BrainsWay Treatment (Deep TMS) in Peer-Reviewed Literature

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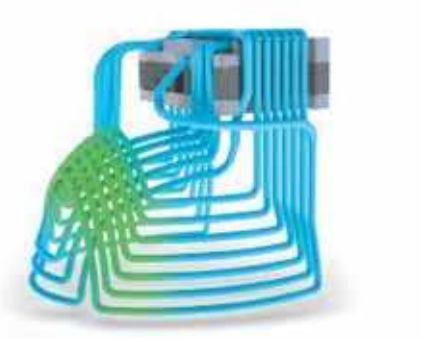
Deep transcranial magnetic stimulation (Deep TMS) using the BrainsWay H-Coils is a non-invasive neurostimulatory technique based on the principle of electromagnetic induction of an electric field in the brain. There follows a compilation of highlights from selected peer-reviewed publications relating to BrainsWay Deep TMS. For further details please refer to the full articles.



The Deep TMS H1-Coil

Section 1

The Deep TMS and H-Coil Technology

BrainsWays' 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 deeper and broader effective electric field at safe and tolerable stimulation levels.

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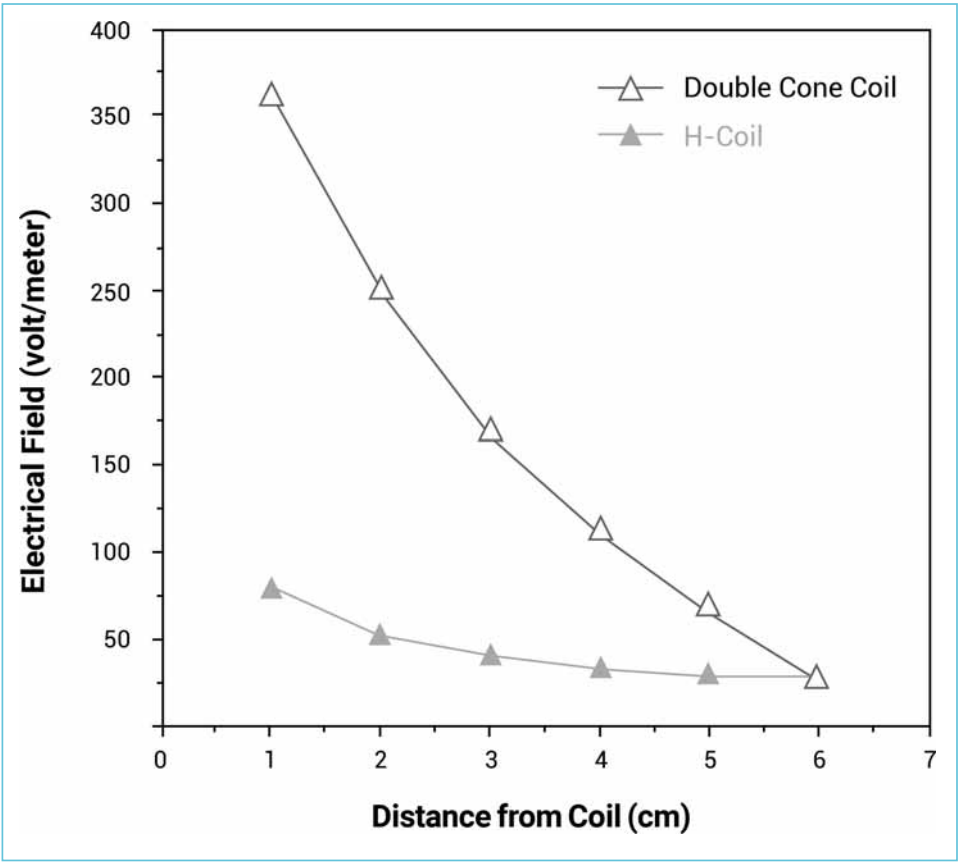
1.1	
Title:	**A Coil Design for Transcranial Magnetic Stimulation of Deep Brain Regions**
Publication & Date:	**Journal of Clinical Neurophysiology 19(4):361-370 (2002)**
Investigators:	**Y Roth, A Zangen, M Hallett**

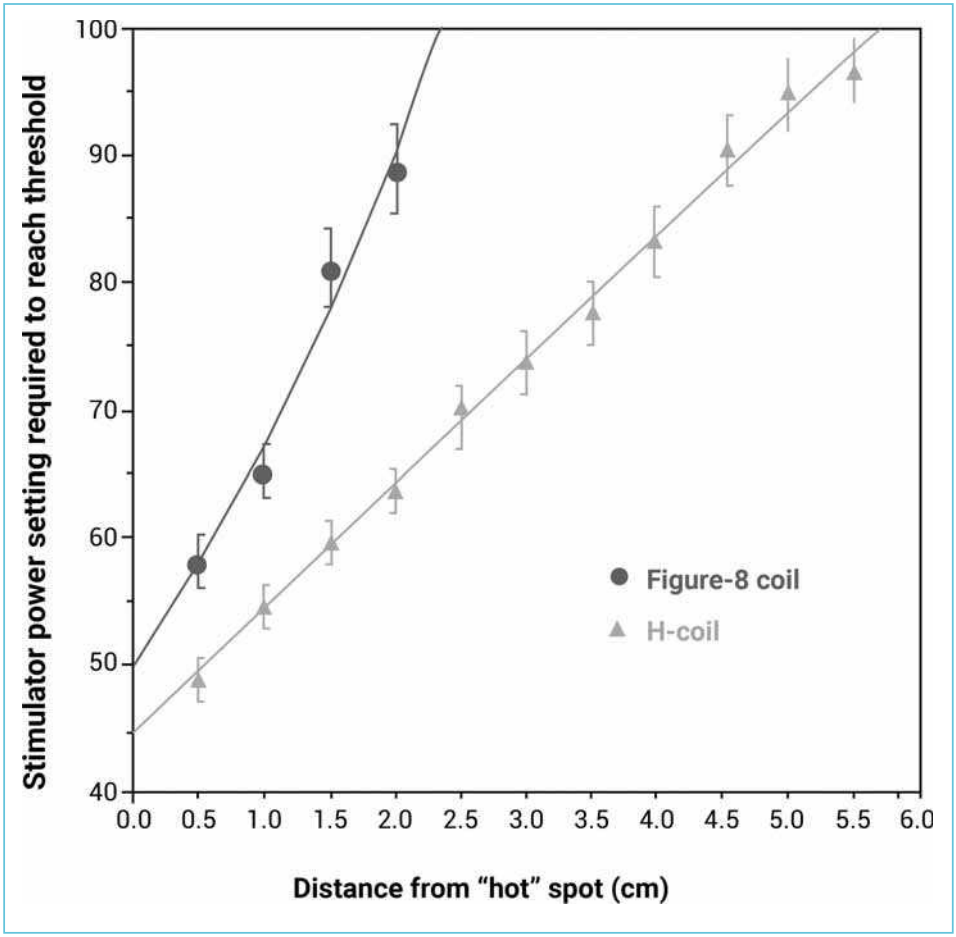
Background:	Noninvasive magnetic stimulation of the human central nervous system has been used in research and the clinic for several years. However, the coils used thus far stimulate mainly the cortical brain regions and could not stimulate deeper brain regions directly.
Objective:	The purpose of the study was to develop a coil to stimulate deep brain regions.
Methods:	Stimulation of the nucleus accumbens and the nerve fibers connecting the prefrontal cortex with the nucleus accumbens was one major target of the authors' coil design. Numeric simulations of the electrical field induced by several types of coils were performed and accordingly an optimized coil for deep brain stimulation was designed. The electrical field induced by the new coil design was measured in a phantom brain and compared with the double-cone coil.
Results:	The numeric simulations show that the electrical fields induced by various types of coils are always greater in cortical regions (closer to the coil placement); however, the decrease in electrical field within the brain (as a function of the distance from the coil) is markedly slower for the new coil design. The phantom brain measurements basically confirmed the numeric simulations.
Conclusions:	The suggested coil is likely to have the ability of deep brain stimulation without the need to increase the intensity to levels that stimulate cortical regions to a much higher extent and possibly cause undesirable side effects.



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.

1.2	
Title:	**Transcranial Magnetic Stimulation of Deep Brain Regions: Evidence for Efficacy of the H-Coil**
Publication & Date:	**Journal of Clinical Neurophysiology 116(4):775-779 (2005)**
Investigators:	**A Zangen, Y Roth, B Voller, M Hallett**

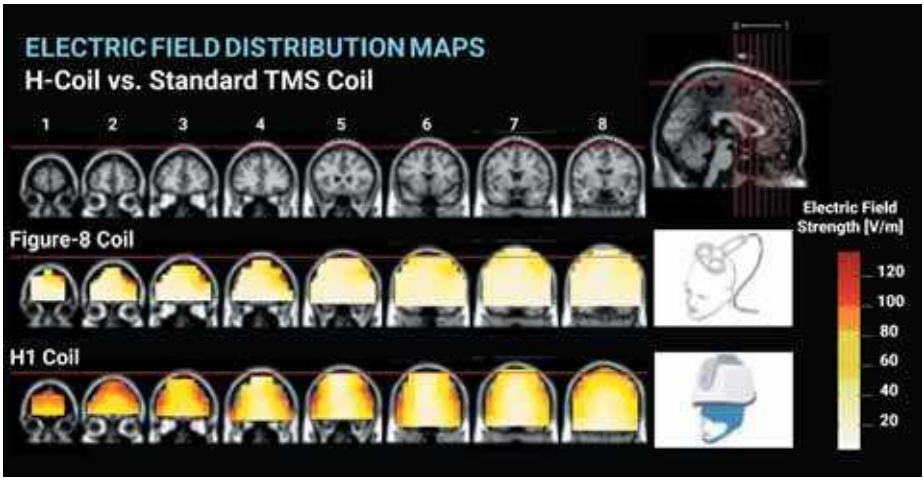
Background:	Standard coils used in research and the clinic for noninvasive magnetic stimulation of the human brain are not capable of stimulating deep brain regions directly. As the fields induced by these coils decrease rapidly as a function of depth, only very high intensities would allow functional stimulation of deep brain regions and such intensities would lead to undesirable side effects. The authors designed a coil based on numerical simulations and phantom brain measurements that allows stimulation of deeper brain regions, termed the Hesed coil (H-coil).
Objective:	To test the efficacy and some safety aspects of the H-coil on healthy volunteers.
Methods:	The H-coil was compared to a regular figure-8 coil in 6 healthy volunteers by measuring thresholds for activation of the abductor pollicis brevis (APB) representation in the motor cortex as a function of distance from each of the coils.
Results:	The rate of decrease in the coil intensity as a function of distance is markedly slower for the H-coil. The motor cortex could be activated by the H-coil at a distance of 5.5 cm compared to 2 cm with the figure-8 coil.
Conclusions:	This study indicates that the H-coil is likely to have the ability of deep brain stimulation and without the need of increasing the intensity to extreme levels that would cause a much greater stimulation in cortical regions.



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.

1.3		
	Title:	**Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils**
	Publication & Date:	**Journal of Clinical Neurophysiology 24(1):31-38 (2007)**
	Investigators:	**Y Roth, A Amir, Y Levkovitz, A Zangen**

Background:	The H-coils are a novel development in transcranial magnetic stimulation (TMS), designed to achieve effective stimulation of deep neuronal regions without inducing unbearable fields cortically, thus broadly expanding the potential feasibility of TMS for research and for treating various neurologic disorders.
Objective:	To compare the field distribution of two H-coil versions, termed H1 and H2, and of a standard figure-8 coil.
Methods:	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 in ahead model filled with physiologic saline solution.
Results:	With stimulator output at 120% of the hand motor threshold, suprathreshold field is induced by the H1-coil at lateral and medial frontal regions at depths of up to 4 to 5 cm, 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.
Conclusions:	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, whereas the depth penetration in each region can be controlled either by adjusting the stimulator output, and/or by varying the distance between various coil elements and the skull.



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.

1.4	
Title:	**Safety and Characterization of a Novel Multi-Channel TMS Stimulator**
Publication & Date:	**Brain Stimulation 7(2): 194-205 (2014)**
Investigators:	**Roth Y, Levkovitz Y, Pell GS, Ankry M, Zangen A.**

Background:	Stimulator technology has not changed significantly since the early days of TMS. Currently available TMS stimulators have a single channel operating a single coil.
Objective:	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.
Methods:	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.
Results:	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.
Conclusions:	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.

1.5	
Title:	**Modelling of the Electric Field Distribution in Deep Transcranial Magnetic Stimulation in the Adolescence, in the Adulthood, and in the Old Age**
Publication & Date:	**Computational and Mathematical Methods in Medicine 9039613 (2016)**
Investigators:	**S Fiocchi, M Longhi, P Ravazzani, Y Roth, A Zangen, M Parazzini**

Background:	In the last few years, deep transcranial magnetic stimulation (dTMS) has been used for the treatment of depressive disorders, which affect a broad range of age populations, from adolescents to aging people. To facilitate its clinical application, particular shapes of coils, including the so-called Hesed (H) coils, were designed.
Objective:	This study aims to provide a picture of the distribution of the induced electric field in four realistic human models of different ages and gender.
Methods:	The electric field distributions were calculated by using numerical techniques in the brain structures potentially involved in the progression of the disease and were quantified in terms of both amplitude levels and focusing power of the distribution.
Results:	The results highlight how the chosen H7 coil is able to induce the maxima levels of E mainly in the prefrontal cortex, particularly for the younger model. Moreover, growing levels of induced electric fields with age were found by going in deep in the brain, as well as a major capability to penetrate in the deepest brain structures with an electric field higher than 50%, 70%, and 90% of the peak found in the cortex.
Conclusions:	This study shows that H7 coil is able to induce levels of electric field in the typical brain target areas for the treatment of depressive disorders comparable with the ones found for other H-family coils. This conclusion is still valid also considering the effect of age.

