TMS continuation treatment for MDD over a longer term of 18 weeks, following 4 weeks of acute treatment. 29 MDD patients received 22 weeks of Deep TMS therapy: 4 weeks of acute daily treatment followed by 18 weeks of continuation treatments. Clinical evaluations were performed weekly throughout the study. A significant decrease from baseline in HDRS scores was found at the end of the acute phase, and was maintained throughout the study. The procedure was well tolerated and no adverse events were reported. This study suggests that Deep TMS continuation treatment could help maintain an antidepressant effect for 18 weeks, following 4 weeks of acute treatment.
2.8

Study Design

Probabilities of response and remission

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<th>Weeks</th>
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Response
Remission
Co-occurrence of MDD and Alcohol Use Disorders (AUDs) is frequent, causing more burden than each disorder separately. Since the dorsolateral prefrontal cortex (DLPFC) is critically involved in both mood and reward, and since it is dysfunctional in both conditions, this study aimed to evaluate the effects of Deep TMS stimulation of bilateral DLPFC with left preference in patients with MDD with or without concomitant AUD.

12 MDD patients and 11 with concomitant MDD and AUD (MDD+AUD) received 20 Deep TMS sessions. Clinical status was assessed through the HDRS and the Clinical Global Impressions severity scale (CGIs), and craving through the Obsessive Compulsive Drinking Scale (OCDS) in the MDD+AUD group.

Percent drops on HDRS and CGIs scores at the end of the sessions were respectively 62.6% and 78.2% for MDD+AUD, and 55.2% and 67.1% for MDD (p<0.001). HDRS, CGIs and GAF scores remained significantly improved after the 6-month follow-up. HDRS scores dropped significantly earlier in MDD+AUD than in MDD.

The authors conclude that high-frequency Deep TMS with the H1-Coil is well tolerated and effective in patients with MDD, with or without AUD. The antidepressant effect of Deep TMS was not affected by alcohol abuse in patients with depressive episodes. The potential use of Deep TMS for mood modulation as an adjunct to treatment in patients with a depressive episode, with or without alcohol abuse, deserves further investigation.
Comparison of the HDRS total score during the study between the MDD±AUD and MDD-only groups. *p<0.05; **p=0.02; ***p<0.01.
Levkovitz et al. conducted a randomized double-blind sham-controlled multicenter trial of Deep TMS for the treatment of MDD at 20 sites in the U.S. (n=13), Israel (n=4), Germany (n=2) and Canada (n=1). This multicenter randomized controlled trial (RCT) led to FDA clearance of the Brainsway Deep TMS device (FDA 510(k) Number K122288).

The study included 212 patients with MDD who had not received benefit from 1 to 4 antidepressant trials or were intolerant to at least 2 antidepressant treatments. Patients were randomly assigned to monotherapy with either active or sham Deep TMS for a 4-week acute treatment phase followed by a 12-week maintenance phase of bi-weekly treatment. The study employed a novel sham TMS coil design that effectively blinded patients and investigators for the duration of the study. Per-protocol analysis revealed a clinically significant improvement on the primary outcome measure, baseline to week 5 change on the 21-item Hamilton Depression Rating Scale (HDRS-21, p=0.008, effect size = 0.76). A statistically significant benefit relative to sham was also apparent in response rates (38.4% vs 21.4%, p=0.013) and remission rates (32.6% vs 14.6%, p=0.05).

The only double-blind sham-controlled trial of continuation Deep TMS was performed in the framework of a 12-week maintenance phase included in this pivotal trial. At the end of the maintenance phase (16 week follow-up), the response rate remained significantly improved by Deep TMS. The difference in response rates between active rTMS (44.3%) and sham groups (25.6%) was significant (p=0.0086). 30 of the 41 patients (73.2%) who achieved remission after acute treatment did not meet the criteria for relapse during the 12-week maintenance phase. Furthermore, out of 32 patients who did not reach remission during weeks 1-5, and continued to receive treatment after week 5, 19 patients (59.4%) reached remission during the maintenance phase.
This study provides the highest class of clinical evidence for the efficacy of a specific protocol of high-frequency prefrontal Deep TMS using the H-Coil in the acute treatment of pharmaco-resistant MDD, and suggests a definite benefit to continuation treatment.