1.6	
Title:	**Deep Transcranial Magnetic Stimulation for the Addiction Treatment: Electric Field Distribution Modeling**
Publication & Date:	**Journal of Electromagnetics, RF, and Microwaves in Medicine and Biology 2:242-248 (2018)**
Investigators:	**S Fiocchi, E Chiaramello, L Luzi, A Ferrulli, M Bonato, Y Roth, A Zangen, P Ravazzani**

Background:	Deep Transcranial Magnetic Stimulation (dTMS) is a neurostimulation technique for deep brain structures that has recently been successfully applied in the clinic for treatment of addiction. In contrast to conventional magnetic stimulation, which uses planar coils (figure 8) to target specific superficial regions of the brain, dTMS requires the design of complex three-dimensional coils in order to induce deeply penetrating fields.
Objective:	Recent clinical studies have focused on the use of H4 coils, which utilizes a left-right symmetric structure for bilateral stimulation of the prefrontal cortex and demonstrated efficacy for therapy such as smoking cessation. The mechanism of activity, however, remains poorly understood, in part because the affected regions of the brain are not known in detail.
Methods:	In this work the authors quantified both electric field E distribution and its penetration depth in prefrontal cortex, induced by the H4 coil that was designed for the addiction treatment and by the traditional figure 8 coil for comparison.
Results:	The results show that H4 coil preferentially targets insula and cingulate cortex. Moreover, it can induce in the deepest tissues E amplitude ranging between the 20-40% of the cortical peak and it can penetrate the cortex up to 4 cm with E>50% of the cortical peak, thus noticeably increasing the penetration depth of the traditional TMS systems.
Conclusions:	This study supports the use of H4 for targeting cortical and subcortical structures involved in addictive disorders.

Section 2

Pre-Clinical Studies

BrainsWay 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.

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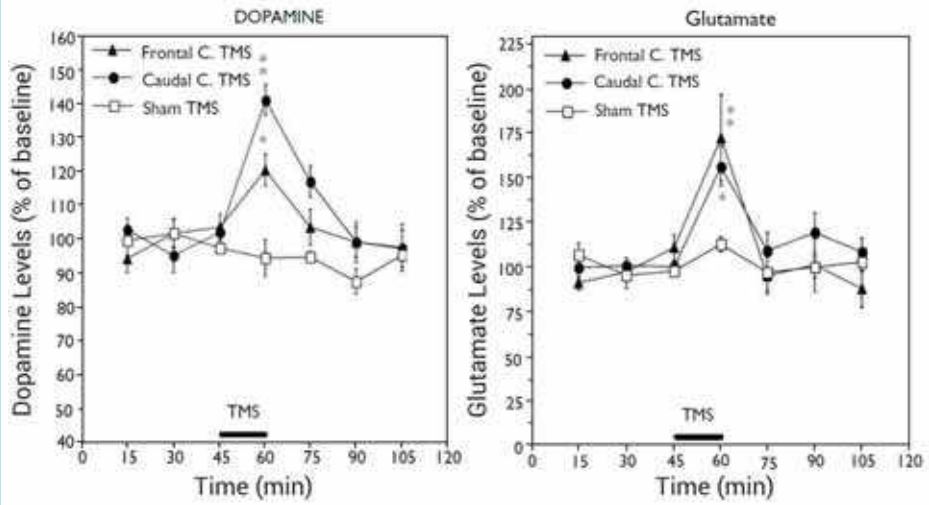
2.1	
Title:	**Transcranial Magnetic Stimulation Induces Increases in Extracellular Levels of Dopamine and Glutamate in the Nucleus Accumbens**
Publication & Date:	**Neuroreport 13(18):2401-2405 (2002)**
Investigators:	**A Zangen, K Hyodo**

Background:	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.
Objective:	Since the nucleus accumbens is a major region implicated in reward circuitry and depressive disorders, the investigators used the microdialysis technique to study some of the neurochemical changes induced in that region during and after acute TMS.
Methods:	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.
Results:	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 such difference was not observed for glutamate levels.
Conclusions:	The changes in dopamine and glutamate extracellular levels in the nucleus accumbens may play a role in the antidepressant effect of TMS and it is therefore suggested that the effect of stimulation over caudal cortical sites on depressive patients will be examined.

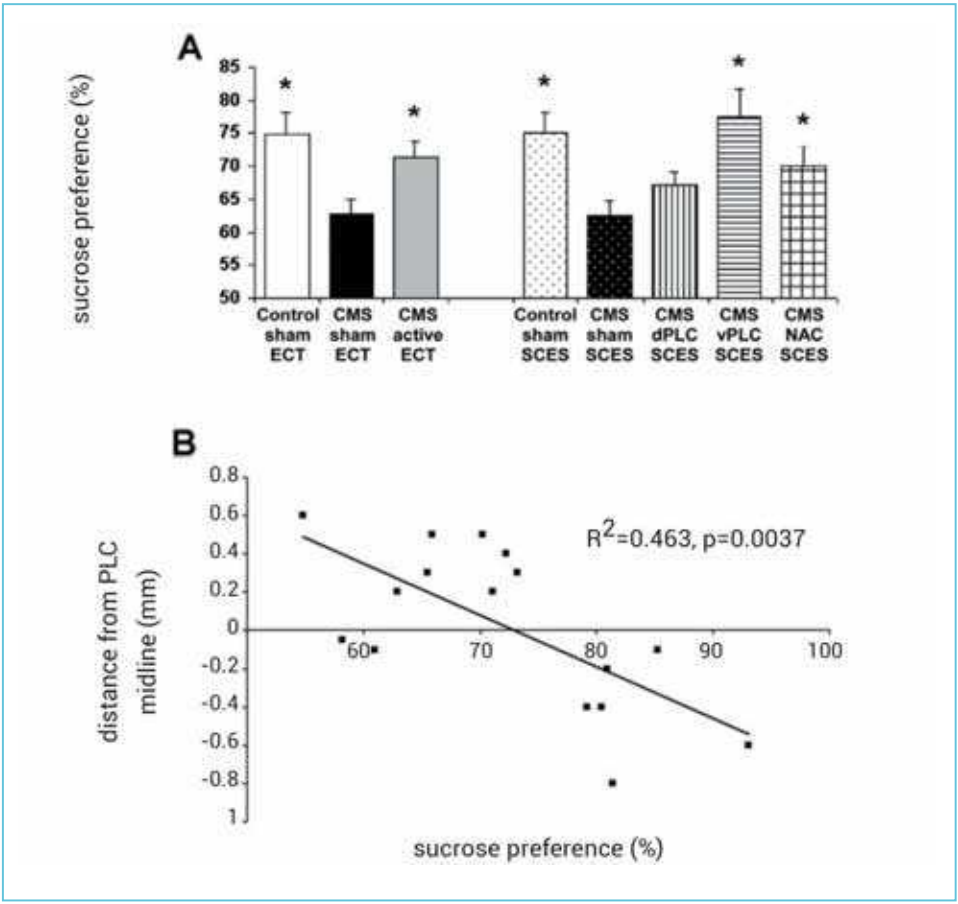


Effect of TMS over the frontal or the caudal cortex on extracellular levels of dopamine and glutamate in the rat nucleus accumbens.

2.2	
Title:	**Site-Specific Antidepressant Effects of Repeated Subconvulsive Electrical Stimulation: Potential Role of Brain-Derived Neurotrophic Factor**
Publication & Date:	**Biological Psychiatry 67(2): 25-132 (2010)**
Investigators:	**R Gersner, E Toth, M Isserles, A Zangen**

Background:	Electroconvulsive therapy (ECT) is a very effective treatment for major depression. This method involves robust nonfocal stimulation of the brain and can normalize both neurochemical alterations and depressive behavior in animal models. The authors hypothesized that short stimulation sessions of specific reward-related brain sites might induce similar effects.
Objective:	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).
Methods:	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 transcranial magnetic stimulation 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.
Results:	Repeated SCES of either the nucleus accumbens (NAC) or the ventral but not the dorsal prelimbic cortex (PLC) reversed the main behavioral deficit and the reduction of BDNF levels in the hippocampus that were induced by CMS. The ECT was more effective because it also normalized a behavioral deficit associated with anxiety but produced a learning and memory impairment.

Conclusions: This study implicated the ventral PLC and the NAC in the pathophysiology of depressive behavior and suggests that local intermittent SCES can induce an antidepressant effect similar to that of ECT, without the cognitive impairment caused by the convulsive treatment.

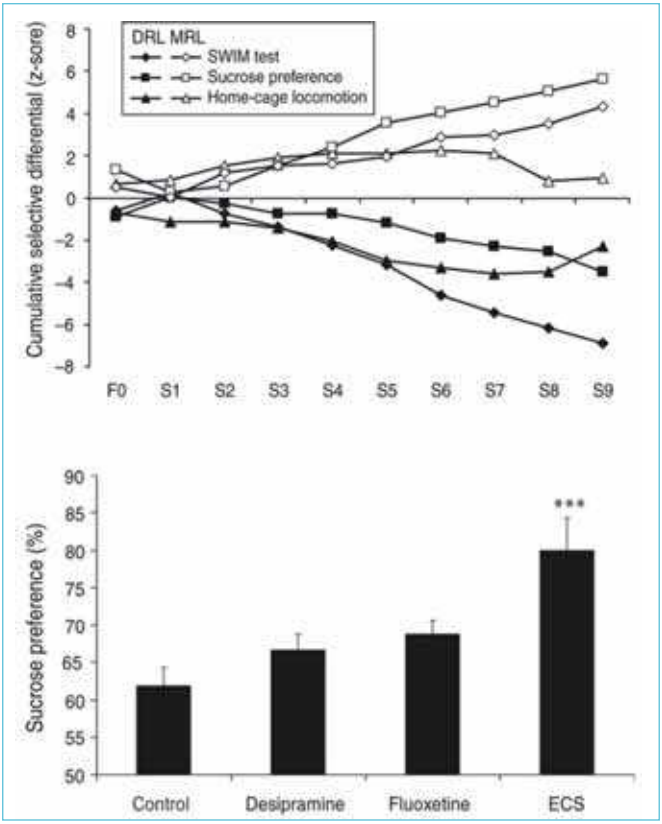


Sucrose preference test. (A) Means + SEMs of the percentage of sucrose (.2%) intake, as calculated from total liquid consumption in the ECT (left) or SCES (right) groups. (B) Sucrose preference as a function of electrode depth in the prelimbic cortex relative to the horizontal midline of the prelimbic cortex (PLC). Deeper subconvulsive electrical stimulation can be seen to elicit greater reductions in depressive behavior. *p < .05, as revealed by Dunnet's post hoc comparisons with the corresponding CMS sham group (ECT or SCES). dPLC, dorsal prelimbic cortex; vPLC, ventral prelimbic cortex; NAC, nucleus accumbens

2.3	
Title:	**Inherited Behaviors, BDNF Expression and Response to Treatment in a Novel Multifactorial Rat Model for Depression**
Publication & Date:	**International Journal of Neuropsychopharmacology 17(6):945-955 (2014)**
Investigators:	**R Gersner, R Gal, O Levit, H Moshe, A Zangen**

Background:	Major depressive disorder (MDD) is a common and devastating mental illness behaviorally characterized by various symptoms, including reduced motivation, anhedonia and psychomotor retardation. Although the etiology of MDD is still obscure, a genetic predisposition appears to play an important role.
Objective:	This study used, for the first time, a multifactorial selective breeding procedure to generate a distinct 'depressed' rat line (DRL).
Methods:	The selection of the rat line 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:	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.

Conclusions: 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.

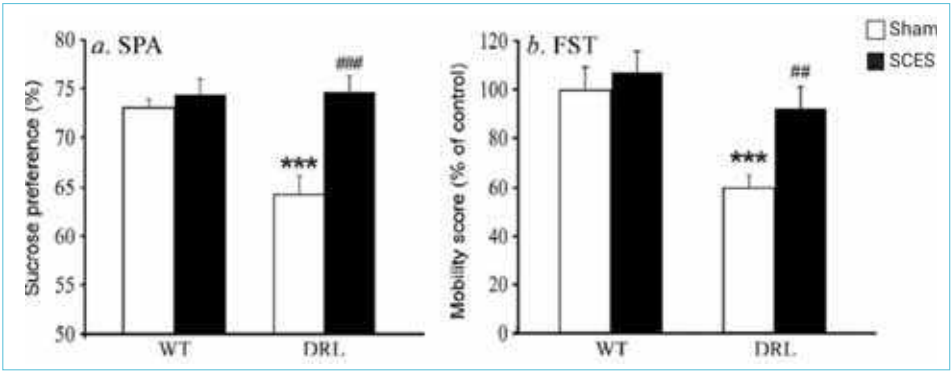


Electroconvulsive shocks (ECS) but not desipramine or fluoxetine normalizes depressive-like behavior in depressed rat line (DRL) rats.

2.4	
Title:	**Prelimbic Stimulation Ameliorates Depressive-Like Behaviors and Increases Regional BDNF Expression in a Novel Drug-Resistant Animal Model of Depression**
Publication & Date:	**Brain Stimulation 9(2):243-250 (2016)**
Investigators:	**H Moshe, R Gal, N Barnea-Ygael, T Gulevsky, U Alyagon, A Zangen**

Background:	Approximately one third of all major depression patients fail to respond to conventional pharmacological antidepressants, and brain stimulation methods pose a promising alternative for this population. Recently, based on repeated multifactorial selective inbreeding of rats for depressive-like behaviors, we introduced a novel animal model for MDD. Rats from this Depressive Rat Line (DRL) exhibit inherent depressive-like behaviors, which are correlated with lower levels of brain-derived neurotrophic factor (BDNF) in specific brain regions. In addition, DRL rats do not respond to antidepressant medication but respond to electroconvulsive treatment, and they can thus be utilized to test the effectiveness of brain stimulation on hereditary, medication-resistant depressive-like behaviors.
Objective:	To test the effect of sub-convulsive electrical stimulation (SCES) of the prelimbic cortex, using TMS-like temporal pattern of stimulation, on depressive-like behaviors and regional BDNF levels in DRL rats.
Methods:	SCES sessions were administered daily for 10 days through chronically implanted electrodes. Temporal stimulation parameters were similar to those used in TMS for major depression in human patients. Depressive-like behaviors were assayed after treatment, followed by brain extraction and regional BDNF measurements.
Results:	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.

Conclusions:	Brain stimulation is effective in a drug-resistant, inherited animal model for depression. BDNF alterations in specific regions may mediate different antidepressant effects.

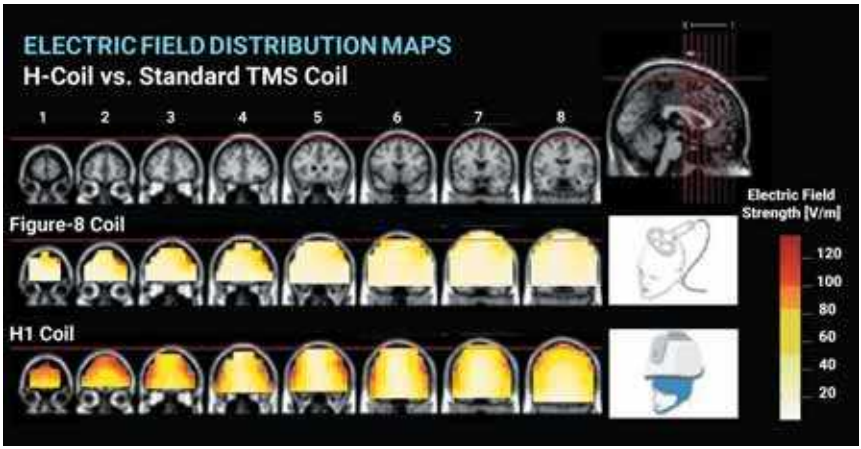


Repeated SCES treatment to the PLC normalizes inherent depressive-like behaviors in DRL rats: (a) Sucrose Preference Assay (SPA); (b) Forced Swim Test (FST)

2.5	
Title:	**Glutamate-Mediated Blood-Brain Barrier Opening: Implications for Neuroprotection and Drug Delivery**
Publication & Date:	**The Journal of Neuroscience 36(29):7727-7739 (2016)**
Investigators:	**U Vazana, R Veksler, G.S Pell, O Prager, M Fassler, Y Chassidim, Y Roth, H Shahar, A Zangen, R Raccah, E Onesti, M Ceccanti, C Colonnese, A Santoro, M Salvati, A D'Elia, V Nucciarelli, M Inghilleri, A Friedman**

Background:	The blood brain barrier is a highly selective anatomical and functional interface allowing a unique environment for neuro-glia networks. Blood-brain barrier dysfunction is common in most brain disorders and is associated with disease course and delayed complications. However, the mechanisms underlying blood-brain barrier opening are poorly understood.
Objective:	The goal of this study was to demonstrate the role of the neurotransmitter glutamate in modulating early barrier permeability in vivo.
Methods:	Using intravital microscopy and ECoG recording, the authors tested whether focally induced cortical seizures are associated with increased vascular permeability in the rat cerebral cortex. To test whether the increase in endothelial permeability was attributed to NMDA receptors, experiments were repeated with cortical perfusion of NMDA and with glutamate in the presence of an NMDA receptor antagonist. The authors then tested whether release of glutamate associated with neuronal activation using rTMS could increase barrier permeability and facilitate drug delivery into the brain. Finally, based on their pre-clinical experiments, the authors conducted a double-blind clinical trial in patients with malignant glial tumors, using contrast-enhanced magnetic resonance imaging to quantitatively assess blood-brain barrier permeability.

Results:	The authors show that recurrent seizures and the associated excessive glutamate release lead to increased vascular permeability in the rat cerebral cortex, through activation of NMDA receptors. NMDA receptor antagonists reduce barrier permeability in the peri-ischemic brain, whereas neuronal activation using high-intensity magnetic stimulation increases barrier permeability and facilitates drug delivery. Furthermore, the study demonstrates the safety of stimulation that efficiently increased blood-brain barrier permeability in 10 of 15 patients with malignant glial tumors.
Conclusions:	This study suggests a novel mechanism for the bidirectional modulation of brain vascular permeability toward increased drug delivery and prevention of delayed complications in brain disorders.

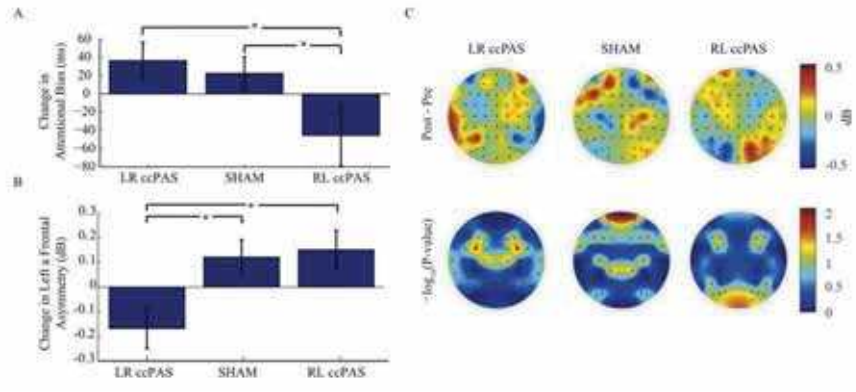


dTMS induces increase in BBB permeability in patients with malignant glial tumors. A, BBB permeability maps superimposed on T1 brain MR images in a representative patient after sham and TMS sessions. Color-coded voxels represent only those with abnormally high slope (permeability) values (ST; see Materials and Methods). B, Percentage of change in apparent permeability values for the patient shown in A. Graphs showing percentage of voxels within the ipsilateral hemisphere with abnormally high permeability after sham and real dTMS. C, Brains were manually segmented (left) to subregions reflecting the tumor bed (TB, red), peri-tumoral brain (PT, green), and ipsilateral (ipsi, blue) and contralateral (contra, yellow) hemispheres. D, Averaged percentage change in permeability (slope values) in real versus sham stimulation was calculated for each subregion (tumor bed, p=0.01; peri-tumor, p=0.05; ipsilateral, p=0.01; contralateral, p=0.009). Note that, although in all regions TMS had a significant effect, maximal change was found in the tumor bed (n=10 patients). E, Percentage change in the number of ST voxels (reflecting abnormally high permeability; see Materials and Methods) is plotted for each subregion. F, CDFs of apparent permeability (slope) values in the different subregions under sham (S) and real (R) dTMS for 10 patients. Note the shift of the curves to the right indicating increased number of voxels with high permeability values, in all regions, most prominently in the tumor bed. *p<0.05, **p<0.01.

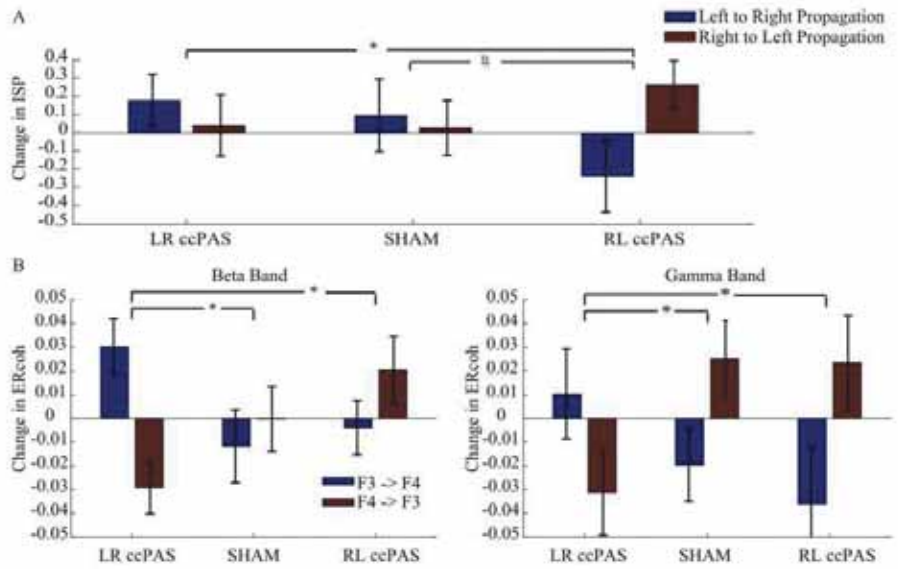
2.6		
	Title:	**Interhemispheric cortico-cortical paired associative stimulation of the prefrontal cortex jointly modulates frontal asymmetry and emotional reactivity**
	Publication & Date:	**Brain Stimulation 12(1):139-147 (2018)**
	Investigators:	**S Zibman, E Daniel, U Alyagon, A Etkin, A Zangen**

Background:	As advances in neuroimaging further our understanding of the brain's functional connectivity, neuropsychology has moved away from a regional approach of attributing behavior to a specific region towards a network approach, attributing behavior to interconnected regions. A prime example of this is the suggested relevance of frontal asymmetry of the lateral prefrontal cortex (LPFC) in emotional processing. Yet, while neuroimaging defines relevant networks, it can only establish correlations and not causality.
Objective:	This study addressed this deficiency by applying cortico-cortical paired associative stimulation (ccPAS) to twenty-seven healthy, human participants (both genders represented equally). ccPAS involves TMS applied to two brain regions contemporaneously, changing the connectivity via Hebbian mechanisms.
Methods:	The investigators evaluated modifications in connectivity following ccPAS between the right and left LPFC that are dependent on the direction of ccPAS, i.e., which hemisphere is stimulated first. Participants performed an emotional reactivity task, assessed by measuring attentional bias, and brain activity was recorded with electroencephalogram (EEG) both at rest and in response to TMS pulses.
Results:	It was found that ccPAS modulates attentional bias bidirectionally depending on the order of stimulation. Furthermore, this modulation is accompanied by a change in frontal asymmetry. Measuring the direction of the information flow using TMS evoked potentials provides evidence that ccPAS strengthens inhibition from the hemisphere stimulated first to the hemisphere stimulated second.

Conclusions: These findings provide causal evidence for the role of frontal asymmetry in emotional processing and establish ccPAS combined with the EEG measures as a tool to causally characterize functionality of neuronal circuits.



ccPAS leads to directional specific changes in both attentional bias and frontal asymmetry. (A) LR ccPAS caused an increase in attentional bias while RL ccPAS caused a decrease in attentional bias. (B) This change is associated with a change in alpha frontal asymmetry. LR ccPAS led to a negative change (Lower Alpha in the left hemisphere comparing to the right hemisphere) while RL ccPAS led to a positive change (Higher Alpha in left hemisphere comparing to right hemisphere). (C) Top panel shows the topoplots of change in asymmetry for each electrode. Asymmetry is calculated as each electrode minus its contralateral homologous pair creating a mirror image. (Electrodes on the left are left e right while electrodes on the right are right e left). Bottom panel shows the p value at each electrode. P values are shown with a minus log transform so that significant regions are in red. The effect can be seen to be clustered to the targeted prefrontal regions. Asterisks indicate significant differences (p 0.05). Error bars represent standard error. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



ccPAS Directionally Increases Interhemispheric Inhibition from H1 to H2. (A) ccPAS induces a directional increase in signal propagation between the stimulated regions exclusively in the direction of the protocol. Changes in propagation between the F3 and F4 electrodes for each protocol type. Positive changes are observed only in the direction of the protocol (LR-ISP following LR ccPAS and RL-ISP following RL ccPAS). (B) ccPAS also induces a directional increase in event related coherence in the beta (left) and gamma (right) bands. Coherence from F3 to F4 increases with LR ccPAS while F4 to F3 coherence increases with RL ccPAS. Asterisk indicate significant differences ($p<0.05$) while hash tag indicates a trend ($p<0.1$). Error bars represent standard error.

Section 3

Clinical Studies in MDD and OCD (FDA-cleared Indications)

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.

More recently, the efficacy of Deep TMS was also proven in OCD. The H-coil's design enables the targeting of deeper brain regions, such as the anterior cingulate cortex that is implicated in OCD. This differentiating quality of Deep TMS explains why it is the first ever non-invasive medical device (and the only TMS device) that is FDA cleared to treat OCD.

BrainsWay®

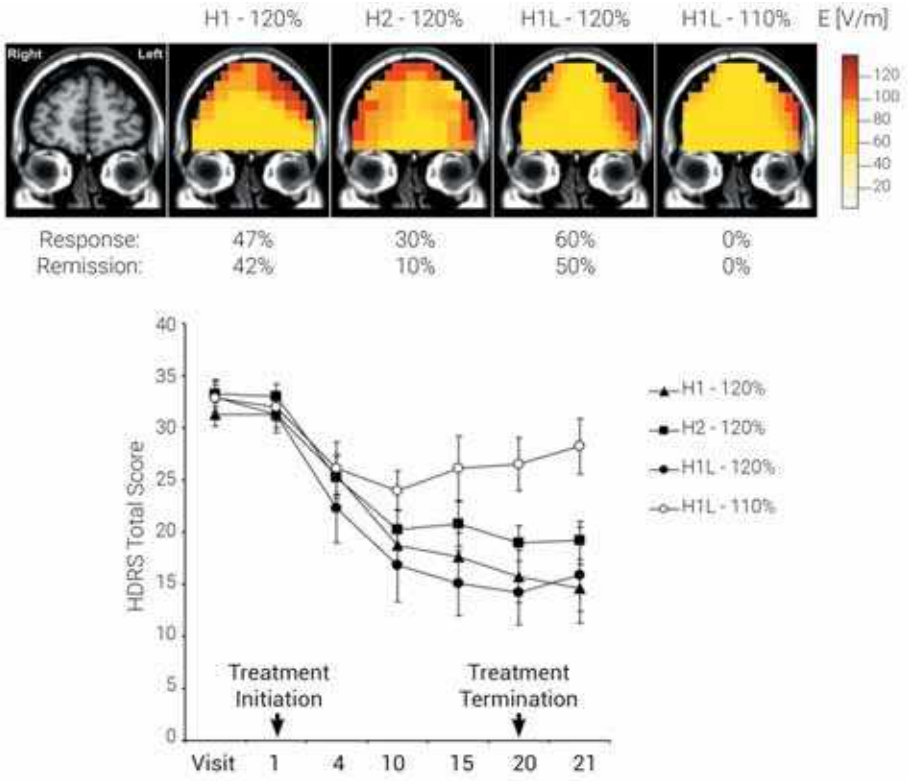
3.1		
	Title:	**A Randomized Controlled Feasibility and Safety Study of Deep Transcranial Magnetic Stimulation**
	Publication & Date:	**Clinical Neurophysiology 118(12):2730-2744(2007)**
	Investigators:	**Y Levkovitz, Y Roth, E.V Harel, Y Braw, A Sheer, A Zangen**

Background:	The H-coils are a new development in transcranial magnetic stimulation (TMS) research, allowing direct stimulation of deeper neuronal pathways than does standard TMS.
Objective:	This study assessed possible health risks, and some cognitive and emotional effects, of two H-coil versions designed to stimulate deep portions of the prefrontal cortex, using several stimulation frequencies.
Methods:	Healthy volunteers (n=32) were randomly assigned to one of four groups: each of two H-coil designs (H1/H2), standard figure-8 coil, and 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 h after the last stimulation.
Results:	The major finding of this study is that stimulation with the novel H-coils was well tolerated, with no adverse physical or neurological outcomes. Computerized cognitive tests found no deterioration in cognitive functions, except for a transient short-term effect of the H1-coil on spatial recognition memory on the first day of rTMS (but not in the following treatment days). On the other hand, spatial working memory was transiently improved by the H2-coil treatment. Finally, the questionnaires showed no significant emotional or mood alterations, except for reports on 'detachment' experienced by subjects treated with the H1-coil.
Conclusions:	This study provides additional evidence for the feasibility and safety of the two H-coil designs (H1/H2). The H-coils offer a safe new tool with potential for both research and clinical applications for psychiatric and neurological disorders.