2.10

**HDRS-21 Score Over Time**

- Deep TMS = -6.39 points
- Sham = -3.28 points
- P-value of Difference = 0.0080

**Response and Remission Rates at Week 5**

- Deep TMS: 38.4% Remission, 21.3% Response
- Sham: 32.6% Remission, 14.6% Response

*Remission - HDRS-21 Score < 10
Response - Improvement of at least 50% from baseline
Deep Transcranial Magnetic Stimulation (DTMS) in the Treatment of Major Depression: An Exploratory Systematic Review and Meta-Analysis
Kedzior KK, Gellersen HM, Brachetti AK, Berlim MT.

This systematic literature review and meta-analysis investigated whether Deep TMS delivered with H-Coils has acute effects in major depression. Data from nine open-labels studies were meta-analyzed using a random-effects model with inverse-variance weights. The outcome measures were the standardized paired mean difference (Cohen's d) in HDRS scores, response, remission, and dropout rates after acute Deep TMS treatment compared to baseline.

A large antidepressant effect was found following acute Deep TMS treatment compared to baseline according to HDRS score changes (overall mean weighted d=2.04, 95% confidence interval: 1.53-2.55; in nine studies and 150 patients). While effect sizes were likely inflated by the open-label nature of the studies analyzed, the authors raise the possibility these large effect sizes may also be partially attributable to the deeper and more widespread stimulation effected by the H-Coils.

Overall weighted response, remission, and dropout rates were 60%, 29%, and 18%, respectively. HDRS score changes and response rates tended to be higher in four studies with 68 patients on concurrent antidepressants compared to two studies with 26 patients who received Deep TMS as a monotherapy.

Although these results are based on data from a low number of open-label studies, the authors conclude that high-frequency Deep TMS is efficacious and acceptable in the acute treatment of MDD, particularly in unipolar and treatment-resistant patients. They further suggest that the efficacy of Deep TMS may be enhanced by concurrent antidepressant pharmacotherapy.

The forest plot below presents the standardized HDRS score changes in the nine open-label Deep TMS studies included in the meta-analysis, and demonstrates the consistent effectiveness observed across studies following treatment with Deep TMS.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Std Paired Difference and 95% CI</th>
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![Graph showing the distribution of Std Paired Difference and 95% CI with markers for DTMS ineffective and DTMS effective.](image-url)
Deep TMS has been investigated in pre-clinical settings with the aid of useful and informative animal models of depression. These models can serve as a substrate for elucidating neurobiological mechanisms underlying depression and drug-resistance, and, by extension, may assist in the development and optimization of novel therapeutic approaches for pharmaco-resistant MDD patients.

These studies also allow direct exploration of such issues as the mechanisms of action whereby TMS induces its antidepressant effects, and the importance of the depth of stimulation.

Although clinical results in human subjects speak for themselves, Brainsway is committed to unraveling the basic scientific underpinnings of Deep TMS.
Transcranial magnetic stimulation (TMS) is a non-invasive approach used for stimulating the human brain. Repetitive stimulation over the prefrontal cortex has proven effective in the treatment of major depression. However, the mechanism of the antidepressant action is unknown.

Since the nucleus accumbens is a major region implicated in reward circuitry and depressive disorders, neurochemical changes induced in that region were measured using microdialysis during and after acute TMS. Magnetic stimulation was applied over the frontal or the caudal cortex of the rat brain using a special coil design and microdialysis samples were collected before, during and after the stimulation session.

The extracellular levels of both dopamine and glutamate in the nucleus accumbens were increased during the stimulation while the extracellular levels of acetylcholine were not affected. Stimulation over the caudal cortex caused a greater increase in dopamine levels than the stimulation over the frontal cortex, while no such difference was observed for glutamate levels.

The changes in dopamine and glutamate extracellular levels in the nucleus accumbens may play a role in the antidepressant effect of TMS.
This study compared behavioral and neurochemical effects produced by ECT and by repeated stimulation of reward-related brain sites, in a widely used rat model for depressive behavior induced by chronic mild stress (CMS). Different groups of rats received 10 sessions of either electroconvulsive shocks or subconvulsive electrical stimulation (SCES) of specific brain sites with an implanted electrode. The SCES temporal parameters were similar to those used in TMS studies in humans.