3.2	
Title:	**Deep Transcranial Magnetic Stimulation Over the Prefrontal Cortex: Evaluation of Antidepressant and Cognitive Effects in Depressive Patients**
Publication & Date:	**Brain Stimulation 2(4):188-200 (2009)**
Investigators:	**Y Levkovitz, E.V Harel, Y Roth, Y Braw, D Most, L.N Katz, A Sheer, R Gersner, A Zangen**

Background:	Electroconvulsive therapy (ECT) is an effective alternative for pharmacotherapy in treatment-resistant depressive patients, but the side effects limit its use. Transcranial magnetic stimulation (TMS) has been proposed as a refined alternative, but most studies do not indicate that TMS is as effective as ECT for severe depression.
Objective:	The investigators of this study propose that the limited effectiveness of standard TMS resides in its superficial effect on the cortex, although much of the pathophysiology of depression is associated with deeper and larger brain regions implicated in the reward system. Therefore, in this study they tested the effectiveness and safety of a novel TMS coil, the ''H-coil,'' which enables direct stimulation of deeper brain regions, at the expense of focality.
Methods:	The antidepressant and cognitive effects induced by 4 weeks of high-frequency (20 Hz) repeated deep TMS (DTMS) over the prefrontal cortex (PFC) were examined on 65 medication-free depressive patients, who have failed to benefit from prior medications. Patients were randomly assigned to various treatment configurations, differing in stimulation intensity and laterality. Effects were assessed by the 24-item Hamilton depression rating scale (HDRS-24) and several secondary outcome measures.
Results:	A significant improvement in HDRS scores was found when high, but not low, stimulation intensity was used. Several cognitive improvements were evident, and no treatment related serious adverse events were observed.

Conclusions: This study provides additional evidence for the feasibility and safety of the two H-coil designs (H1/H2). The H-coils offer a safe new tool with potential for both research and clinical applications for psychiatric and neurological disorders associated with dysfunctions of deep brain regions.



A Response and remission rates relative to stimulation site based on phantom brain measurements. B Effect of dTMS on HDRS scores over time for each treatment group (mean+SE).

3.3		
	Title:	**Deep TMS in a Resistant Major Depressive Disorder: A Brief Report**
	Publication & Date:	**Depression and Anxiety 27(5):465-469 (2010)**
	Investigators:	**O Rosenberg, N Shoenfeld, A Zangen, M Kotler, P.N Dannon**

Background:	Repetitive transcranial magnetic stimulation (rTMS) has proven effective. Recently, a greater intracranial penetration coil has been developed.
Objective:	The study tested the efficacy of the coil in the treatment of resistant major depression.
Methods:	The study 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:	A significant improvement in HDRS scores was found when high, but not low, stimulation intensity was used. Several cognitive improvements were evident, and no treatment-related serious adverse events were observed.
Conclusions:	This study provides additional evidence for the feasibility and safety of the two H-coil designs (H1/H2). The H-coils offer a safe new tool with potential for both research and clinical applications for psychiatric and neurological disorders associated with dysfunctions of deep brain regions.

	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

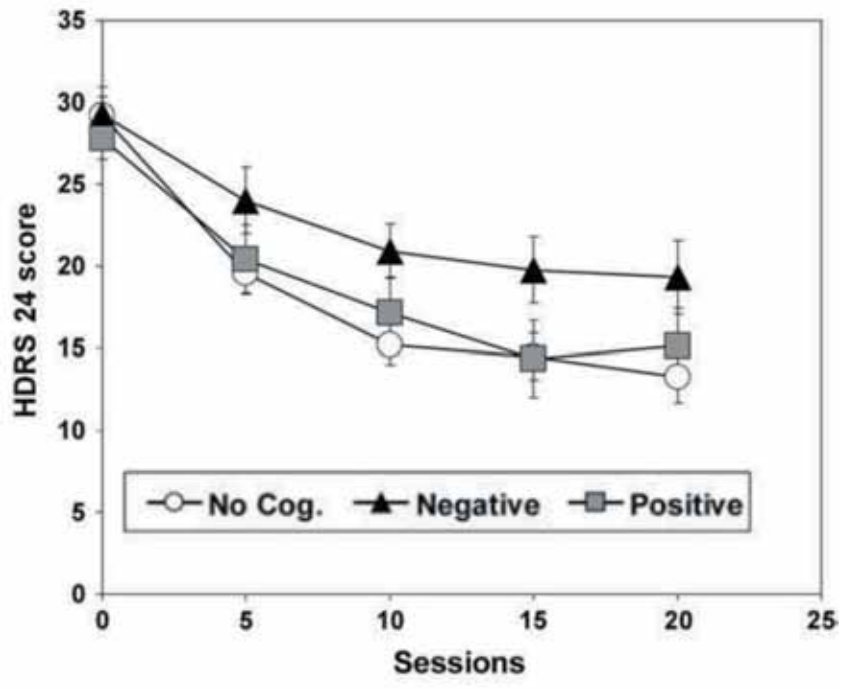
3.4	Title:	Response to Deep TMS in Depressive Patients With Previous Electroconvulsive Treatment
	Publication & Date:	Brain Stimulation 3(4):211-217 (2010)
	Investigators:	O Rosenberg, A Zangen, R Stryjer, M Kotler, P.N Dannon

Background:	The efficacy of transcranial magnetic stimulation (TMS) in the treatment of major depression has already been shown. Novel TMS coils allowing stimulation of deeper brain regions have recently been developed and studied.
Objective:	This study aimed at exploring the possible efficacy of deep TMS in patients with resistant depression, who previously underwent electroconvalsive therapy (ECT).
Methods:	Using Brainsway's deep TMS H1 coil, six patients who previously underwent ECT, were treated with 120% power of the motor threshold at a frequency of 20 Hz. Patients underwent five sessions per week, up to 4 weeks. Before the study, patients were evaluated using the Hamilton depression rating scale (HDRS, 24 items), the Hamilton anxiety scale, and the Beck depression inventory and were again evaluated after 5, 10, 15, and 20 daily treatments. Response to treatment was considered a reduction in the HDRS of at least 50%, and remission was considered a reduction of the HDRS-24 below 10 points.
Results:	Two of six patients responded to the treatment with deep TMS, including one who achieved full remission.
Conclusions:	The results suggest the possibility of a subpopulation of depressed patients who may benefit from deep TMS treatment, including patients who did not respond to ECT previously. However, the power of the study is small and similar larger samples are needed.

3.5	
Title:	**Cognitive-Emotional Reactivation During Deep Transcranial Magnetic Stimulation Over the Prefrontal Cortex of Depressive Patients Affects Antidepressant Outcome**
Publication & Date:	**Journal of Affective Disorders 128(3):235-242 (2011)**
Investigators:	**M Isserles, O Rosenberg, P Dannon, Y Levkovitz, M Kotler, F Deutsch, B Lerer, A Zangen**

Background:	Transcranial magnetic stimulation (TMS) enables non-surgical activation of specific brain areas. TMS over the prefrontal cortex (PFC) is emerging as a significant tool that can augment or replace non/partially effective antidepressant medications. Deep TMS (dTMS) utilizes newly developed coils that enable effective stimulation of deeper cortical layers involved in the pathophysiology of depression.
Objective:	This study aimed to assess the H1-DTMS coil as an add-on to antidepressants in treating patients with major depression. We also intended to evaluate whether the antidepressant outcome of DTMS treatment is affected by a cognitive-emotional procedure performed during stimulation.
Methods:	57 patients were enrolled in the study that included 4 weeks of daily 20 Hz stimulation sessions and additional 4 weekly sessions as a short maintenance phase. Two subgroups of patients received either positive or negative cognitive-emotional reactivation along with the stimulation sessions.
Results:	21 of 46 patients (46%) who received at least 10 stimulation sessions achieved response (improvement of 50% in the Hamilton Depression Rating Scale (HDRS)) and 13 of them (28%) achieved remission (HDRS-24 10) by the end of the daily treatment phase. Improvements were smaller in the negatively reactivated group and Beck Depression Inventory scores were not significantly improved in this group.

Conclusions:	dTMS over the PFC proved to be safe and effective in augmenting antidepressant medications. Negative cognitive-emotional reactivation can disrupt the therapeutic effect of dTMS. A large sham controlled study is required to further establish the effectiveness of dTMS as an augmentation treatment and the role of cognitive reactivation during stimulation.



Time course of DTMS effect on depressive symptoms. Panel A depicts the 24 item Hamilton Depression Rating Scale (HDRS-24) change over the four weeks of acute treatment course for the negative, positive and non-provocated groups.

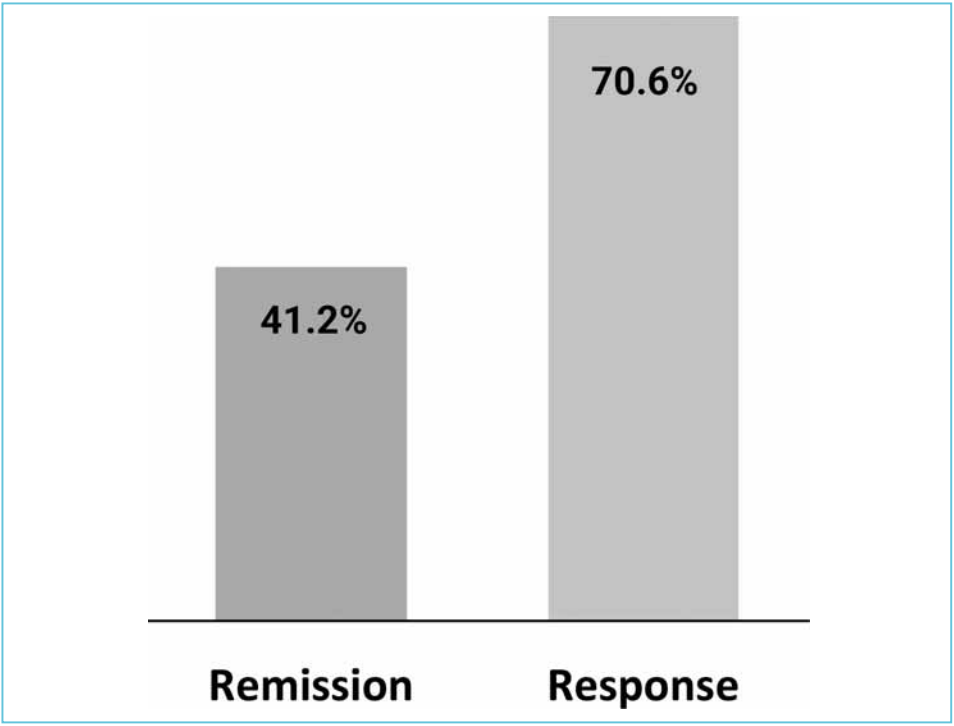
3.6	
Title:	**Effectiveness of a Second Deep TMS in Depression: A Brief Report**
Publication & Date:	**Progress in Neuro-Psychopharmacology & Biological Psychiatry 35(4):1041-1044 (2011)**
Investigators:	**O Rosenberg, M Isserles, Y Levkovitz, M Kotler, A Zangen, P.N Dannon**

Background:	Deep transcranial magnetic stimulation (dTMS) is an emerging and promising treatment for major depression. In our study, we explored the effectiveness of a second antidepressant course of dTMS in major depression.
Objective:	To evaluate whether a second course of dTMS would be effective.
Methods:	Eight depressive patients who relapsed after a previous successful deep TMS course expressed their wish to be treated again. Upon their request, they were recruited and treated with 20 daily sessions of dTMS at 20 Hz using the Brainsway's H1 coil. The Hamilton depression rating scale (HDRS), Hamilton anxiety rating scale (HARS) and the Beck depression inventory (BDI) were used weekly to evaluate the response to treatment.
Results:	Similar to the results obtained in the first course of treatment, the second course of treatment (after relapse) induced significant reductions in HDRS, HARS and BDI scores, compared to the ratings measured prior to treatment. The magnitude of response in the second course was smaller relative to that obtained in the first course of treatment.
Conclusions:	These results suggest that depressive patients who previously responded well to deep TMS treatment are likely to respond again. However, the slight reduction in the magnitude of the response in the second treatment raises the question of whether tolerance or resistance to this treatment may eventually develop.

3.7	
Title:	**Augmenting Antidepressants with Deep Transcranial Magnetic Stimulation (dTMS) in Treatment-Resistant Major Depression**
Publication & Date:	**World Journal of Biological Psychiatry 15(7):570-578 (2014)**
Investigators:	**M.T Berlim, F Van den Eynde, S Tovar-Perdomo, E Chachamovich, A Zangen, G Turecki**

Background:	Deep transcranial magnetic stimulation (dTMS) has been shown to be efficacious and relatively safe for major depressive disorder (MDD). However, its clinical utility as an augmenting strategy for treatment-resistant depression (TRD) remains unexplored.
Objective:	To evaluate the clinical utility of dTMS as an augmenting strategy for patients with TRD.
Methods:	In an open label trial, 17 outpatients with severe TRD received 4 weeks of daily high frequency dTMS over the left dorsolateral prefrontal cortex. Depressive and anxious symptoms, suicidality and quality of life (QOL) were measured at baseline (i.e., in the week prior to the start of the dTMS treatment) and at week 5 (i.e., in the week following the end of the dTMS treatment). Primary outcome measures were rates of response and remission at week 5 using an intention-to-treat approach.
Results:	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 (with hedges' g estimates ranging from 0.6 to 1.72), as well as four of the five QOL domain scores (i.e., global, psychological, environmental and social). Finally, two patients dropped out of the study at week 1 because of significant scalp discomfort during stimulation.

Conclusions:	This study suggests that dTMS, when used as an augmenting strategy for antidepressants in severe TRD, is efficacious, safe and relatively well tolerated. However, controlled studies with larger samples are needed to confirm and expand these preliminary findings.

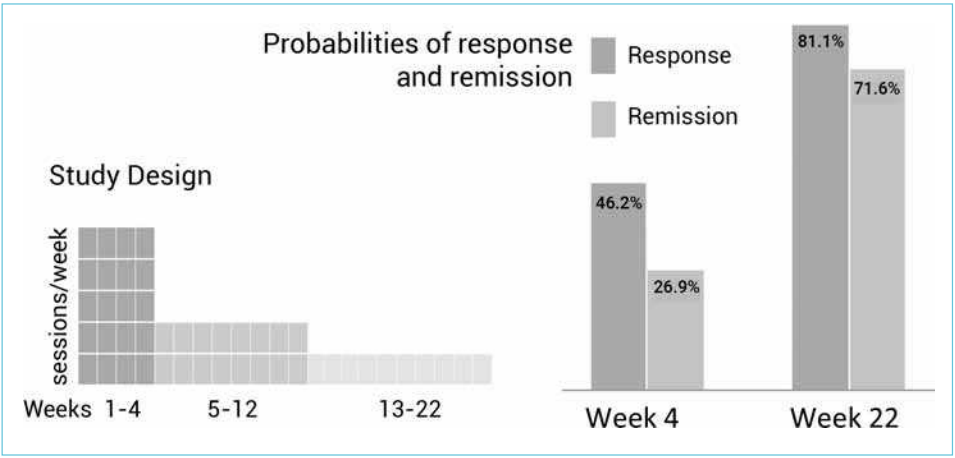


Remission and response rates at the end of the acute treatment (4 weeks).

3.8	
Title:	**H-coil Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Major Depressive Disorder: An 18-week Continuation Safety and Feasibility Study**
Publication & Date:	**The World Journal of Biological Psychiatry 15(4): 298-306 (2014)**
Investigators:	**E.V Harel, L Rabany, L Deutsch, Y Bloch, A Zangen, Y Levkovitz**

Background:	Evidence has shown that repetitive transcranial magnetic stimulation (rTMS) can be effective as an acute treatment for major depressive disorder (MDD). However, few studies have examined the safety and feasibility of rTMS as a long-term\continuation treatment. Deep-TMS is a novel tool enabling deeper stimulation than standard coils.
Objective:	This study examined the safety and feasibility of repetitive deep-TMS continuation treatment for MDD over the course of 18 weeks, following 4 weeks of acute treatment.
Methods:	A total of 29 MDD patients were enrolled in the study. rTMS sessions (20 Hz) were given for a total of 22 weeks, divided into: 4 weeks of acute daily treatments, followed by 18 weeks of continuation treatments. Clinical evaluations were performed weekly throughout the study.
Results:	A significant decrease from baseline in Hamilton Depression Rating Scale (HDRS) score was found at the end of the acute phase, and maintained throughout the study ($P<0.0001$). The Kaplan-Meier estimated probability of response was 46.15% (SE=9.78%) at the end of the acute phase, and 81.12% (SE=9.32%) at the end of the study (22 weeks). probability of remission at the end of the acute phase was 26.92% (SE=8.70%) and 71.45% (SE=10.99%) at the end of the study. Response in the acute phase was indicative of response in the continuation phases. The procedure was generally well tolerated and no adverse events were reported.

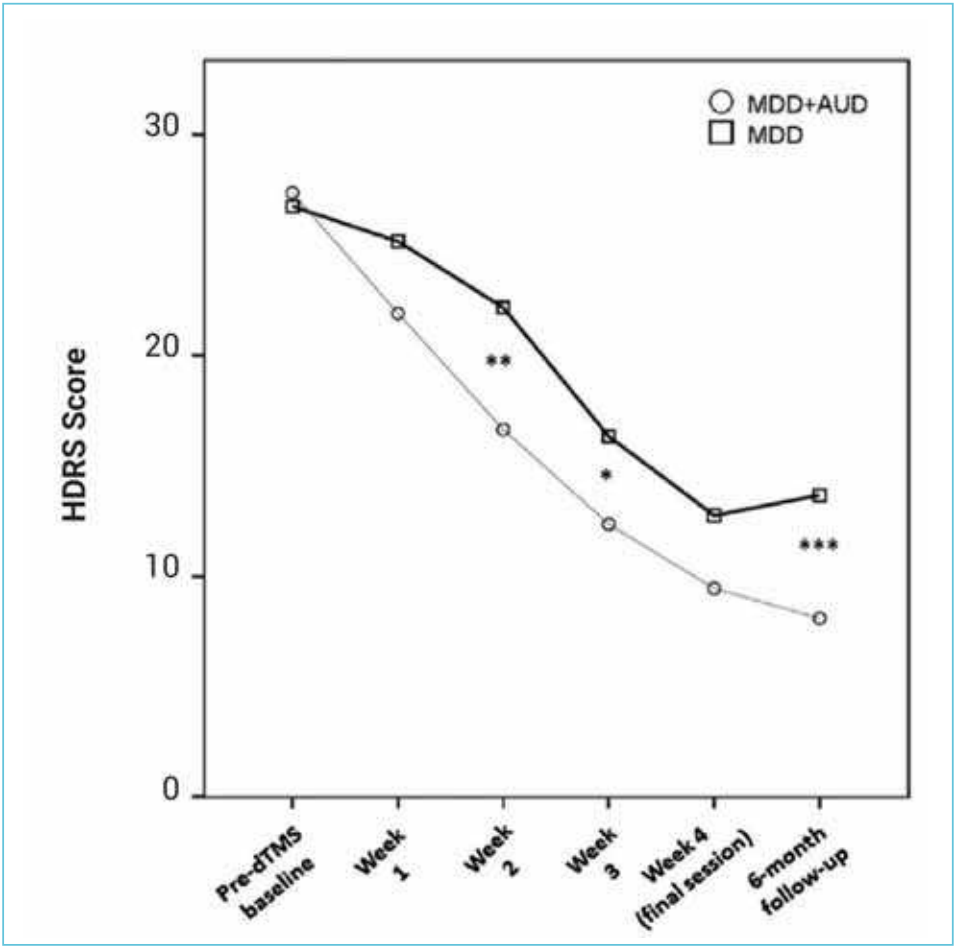
Conclusions:	The results suggest that H-coil deep TMS administered continuation treatment can help maintain an antidepressant effect for 18 weeks, following 4 weeks of acute treatment.



3.9	
Title:	**Antidepressant Effectiveness of Deep Transcranial Magnetic Stimulation (dTMS) in Patients With Major Depressive Disorder (MDD) With or Without Alcohol Use Disorders (AUDs): A 6-month, Open Label, Follow-up Study**
Publication & Date:	**Journal of Affective Disorders 174:57-63 (2015)**
Investigators:	**C Rapinesi, M Curto, G.D Kotzalidis, A Del Casale, D Serata, V.R Ferri, S D Pietro, P Scatena, F.S Bersani, R.N Raccah, V Digiacomantonio, S Ferracuti, G Bersani, A Zangen, G Angeletti, P Girardi**

Background:	Co-occurrence of Major Depressive (MDD) and Alcohol Use Disorders (AUDs) is frequent, causing more burden than each disorder separately. The dorsolateral prefrontal cortex (DLPFC) is critically involved in both mood and reward and dysfunctional in both conditions.
Objective:	The investigators aimed to evaluate the effects of dTMS stimulation of bilateral DLPFC with left prevalence in patients with MDD with or without concomitant AUD.
Methods:	Twelve MDD patients and 11 with concomitant MDD and AUD (MDD+AUD) received 20 dTMS sessions. Clinical status was assessed through the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impressions severity scale (CGIs), craving through the Obsessive-Compulsive Drinking Scale (OCDS) in MDD+AUD, and functioning with the Global Assessment of Functioning (GAF).
Results:	There were no significant differences between the two groups in sociodemographic (age, sex, years of education and duration of illness) and baseline clinical characteristics, including scores on assessment scales. Per cent 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.

Conclusions:	High frequency bilateral DLPFC dTMS with left preference was well tolerated and effective in patients with MDD, with or without AUD. The antidepressant effect of dTMS is not affected by alcohol abuse in patients with depressive episodes. The potential use of dTMS for mood modulation as an adjunct to treatment in patients with a depressive episode, with or without alcohol abuse, deserves further investigation.

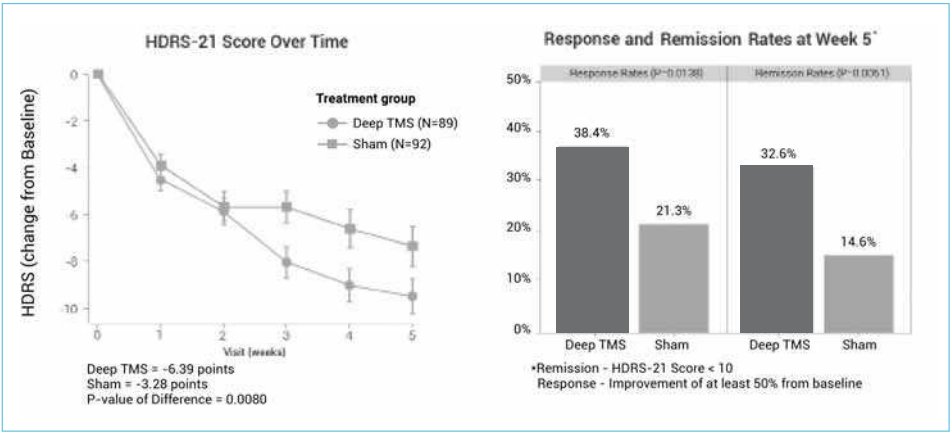


Comparison of the HDRS total score during the study between the MDD+AUD and MDD-only groups. *p<0.05; **p<0.02; ***p<0.01.

3.10	
Title:	**Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Major Depression: A Prospective Multicenter Randomized Controlled Trial**
Publication & Date:	**World Psychiatry 14(1):64-73 (2015)**
Investigators:	**Y Levkovitz, M Isserles, F Padberg, S.H Lisanby, A Bystritsky, G Xia, A Tendler, Z.J Daskalakis, J.L Winston, P Dannon, H.M Hafez, I.M Reti, O.G Morales, T.E Schlaepfer, E Hollander, J.A Berman, M.M Husain, U Sofer, A Stein, S Adler, L Deutsch, F Deutsch, Y Roth, M.S George, A Zangen**

Background:	Major depressive disorder (MDD) is a prevalent and disabling condition, and many patients do not respond to available treatments. Deep transcranial magnetic stimulation (dTMS) is a new technology allowing non surgical stimulation of relatively deep brain areas.
Objective:	This was the first double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS in MDD. This study led to FDA clearance of the Brainsway dTMS device (FDA 510(k) Number K122288).
Methods:	212 MDD outpatients, aged 22-68 years, who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments during the current episode were recruited. They were randomly assigned to monotherapy with active or sham dTMS. Twenty sessions of dTMS (18 Hz over the prefrontal cortex) were applied during 4 weeks acutely, and then biweekly for 12 weeks. Primary and secondary efficacy endpoints were the change in the Hamilton Depression Rating Scale (HDRS-21) score and response/remission rates at week 5, respectively.
Results:	dTMS induced a 6.39 points improvement in HDRS-21 scores, while a 3.28 points improvement was observed in the sham group (p=0.008), resulting in a 0.76 effect size. Response and remission rates were higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, p=0.013; remission: 32.6 vs. 14.6%, p=0.005). These differences between active and sham treatment were stable during the 12-week maintenance phase. dTMS was associated

	with few and minor side effects apart from one seizure in a patient where a protocol violation occurred.
Conclusions:	These results suggest that dTMS constitutes a novel intervention in MDD, which is efficacious and safe in patients not responding to antidepressant medications, and whose effect remains stable over 3 months of maintenance treatment.



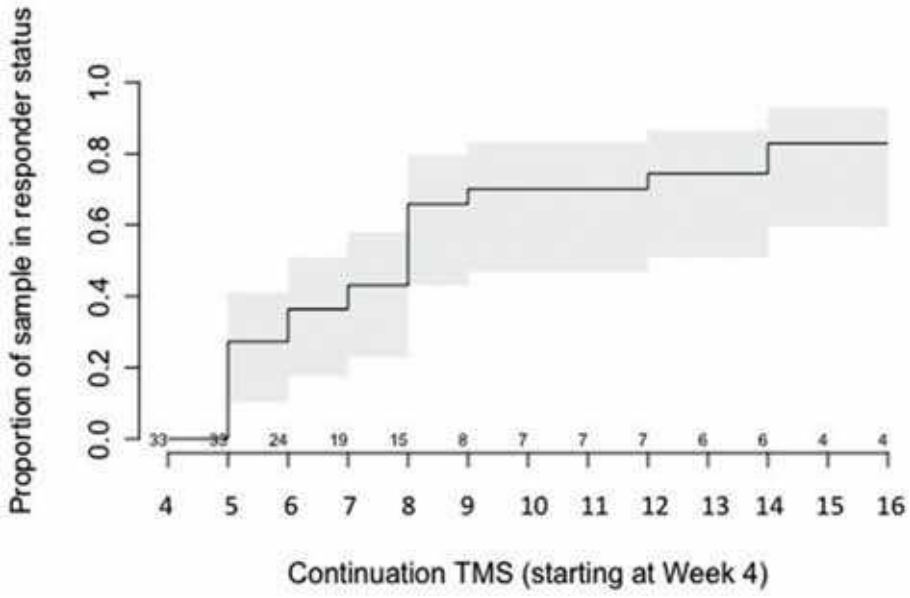
3.11	Title:	**Deep Transcranial Magnetic Stimulation (DTMS) in the Treatment of Major Depression: An Exploratory Systematic Review and Meta-analysis**
	Publication & Date:	**Journal of Affective Disorders 187:73-83 (2015)**
	Investigators:	**K.K Kedzior, H.M Gellersen, A.K Brachetti, M.T Berlim**

Background:	Deep transcranial magnetic stimulation (DTMS) is a relatively new, non-invasive method of stimulating larger and, presumably, deeper brain regions.
Objective:	This study investigated if DTMS delivered with H-coils has acute antidepressant effects in major depression using a systematic literature review and a quantitative meta-analysis.
Methods:	Seventeen studies on 'DTMS or H-coil' and 'depression' were identified on Medline, PsycInfo, and Google Scholar (until November 2014). Data from nine open-label studies were meta-analysed using a random-effects model with inverse-variance weights. The outcome measures were the standardised paired mean difference (Cohen's d) in depression scores on Hamilton Depression Rating Scale (HDRS), response, remission, and dropout rates after acute DTMS treatment compared to baseline.
Results:	There was a large antidepressant effect after 20 acute, high-frequency DTMS sessions compared to baseline according to HDRS change scores (overall mean weighted d=2.04, 95% confidence interval: 1.53-2.55; nine studies; 150 patients). Overall weighted response, remission, and dropout rates were 60%, 29%, and 18% respectively. HDRS change scores 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 DTMS as a monotherapy.

Conclusions:	These results are based on data from a low number of open-label studies. High-frequency DTMS appears to have acute antidepressant effects after 20 sessions in mostly unipolar and treatment-resistant patients. Concurrent treatment with antidepressants might enhance the efficacy of DTMS.