A battery of behavioral tests and measurements of brain-derived neurotrophic factor (BDNF) levels were used to assess the effectiveness of these treatments relative to sham treatments.
Repeated SCES of either the nucleus accumbens (NAc) or the ventral but not the dorsal prelimbic cortex (PLC, homologous to the medial PFC in humans) reversed the main behavioral deficit and the reduction of BDNF levels in the hippocampus that were induced by CMS. ECT was more effective because it also normalized a behavioral deficit associated with anxiety, but it produced a learning and memory impairments.

This study implicates the ventral PLC and the NAc in the pathophysiology of depressive behavior, and shows that the depth of stimulation is critical in modulating the brain's reward system and relieving depressive symptoms. It further suggests that local intermittent SCES can induce an antidepressant effect similar to that of ECT, without the cognitive impairment caused by the convulsive treatment.

3.2 Sucrose preference test. (A) Means ± SEMs of the percentage of sucrose (.2%) intake, as calculated from total liquid consumption in the ECT (left) or SCES (right) groups. (B) Sucrose preference as a function of electrodedepth in the prelimbic cortex relative to the horizontal midline of the prelimbic cortex (PLC). Deeper subconvulsive electrical stimulation can be seen to elicit greater reductions in depressive behavior.
Although the etiology of MDD is still obscure, a genetic predisposition appears to play an important role.

This study used, for the first time, a multifactorial selective breeding procedure to generate a distinct ‘depressed’ rat line (DRL) and a "motivated" rat line (MRL). Selection was based upon mobility in the forced swim test, sucrose preference and home-cage locomotion, three widely used tests associated with core characteristics of MDD. Other behavioral effects of the selection process, as well as changes in brain-derived neurotrophic factor (BDNF) and the response to three antidepressant treatments, were also examined.

Results indicate that decreased mobility in the forced swim test and decreased sucrose preference (two directly selected traits), as well as decreased exploration in the open field test (an indirectly selected trait), are hereditary components in DRL rats. In addition, lower BDNF levels are observed in the dorsal hippocampus of DRL rats, complying with the neurotrophic hypothesis of depression. Finally, electroconvulsive shocks (ECS) but not pharmacological treatment normalizes both the depressive-like behavioral impairments and the BDNF-related molecular alterations in DRL rats, highlighting the need for robust treatment when the disease is inherited and not necessarily triggered by salient chronic stress.

This study provides a novel multifactorial genetic rat model for depression-related behaviors. The model can be used to further study the etiology of the disease and suggest molecular correlates and possible treatments for the disease.
Three behavioral tests demonstrate the existence of depressive-like behaviors in ‘depressed’ but not in ‘motivated’ rat lines (DRL and MRL, respectively).

Electroconvulsive shocks (ECS) but not desipramine or fluoxetine normalizes depressive-like behavior in depressed rat line (DRL) rats.
Approximately one third of all major depression patients fail to respond to conventional pharmacological treatments, and brain stimulation methods pose a promising alternative for this population.

This study sought to evaluate the effect of sub-convulsive electrical stimulation (SCES) at the prelimbic cortex (PLC) of Depressive-Rat-Line (DRL) rats, using TMS-like temporal patterns of stimulation (with the same stimulation parameters as those used in human TMS studies). The authors used the DRL model presented in the previous study.

The results of the study showed that SCES normalized both the depressive-like behaviors and the reduced BDNF levels observed in DRL rats. Correlation analyses suggest that changes in specific behaviors are mediated, at least in part, by BDNF expression in reward-related brain regions.

Brain stimulation is thus shown to be effective in a drug-resistant, inherited animal model of depression. BDNF alterations in specific regions may mediate different antidepressant effects.
The largest volume of evidence for the efficacy of the H-Coils exists for MDD, for which the Deep TMS technology is cleared by the FDA. The H-Coils' ability to target deep neuronal regions broadly expands the potential utility of Deep TMS. Indeed, the therapeutic efficacy of Deep TMS using different H-Coils has been explored in a number of additional psychiatric and neurological conditions, with some promising results. These applications are still considered investigational.
Harel et al. conducted an open-label pilot trial at the Shalvata Mental Health Center, Israel, to evaluate the safety and efficacy of Deep TMS with the H1-Coil as an adjunctive treatment for treatment-resistant bipolar depression. 19 bipolar depression patients on concomitant medication received daily 20-Hz Deep TMS sessions over 4 weeks (1,680 pulses per session).