3.12	
Title:	**61% of Unmedicated Treatment Resistant Depression Patients Who Did Not Respond to Acute TMS Treatment Responded After Four Weeks of Twice Weekly Deep TMS in the BrainsWay Pivotal Trial**
Publication & Date:	**Brain Stimulation 10(4):847-849 (2017)**
Investigators:	**A.G Yip, M.S George, A Tendler, Y Roth, A Zangen, L.L Carpenter**

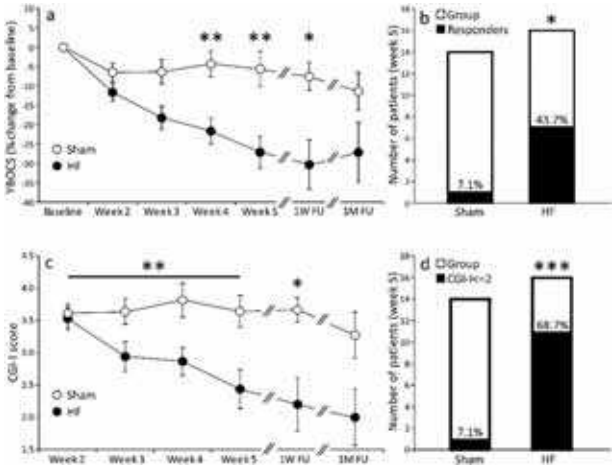
Background:	An acute course of dTMS typically involves treatments delivered 5 days a week, for 4 weeks. Should more treatments be given if the patient has not responded? Data are needed to inform decisions about the best next steps for acute non-responders.
Objective:	To characterize response among acute-phase non-responders in a randomized controlled trial of deep repetitive transcranial magnetic stimulation (dTMS) monotherapy for medication-resistant depression.
Methods:	Summary statistics and Kaplan-Meier curves were used to characterize outcomes of 33 medication-free BrainsWay dTMS non-responders to double blind but active treatment at the end of 4 weeks (20 sessions), who then continued double blind but active twice weekly treatment for up to 12 additional weeks.
Results:	24 participants (72.7%) achieved responder status during at least one rating with dTMS continuation - 20 (60.6%) within four weeks, with 13 (39.4%) consistently meeting response criteria for the duration of the study. 20 (63.6%) achieved remission status at some point during treatment continuation.
Conclusions:	A significant proportion of acute course non-responders to dTMS treatment eventually respond with continued treatment. Continuing TMS treatment beyond the acute course for non-responders may result in eventual response in over half of these individuals.



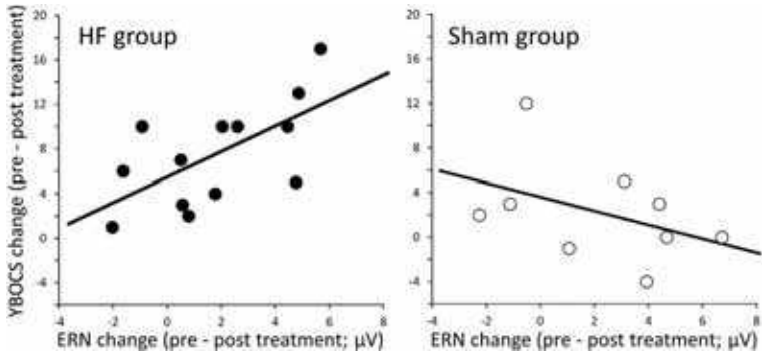
Cumulative incidence (1- survival) plot among non-responders to acute-phase dTMS. The event is 50% improvement from baseline (pre-treatment) HDRS-21 score (first occurrence of) among individuals remaining in the study at a given time point. The small numbers above the x axis indicate numbers 'at risk' for the event (i.e., those who have not achieved response and remained in the study at a particular time point). Gray area indicates 95% confidence interval.

3.13	Title:	**Clinical and Electrophysiological Outcomes of Deep TMS Over the Medial Prefrontal and Anterior Cingulate Cortices in OCD Patients**
	Publication & Date:	**Brain Stimulation 11(1):158-165 (2018)**
	Investigators:	**L Carmi, U Alyagon, N Barnea-Ygael, J Zohar, R Dar, A Zangen**

Background:	Obsessive Compulsive Disorder (OCD) is a chronic and disabling disorder with poor response to pharmacological treatments. Converging evidences suggest that OCD patients suffer from dysfunction of the cortico-striato-thalamo-cortical (CSTC) circuit, including in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC).
Objective:	The authors set out to examine whether modulation of mPFC ACC activity by deep TMS affects OCD symptoms.
Methods:	Forty-one treatment resistant OCD patients were treated with either high frequency (HF; 20 Hz) or sham deep TMS of the mPFC and ACC for five weeks in a double-blinded manner. Both treatments were administered following symptoms provocation. EEG measurements during a Stroop task were acquired o examine changes in error-related activity. Clinical response to treatment was determined using the Yale-Brown-Obsessive-Compulsive-Scale (YBOCS).
Results:	Following completion of the study, the response rate in the HF group (n=18) was significantly higher than that of the sham group (n=15) for at least one month following the end of the treatment. Notably, the clinical response in the HF group correlated with increased Error Related Negativity (ERN) in the Stroop task, an electrophysiological component that is attributed to ACC activity.
Conclusions:	This study indicates that HF DTMS over the mPFC-ACC, when applied following provocation of OCD symptoms, is safe, tolerable and effective in reducing OCD symptoms.



Clinical effect of treatment. Panel a presents mean + SEM changes in YBOCS scores from baseline along the study, for the HF and sham groups. Panel b presents the number and percentage of participants who responded to treatment (i.e. 30% reduction in symptoms at week 5) in each group. Panel c and d presents changes from baseline in CGI-I scores and the percentage of participants that benefit from the treatment, in each group. *p<0.005, **p<0.01, ***p<0.001.



Correlation between the clinical and the electrophysiological changes. Correlation between changes in YBOCS scores and ERN amplitudes (pre- minus post-treatment) are presented for the HF and sham groups. Analysis revealed a significant positive correlation between the two measurements only in the HF group (r=0.63, p<0.01).

Section 4

Clinical Studies in Other Psychiatric Indications

The largest volume of evidence for the efficacy of the H-Coils exists for MDD and OCD, for which the Deep TMS technology is cleared by the FDA.

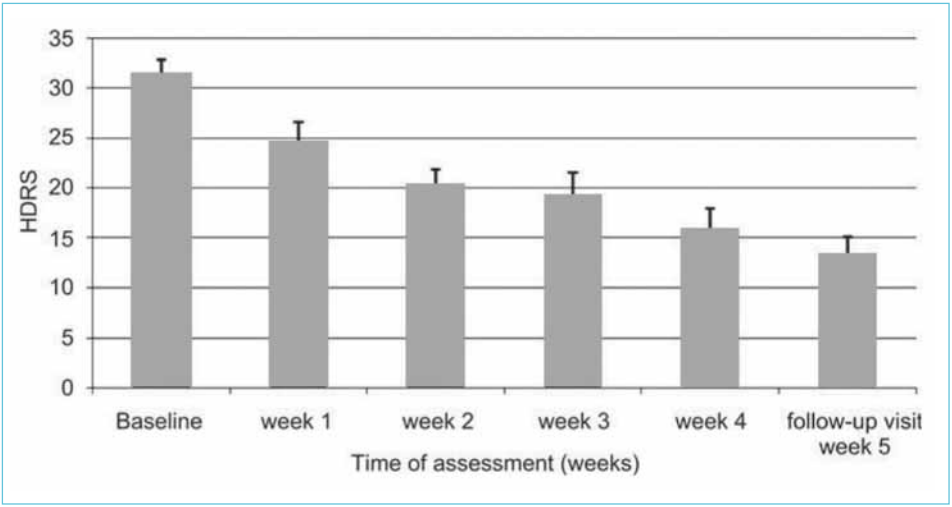
The H-Coils' ability to target deep neuronal regions broadly expands the potential utility of Deep TMS.

Indeed, the therapeutic efficacy of Deep TMS using different H-Coils has been explored in several psychiatric conditions, with some promising results. These applications are still considered investigational.

BrainsWay®

4.1	
Title:	**H-coil Repetitive Transcranial Magnetic Stimulation For the Treatment of Bipolar Depression: An Add-on, Safety and Feasibility Study**
Publication & Date:	**The World of Biological Psychiatry 12:(2)119-126 (2011)**
Investigators:	**E.V Harel, A Zangen, Y Roth, I Reti, Y Braw, Y Levkovitz**

Background:	The H1-Coil is a novel transcranial magnetic stimulation (TMS) device capable of inducing a magnetic field with a deeper and wider distribution than standard coils.
Objective:	This pilot study evaluated the safety and feasibility of the H1-Coil as adjuvant treatment for bipolar depression (BPD).
Methods:	Nineteen patients diagnosed as having BPD and under treatment with psychotropic medication were enrolled in the study. They received daily prefrontal repetitive TMS (rTMS: 20 Hz, 2 seconds on, 20 seconds off, totaling 1680 stimuli) every weekday for four consecutive weeks. The primary outcome measure was the change from baseline in the Hamilton Depression Rating Scale (HDRS-24) score a week after the last treatment session.
Results:	A significant mean decrease of 12.9 points in the HDRS-24 scale ($p<0.001$) was found. Response rate was 63.2% and remission rate was 52.6%. Treatment was well tolerated in terms of headache and overall discomfort, and there was no significant change in cognitive functioning or mood switches. One patient had a short induced generalized seizure without complications.
Conclusions:	An add-on H-coil rTMS treatment protocol in BPD subjects indicated improvement in bipolar depression symptoms. Sham-control studies to further determine the efficacy and safety of the H-Coil for BPD are warranted.

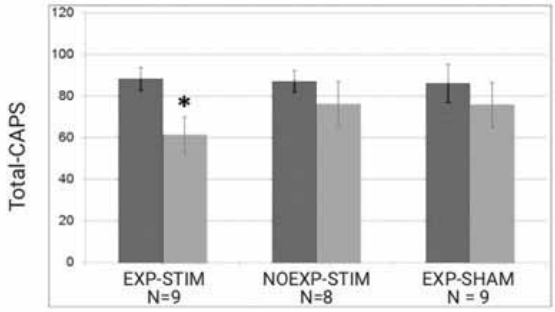


Hamilton Depression Rating Scale (HDRS) scores from baseline to the follow-up visit 1 week after the last treatment day.

4.2	
Title:	**Effectiveness of Deep Transcranial Magnetic Stimulation Combined with a Brief Exposure Procedure in Post-Traumatic Stress Disorder - A Pilot Study**
Publication & Date:	**Brain Stimulation 6:(3)377-383 (2013)**
Investigators:	**M Isserles, A.Y Shalev, Y Roth, T Peri, I Kutz, E Zlotnick, A Zangen**

Background:	Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder induced by traumatic experiences. To date, psychotherapy and drug treatment achieve only partial success, indicating need for further development of treatment strategies. Recent research has found that impaired acquired fear extinction capability serves as an important factor at the pathogenesis of the disorder. Medial prefrontal cortex (mPFC) hypo-activity has been implicated in this extinction impairment, providing insight as to why some trauma exposed individuals will develop PTSD.
Objective:	To test whether fear extinction can be facilitated and therapeutic effect achieved by repeated mPFC deep transcranial magnetic stimulation (DTMS) of PTSD patients resistant to standard treatment.
Methods:	In a double-blind study, 30 PTSD patients were enrolled and randomly assigned into 3 treatment groups: A) DTMS after brief exposure to the traumatic event with the script-driven imagery procedure; B) DTMS after brief exposure to a non-traumatic event; C) sham stimulation after brief exposure to the traumatic event.
Results:	Significant improvement was demonstrated in the intrusive component of the CAPS scale in patients administered DTMS after exposure to the traumatic event script, while patients in the control groups showed no significant improvement. Similar trend was demonstrated in the Total-CAPS score as in the other rating scales. A significant reduction in the HR response to the traumatic script was evident in group A, further supporting the above results.

Conclusions:	Combining brief script-driven exposure with DTMS can induce therapeutic effects in PTSD patients. A wide multi-center study is suggested to substantiate these findings.



Total-CAPS severity score at baseline and post treatment.
*P < 0.05, relative to baseline.

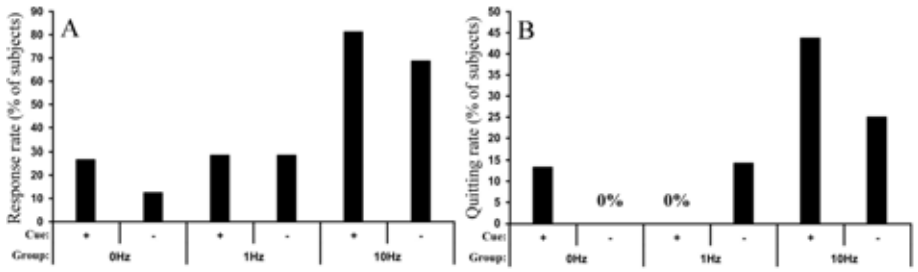
Baseline

Post treatment

4.3	
Title:	**Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial**
Publication & Date:	**Biological Psychiatry 76(9):742-749 (2014)**
Investigators:	**L Dinur-Klein, P Dannon, A Hadar, O Rosenberg, Y Roth, M Kotler, A Zangen**

Background:	Tobacco smoking is the leading cause of preventable death in developed countries. This group of investigators' previous studies in animal models and humans suggest that repeated activation of cue-induced craving networks followed by electromagnetic stimulation of the dorsal prefrontal cortex (PFC) can cause lasting reductions in drug craving and consumption.
Objective:	The investigators hypothesized that disruption of these circuitries by deep transcranial magnetic stimulation (TMS) of the PFC and insula bilaterally can induce smoking cessation.
Methods:	Adults (N=115) 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 smoking cues. Deep TMS was administered using an H-coil version targeting the lateral PFC and insula bilaterally. 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.
Results:	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.

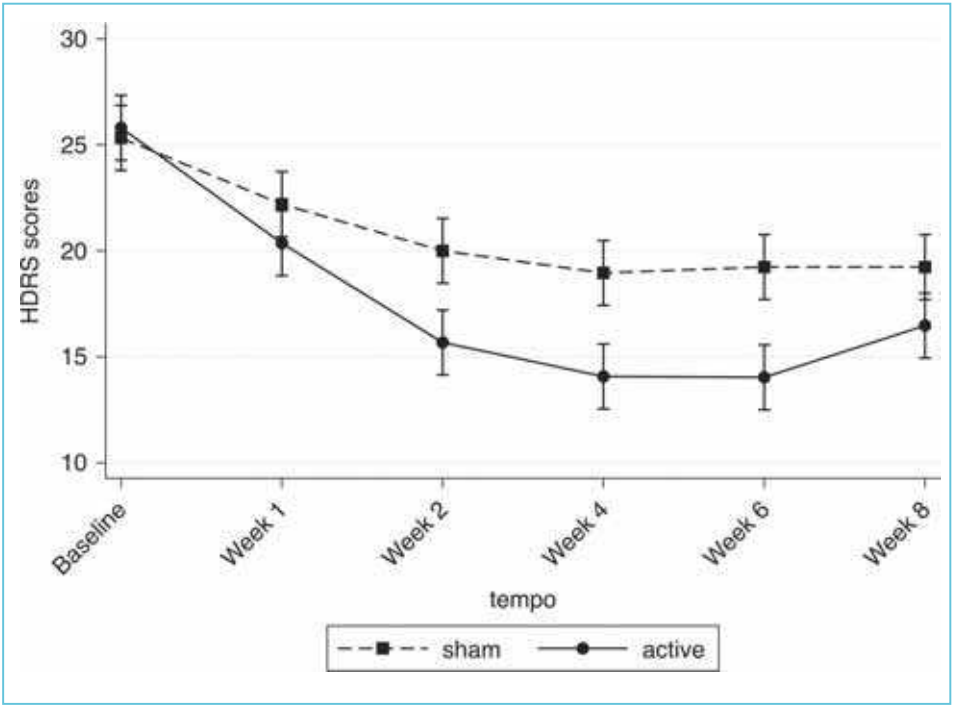
Conclusions: This study further implicates the lateral PFC and insula in nicotine addiction and suggests the use of deep high-frequency TMS of these regions following presentation of smoking cues as a promising treatment strategy.