A significant mean decrease of 12.9 points on the HDRS-24 scale (P< 0.001) was found when comparing pre- and post-treatment scores. The response rate was 63.2% and the remission rate was 52.6%. Treatment was well tolerated in terms of headache and overall discomfort, and there were no significant changes in cognitive functioning or mood switches.

The study results suggest an antidepressant effect of Deep TMS in bipolar depression. However, the data are based on a small sample and are awaiting confirmation in an ongoing large-scale multicenter RCT.

**TRIAL REGISTRATION:** ClinicalTrials.gov Identifier NCT01566591
Effectiveness of Deep Transcranial Magnetic Stimulation Combined with a Brief Exposure Procedure in Post-Traumatic Stress Disorder-A Pilot Study
Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, Zlotnick E, Zangen A. 
*Brain Stimulation, 6:377-83 (2013)*

In a pilot study conducted at the Hadassa Medical Center, Israel, to explore the effectiveness of Deep TMS combined with a brief exposure to trauma cues in the treatment of PTSD, 30 PTSD patients were enrolled and randomly assigned into 3 treatment groups: A) Deep TMS after brief exposure to the traumatic event using a script-driven imagery procedure (EXP-TMS); B) Deep TMS after brief exposure to a non-traumatic event (NOEXP-TMS); C) sham stimulation after brief exposure to the traumatic event (EXP-SHAM). Response criteria, defined as an improvement of 50% or more relative to the baseline Total Clinician-Administered PTSD Scale (CAPS) score were achieved in 4/9 patients (44%) in the EXP-TMS group, in 1/8 patients (12.5%) in the NOEXP-TMS group and in none of the 9 patients (0%) in the EXP-SHAM group (P < 0.055, Fisher’s exact test).

The primary outcome measure was the CAPS score, measured after 4 treatment weeks. Mean CAPS scores improved from 88(±5.5) at baseline to 61(±8.8) [mean ± SE] in the EXP-STIM group (N = 9), from 86(±5.4) to 76(±10.9) in the NOEXP-STIM group (N = 8) and from 86 (±9.2) to 76(±10.7) in the EXP-SHAM group (N = 9). This improvement in scores was only significant in the EXP-STIM group, as were improvements on the individual components of the CAPS (intrusion, avoidance/numbing, and arousal).

The results indicate that Deep TMS may be used to modify highly salient traumatic memories and induce therapeutic effects in PTSD patients. Here too, the results await substantiation in an ongoing large-sample multicenter RCT.

**TRIAL REGISTRATION:** ClinicalTrials.gov Identifier NCT02479906

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### 4.2

<table>
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<tr>
<th>Total-CAPS severity score at baseline and post treatment. *P &lt; 0.05, relative to baseline.</th>
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<tbody>
<tr>
<td>EXP-STIM</td>
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<td>NOEXP-STIM</td>
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<td>EXP-SHAM</td>
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<td>Baseline</td>
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In a clinical trial of Brainsway’s Deep TMS for the treatment of neuropathic pain at the University of Rome ‘La Sapienza’, Italy, 25 patients with neuropathic pain due to diabetic symmetric polyneuropathy in the lower limbs were randomly assigned to receive daily real or sham Deep TMS for 5 consecutive days, using an H-Coil designed to target the representation of the lower limbs in the motor cortex, located within the inter-hemispheric fissure. After a 5-week washout period, patients crossed over to the alternative treatment for an additional 5 days (according to a crossover study design). Outcome measures were changes in the visual analogue scale (VAS) for pain and in area and threshold of RIII nociceptive flexion reflex (RIII reflex).

Of the 25 patients randomized, 23 completed the study. After real Deep TMS, VAS scores decreased significantly (p=0.01), as did the area of the RIII reflex area (p < 0.01), while no significant effects in these variables were induced by the sham TMS treatment. The induced changes in the outcome measures disappeared about 3 weeks after stimulation. All patients tolerated stimulation well.