Response and abstinence rates at the end of treatment. Response (A) for each subject was defined if cigarette consumption (according to the self-reported number of cigarettes smoked/day) was reduced by at least 50% in the last treatment session relative to that on the screening day just prior to the initiation of treatment. Abstinence (B) for each subject was defined based on the self-reported measure (complete abstinence) which was corroborated by the objective cotinine test (undetected in the last urine sample). 0+ (n=15), 0- (n=16), 1+ (n=7), 1- (n=7), 10+ (n=16), 10- (n=16).

4.4	
Title:	**Treatment of Bipolar Depression with Deep TMS: Results from a Double-Blind, Randomized, Parallel Group, Sham-Controlled Clinical Trial**
Publication & Date:	**Neuropsychopharmacology 42(13):2593-2601 (2017)**
Investigators:	**D.F Tavares, M.L Myczkowski, R.L Alberto, L Valiengo, R.M Rios, P Gordon, B de Sampaio-Junior, I Klein, C.G Mansur, M.A Marcolin, B Lafer, R.A Moreno, W Gattaz, Z.J Daskalakis, A.R Brunoni**

Background:	Bipolar depression (BD) is a highly prevalent condition with limited therapeutic options. Deep (H1-coil) transcranial magnetic stimulation (dTMS) is a novel TMS modality with established efficacy for unipolar depression.
Objective:	This study was a randomized sham-controlled trial to evaluate the efficacy and safety of dTMS in treatment-resistant BD patients.
Methods:	Fifty patients received 20 sessions of active or sham dTMS over the left dorsolateral prefrontal cortex (H1-coil, 55 18 Hz 2 s 120% MT trains). The primary outcome was changes in the 17-item Hamilton Depression Rating Scale (HDRS-17) from baseline to endpoint (week 4). Secondary outcomes were changes from baseline to the end of the follow-up phase (week 8), and response and remission rates. Safety was assessed using a dTMS adverse effects questionnaire and the Young Mania Rating Scale to assess treatment-emergent mania switch (TEMS).
Results:	Out of 50 patients, 43 finished the trial. There were 2 and 5 dropouts in the sham and active groups, respectively. Active dTMS was superior to sham at end point (difference favoring dTMS=4.88; 95% CI 0.43 to 9.32, p=0.03) but not at follow-up. There was also a trend for greater response rates in the active (48%) vs sham (24%) groups (OR=2.92; 95% CI=0.87 to 9.78, p=0.08). Remission rates were not statistically different. No TEMS episodes were observed.
Conclusions:	Deep TMS is a potentially effective and well-tolerated add-on therapy in resistant bipolar depressed patients receiving adequate pharmacotherapy.



Primary Outcome.

4.5	
Title:	**Transcranial Magnetic Stimulation of Medial Prefrontal and Cingulate Cortices Reduces Cocaine Self-Administration: A Pilot Study**
Publication & Date:	**Frontiers in Psychiatry 9:80 (2018)**
Investigators:	**D Martinez, N Urban, A Grassetti, D Chang, M.C Hu, A Zangen, F.R Levin, R Foltin, E.V Nunes**

Background:	Previous studies have shown that deep transcranial magnetic stimulation (dTMS) to the dorsolateral prefrontal cortex may serve as a potential treatment for cocaine use disorder (CUD), which remains a public health problem that is refractory to treatment. Previous imaging studies have demonstrated alterations in the activation and connectivity of the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) in CUD.
Objective:	The goal of this pilot study was to investigate the effect of dTMS over the mPFC and ACC on cocaine self-administration in the laboratory.
Methods:	Volunteers with CUD were admitted to an inpatient unit for the entire study and assigned to one of three dTMS groups: high frequency (10 Hz), low frequency (1 Hz), and sham. Six participants were included in each group and the dTMS was delivered using the H7 coil on weekdays for 3 weeks. The cocaine self-administration sessions, in which participants chose between cocaine and an alternative reinforcer (money), were performed at three time points: at baseline (pre-TMS, session 1), after 4 days of dTMS (session 2), and after 13 days of dTMS (session 3). During each self-administration session, the outcome measure was the number of choices for cocaine.
Results:	The results showed a significant group by time effect ($p=0.02$), where the choices for cocaine decreased between sessions 2 and 3 in the high frequency group. There was no effect of dTMS on cocaine self administration in the low frequency or sham groups.

Conclusions:	Taken in the context of the existing literature, these results contribute to the data showing that high frequency rTMS to the prefrontal cortex may serve as a potential treatment for CUD.

Choices for cocaine			
Session 1	3.83 (4.0)	4.7 (3.3)	4.8 (3.8)
Session 2	5.0 (2.5)	6.5 (2.7)	5.0 (3.9)
Session 3	1.8 (1.9)*	5.5 (3.5)	4.7 (4.0)
Break point			
Session 1	1,333.33 (1,608.31)	1,700 (1,275.93)	1,766.67 (1,477.39)
Session 2	1,800 (1,011.93)	2,400 (1,095.45)	1,833.33 (1,488.17)
Session 3	600 (704.27)	2,033.33 (1,341.14)	1,733.33 (1,521.40)

The number of choices participants made for smoked cocaine by three repetitive transcranial magnetic stimulation (rTMS) groups (Sham, low frequency, or high frequency treatment) on cocaine self-administration sessions.

Session 1 is the baseline (pre-rTMS session), session 2 followed 4 days of rTMS, and session 3 occurred following 13 days of rTMS. Treatment by session interaction with rTMS group is significant [$F(2, 15) = 5.36$, $p = 0.02$]. *Session 2 compared to session 3, $p = 0.03$.

Section 5

Clinical Studies in Neurological Indications

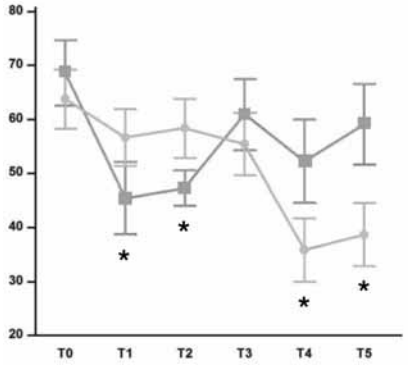
While most of the proof for efficacy of the H-Coils, a novel patented structure that maximizes electrical stimulation of deep brain regions, is mainly for psychiatric indications, it has been proven to stimulate a variety of brain regions in various neurological indications, with some promising results.

In this compendium, the focus is on stimulation of the leg and hand primary motor cortex for chronic pain relief, stroke rehabilitation and MS fatigue. These applications are still considered investigational.

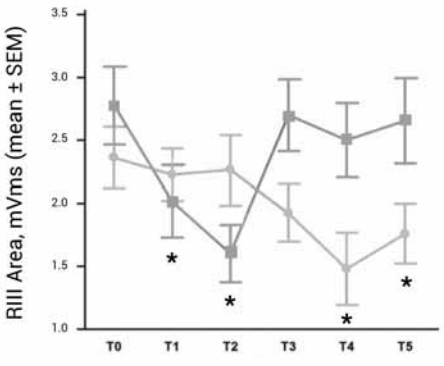
BrainsWay®

5.1	
Title:	**H-coil Repetitive Transcranial Magnetic Stimulation for Pain Relief in Patients With Diabetic Neuropathy**
Publication & Date:	**European Journal of Pain 17(9):1347-1356 (2013)**
Investigators:	**E Onesti, M Gabriele, C Cambieri, M Ceccanti, R Raccah, G Di Stefano, A Biasiotta, A Truini, A Zangen, M Inghilleri**

Background:	Painful neuropathy is associated with plasticity changes in the nervous system. Standard repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique used to study changes in cortical excitability and to inhibit pain perception. Deep rTMS is a newer development that allows direct activation of deeper neuronal populations, by a unique coil design termed the H-coil.
Objective:	This study was designed to assess whether deep rTMS applied over the motor cortical lower-limb representation relieves pain in patients with diabetic neuropathy.
Methods:	Patients were randomly assigned to receive daily real or sham H-coil rTMS for 5 consecutive days. After a 5-week washout period, they crossed over to the alternative treatment for 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).
Results:	Of the 25 patients randomized, 23 completed the study. After real rTMS, the VAS scores decreased significantly ($p=0.01$), and so did RIII reflex area ($p<0.01$), while no significant effects in these variables were induced by the sham rTMS treatment. The rTMS-induced changes in the outcome measures disappeared about 3 weeks after stimulation. All patients tolerated stimulation well.
Conclusions:	Deep H-coil rTMS provides pain relief in patients with diabetic neuropathy. This innovative technique can induce a therapeutic effect on brain areas that otherwise remain difficult to target. rTMS may produce its analgesic effects, inducing motor cortex plasticity and activating descending inhibitory pain control systems.



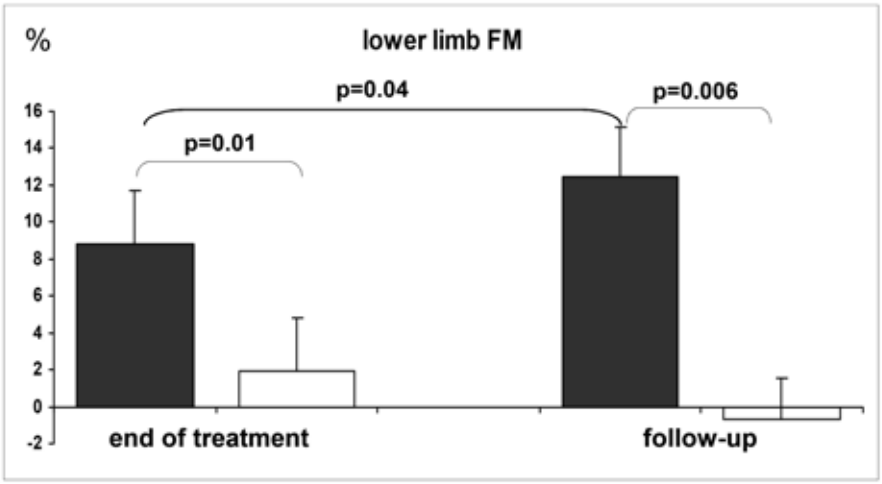
Mean + standard error of the mean (SEM) changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on visual analogue scale (VAS) scores over time in patients with painful drug-resistant chronic diabetic neuropathy. Repeated measures analysis of variance (ANOVA) disclosed a significant treatment x time interaction (F=3.968; p=0.01).
*p<0.01 with respect to the baseline value.



Mean + standard error of the mean (SEM) changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on changes in RIII area over time in patients with painful drug-resistant chronic diabetic neuropathy. Repeated measure analysis of variance (ANOVA) disclosed a significant treatment x time interaction (F=4.137; p<0.01).

5.2	
Title:	**Deep Repetitive Transcranial Magnetic Stimulation with H-coil on Lower Limb Motor Function in Chronic Stroke: A Pilot Study**
Publication & Date:	**Archives of Physical Medicine and Rehabilitation 95(6):1141-1147 (2014)**
Investigators:	**R Chieffo, S De Prezzo, E Houdayer, A Nuara, G Di Maggio, E Coppi, L Ferrari, L Straffi, F Spangnolo, S Velikova, M Sessa, M Comola, A Zangen, G Comi, L Leocani**
Background:	Stroke is a leading cause of long term disability and non-invasive brain stimulation techniques have been recognized as a promising intervention for the treatment of post-stroke motor deficits. Although the ability to walk is impaired in more than 80% of post-stroke subjects, the pathophysiological reorganization of lower limb motor areas after stroke is still unclear as relatively fewer data are available compared with the upper extremity. The lower limb cortical motor areas are located deeply in the mesial cortical surface of the hemispheres. The H-coil, that effectively stimulates at a depth of about 3-5 cm below the skull, has been reported to require lower intensities of stimulation to obtain lower limb motor responses.
Objective:	To assess the efficacy of bilateral excitatory high frequency (20 Hz) stimulation over the lower limb motor area on lower limb motor function in subjects with chronic (> 6 months) subcortical stroke in a double-blind, placebo-controlled crossover study.
Methods:	This was a double-blind, placebo controlled, crossover study. Ten right-handed subjects affected by a first-ever subcortical stroke more than 6 months prior participated in the study. 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.
Results:	Real rTMS treatment was associated with a significant improvement in lower limb. This effect persisted over time (follow-up) and was significantly greater than that observed with sham stimulation. A significant increase in walking speed was also found after real rTMS but this effect did not reach statistical significance in comparison with the sham stimulation.
Conclusions:	These data demonstrated that 3 weeks of high-frequency deep rTMS could induce long-term improvements in lower limb functions in the chronic post-stroke period, lasting at least 1 month after the end of the treatment.