These data demonstrate an analgesic effect of Deep TMS in painful diabetic neuropathy. Future studies are warranted to confirm these results, and to evaluate whether longer and more intense stimulation periods will produce long-lasting beneficial effects, and whether chronic maintenance TMS sessions are practicable.
Real, but not sham, Deep TMS over the motor cortex produced improvements in both objective and subjective measures of pain sensation. *p ≤ 0.01 with respect to baseline value.
The majority of studies using standard TMS coils as a tool for decreasing cravings in substance abuse disorder patients have targeted superficial areas such as the DLPFC. However, combined evidence suggests a crucial role of the insular cortex (IC) in cravings for food, cocaine, and cigarettes; and that IC damage interrupts addictive behaviors.

Dinur-Klein et al. conducted a prospective, randomized, double-blind sham-controlled trial at the Beer Yaakov Mental Health Center to assess the efficacy of Deep TMS targeting the PFC and IC as a smoking cessation strategy.

115 adult subjects who smoke at least 20 cigarettes/day and failed previous treatments were recruited from the general population. Participants were randomized to receive 13 daily sessions of high-frequency, low-frequency or sham stimulation following, or without, presentation of cues that induce cigarette craving. Cigarette consumption was evaluated during the treatment by measuring cotinine levels in urine samples and recording participants’ self-reports as a primary outcome variable. Dependence and craving were assessed using standardized questionnaires.

High (but not low) frequency Deep TMS treatment significantly reduced cigarette consumption and nicotine dependence. The combination of this treatment with exposure to smoking cues enhanced reduction in cigarette consumption leading to an abstinence rate of 44% at the end of the treatment and an estimated 33% 6 months following the treatment. This study further implicates the lateral PFC and insula in nicotine addiction and suggests the use of high-frequency Deep TMS of these regions following presentation of smoking cues as a promising treatment strategy. Here again, the results are now followed by a multicenter clinical trial.

**TRIAL REGISTRATION:** ClinicalTrials.gov Identifier NCT02126124
Abstinence rates after 6 months. Rates were calculated for all groups by using subjective self-reported number of cigarettes 6 months after the last treatment session. Groups sizes were: 0+ (n=11), 0- (n=13), 1+ (n=5), 1- (n=7), 10+ (n=15), 10- (n=13).
Deep Repetitive Transcranial Magnetic Stimulation with H-Coil on Lower Limb Motor Function in Chronic Stroke: A Pilot Study


*Archives of Physical Medicine and Rehabilitation, 95:1141-7 (2014)*

Chieffo et al. performed a double-blind, placebo-controlled crossover study at the San Raffaele University Hospital, Milan, Italy, to assess the efficacy of high-frequency (20 Hz) Deep TMS on lower limb motor function in 10 right-handed chronic subcortical stroke patients, who suffered their first-ever stroke more than 6 months previously.

Deep TMS was delivered with an H-Coil targeting the lower limbs motor cortex representation. Each subject received both real and sham Deep TMS according to a random sequence crossover design. The two TMS cycles (real or sham) were composed of 11 sessions each, administered over 3 weeks and separated by a 4-week washout period.

Lower limb functions were assessed by the lower limb Fugl-Meyer Assessment (FMA), used to evaluate and measure recovery in post-stroke patients, the 10-m walk test, and the 6-minute walk test, before and 1 day after the end of each treatment period, as well as at a 4-week follow-up.

Real Deep TMS treatment was associated with a significant improvement in lower limb motor function, as indicated by improvement on the FMA. This effect persisted at follow-up 1 month after the end of treatment. These findings suggest a possible beneficial role for Deep TMS in motor recovery from chronic stroke.
% Change on the lower limb Fugl-Meyer Assessment (FMA) of Motor Recovery. Real versus sham comparison (9 vs. 9 patients) revealed a significant improvement at the end of treatment (P=.01) as well as at follow-up (P=.006). Amelioration was greater after 4 weeks from the end of real treatment as confirmed by a significant difference in baseline percent change at the end of treatment versus follow-up (P=.04).