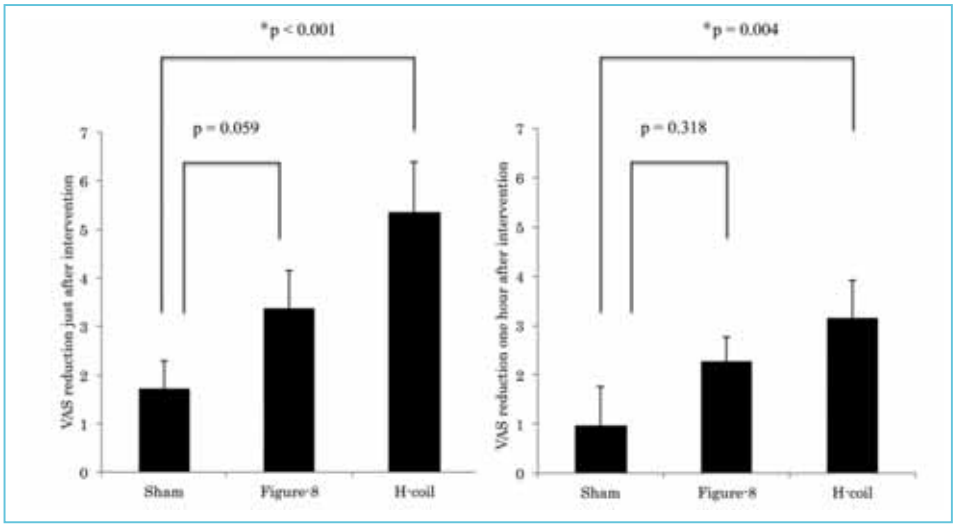


% Change on the lower limb Fugl-Meyer Assessment (FMA) of motor recovery. Real (n=9) vs. sham (n=9) comparison revealed a significant improvement at the end of treatment (p=0.01) as well as at follow-up (p=0.006). Amelioration was greater after 4 weeks from the end of real treatment as confirmed by a significant difference in baseline percent change at the end of treatment vs follow-up (p=0.04).

5.3	
Title:	**Efficacy of Deep rTMS for Neuropathic Pain in the Lower Limb: A Randomized, dDouble-blind Crossover Trial of an H-coil and Figure-8 Coil**
Publication & Date:	**Journal of Neurosurgery 127(5):1172-1180 (2017)**
Investigators:	**T Shimizu, K Hosomi, T Maruo, Y Goto, M Yokoe, Y Kageyama, T Shimokawa, T Yoshimine, Y Saitoh**

Background:	Electrical motor cortex stimulation can relieve neuropathic pain (NP), but its use requires patients to undergo an invasive procedure. Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) using a figure-8 coil can relieve NP noninvasively, but its ability to relieve lower limb pain is still limited. Deep rTMS using an H-coil can effectively stimulate deep brain regions and has been widely used for the treatment of various neurological diseases; however, there have been no clinical studies comparing the effectiveness of figure-8 coils and H-coils.
Objective:	This study assessed the clinical effectiveness of 5 once-daily stimulations with H-coils and figure-8 coils in patients with NP.
Methods:	This randomized, double-blind, 3-way crossover trial examined 18 patients with NP who sequentially received 3 types of stimulations in the M1 for 5 consecutive days; each 5-day stimulation period was followed by a 17-day follow-up period before crossing over to the next type of stimulation. During each rTMS session, patients received a 5-Hz rTMS to the M1 region corresponding to the painful lower limb. The visual analog scale (VAS) and the Japanese version of the short-form McGill Pain Questionnaire 2 (SF-MPQ2-J) were used to measure pain intensity. The primary outcome was VAS score reduction immediately after and 1 hour after intervention.
Results:	Both the VAS and SF-MPQ2-J showed significant pain improvement immediately after deep rTMS with an H-coil as compared with the sham group ($p < 0.001$ and $p = 0.049$, respectively). However, neither outcome measure showed significant pain improvement when using a figure-8 coil.

	The VAS also showed significant pain improvement 1 hour after deep rTMS with an H-coil (p = 0.004) but not 1 hour after rTMS using a figure-8 coil. None of the patients exhibited any serious adverse events.
Conclusions:	The findings suggest that the use of deep rTMS with an H-coil in the lower limb region of the M1 in patients with NP was tolerable and could provide significant short-term pain relief.

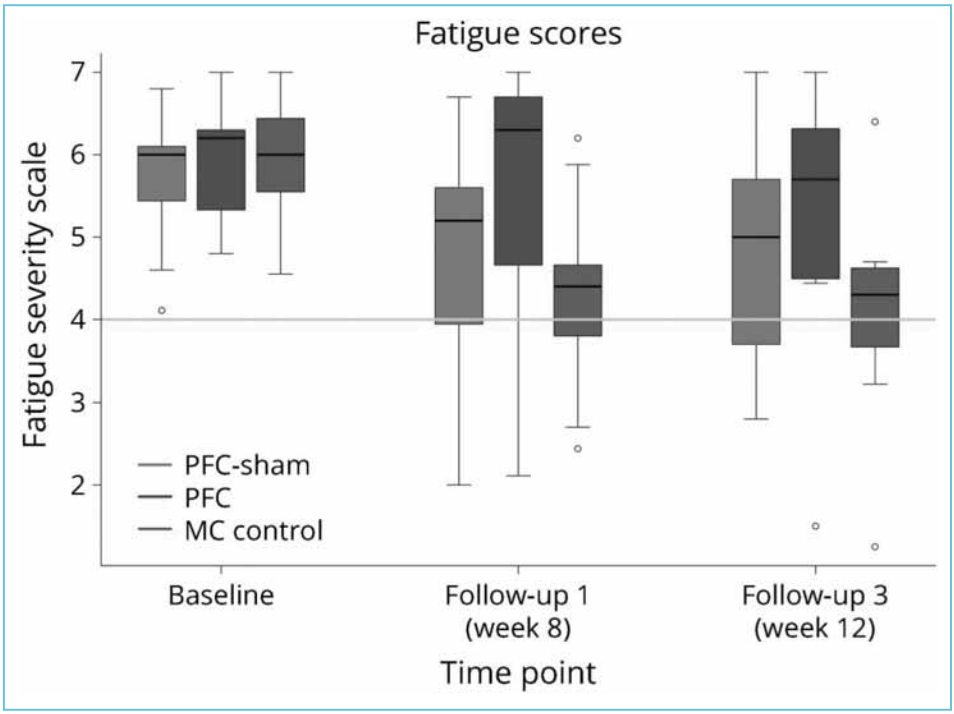


The mean VAS reduction in the short term (primary outcome). The mean VAS reduction just after stimulation was 5.36 (SEM 1.03) using rTMS with a H-coil, 3.36 (3.33) using rTMS with a figure-8 coil, and 1.71 (2.50) for sham stimulation. The mean VAS reduction 1 hour after stimulation was 3.14 (0.77) with the H-coil, 2.25 (0.51) with the figure-8 coil, and 0.97 (0.80) with sham.

5.4	
Title:	**Safety and Preliminary Efficacy of Deep Transcranial Magnetic Stimulation in MS-related Fatigue**
Publication & Date:	**Neurology Neuroimmunology & Neuroinflamation 5(1):e423 (2017)**
Investigators:	**G Gaede, M Tiede, I Lorenz, A.U Brandt, C Pfueller, J Dörr, J Bellmann-Strobl, S.K Piper, Y Roth, A Zangen, S Schippling, F Paul**

Background:	MS is the most common autoimmune inflammatory and neurodegenerative disease of the CNS. Fatigue is one of the most frequent symptoms experienced in MS, affecting up to 90% of patients. Neuroimaging studies suggest that structural and functional connectivity alterations, particularly to interconnections between the basal ganglia and the prefrontal cortex (PFC), the posterior cingulate cortex and cortical motor areas, may contribute to fatigue in MS. A potential treatment of functional connectivity impairment is noninvasive neuromodulation by means of repetitive transcranial magnetic stimulation (rTMS).
Objective:	To conduct a randomized, sham-controlled phase I/IIa study to evaluate the safety and preliminary efficacy of deep brain H-coil repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex (PFC) and the primary motor cortex (MC) in patients with MS with fatigue or depression.
Methods:	Thirty-three patients with MS were recruited to undergo 18 consecutive rTMS sessions over 6 weeks, followed byfollow-up (FU) assessments over 6weeks. Patients were randomized to receive high-frequency stimulation of the left PFC, MC, or sham stimulation. Primary end point was the safety of stimulation. Preliminary efficacy was assessed based on changes in Fatigue Severity Scale (FSS) and Beck Depression Inventory scores. Randomization allowed only analysis of preliminary efficacy for fatigue.
Results:	No serious adverse events were observed. Five patients terminated participation during treatment due to mild side effects. Treatment resulted in a significant median FSS decrease of 1.0 point (95%CI [0.45,1.65]), which was sustained during FU.

Conclusions:	H-coil rTMS is safe and well tolerated in patients with MS. The observed sustained reduction in fatigue after subthreshold MC stimulation warrants further investigation.

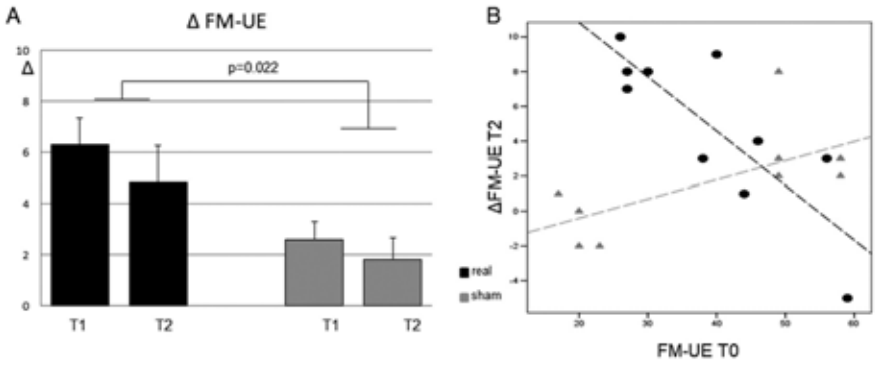


FSS changes during the study using standard boxplots. Treatment group "PFC" is shown in purple, treatment group "MC" in green, and sham group "PFC sham" in gray. Post-treatment visits are termed "follow-up" (plus follow-up visit number). The yellow line indicates FSS cutoff between fatigued (FSS>4) and nonfatigued values.
FSS = Fatigue Severity Scale; MC = motor cortex; PFC = prefrontal cortex.

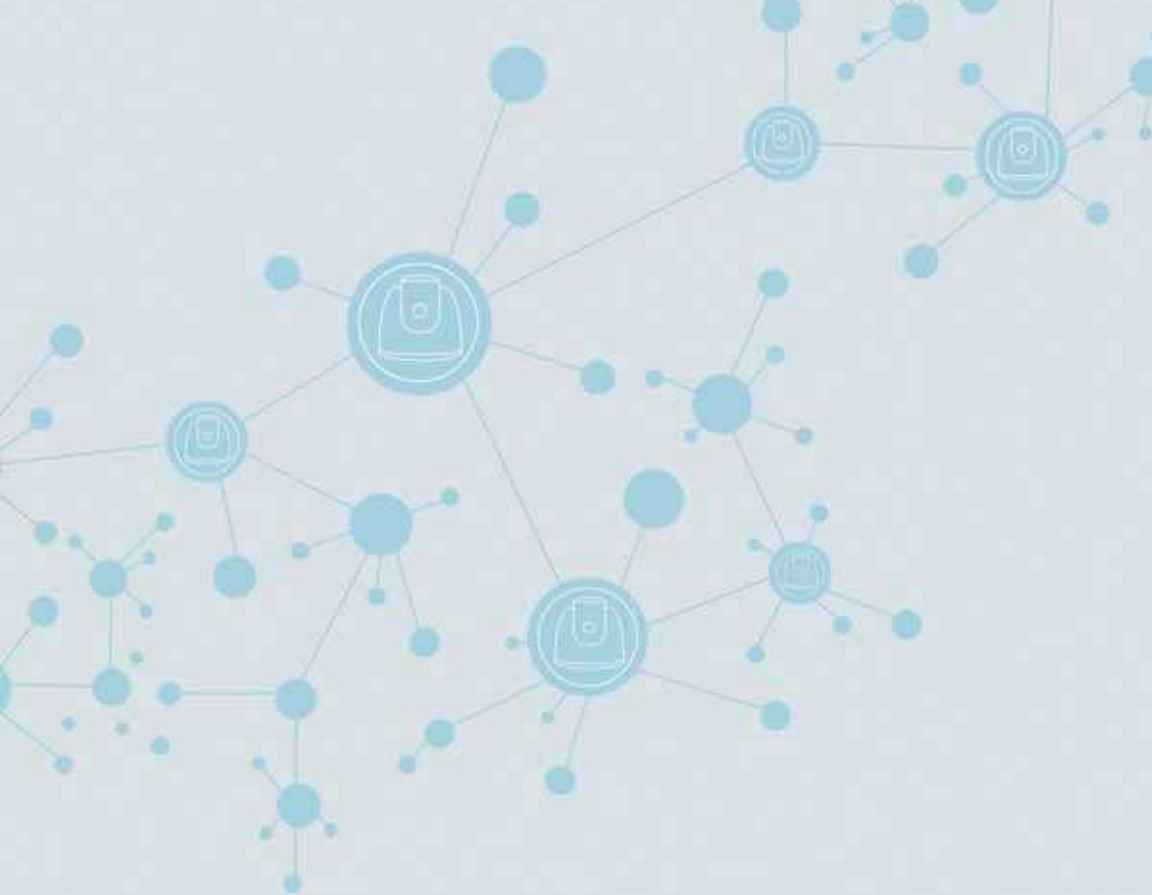
5.5	
Title:	**Bi-hemispheric Repetitive Transcranial Magnetic Stimulation for Upper Limb Motor Recovery in Chronic Stroke: A Feasibility Study**
Publication & Date:	**Brain Stimulation 11(4):932-934 (2018)**
Investigators:	**R Chieffo, G Scopelliti, M Fichera, R Santangelo, S Guerrieri, A Zangen, G Comi, L Leocani**

Background:	The emerging crucial role of non-primary and contralesional motor areas in the recovery of upper extremity (UE) after acute stroke led to the proposal of the "bimodal-balance recovery model", with the hypothesis that the contribution of ipsi- and contralesional primary and secondary motor areas might vary according to the structural reserve of the ipsilesional cortico-spinal tract. This model offers itself to novel non-invasive brain stimulation approaches for improving the effects of neurorehabilitation, targeting bilateral, wide motor cortical regions rather than focusing on the ipsilateral or contralesional M1.
Objective:	To test the safety, feasibility and efficacy of simultaneous high-frequency rTMS of bilateral motor/premotor areas using the H5-coil, associated with unilateral motor training of the paretic UE.
Methods:	Twenty patients with UE motor involvement from first-ever chronic stroke underwent 11 sessions of 30 minutes of upper limb motor training (MT) of the paretic UE, each followed by rTMS with the symmetric H5-coil, designed to stimulate both hemispheres simultaneously (40 2s-trains at 20 Hz, 20 sec inter-train interval, 1600 pulses), at 90% of resting motor threshold (RMT). Clinical measurements were collected before the first (T0) and after the last treatment session (T1), plus one-month follow-up (T2) and included: FM-UE score, modified Ashworth scale (MAS) global score as the sum of shoulder, elbow and wrist scores (range 0-12), handgrip strength (JAMAR dynamometer).

Results:	In this study that included participants with mild to severe-moderate UE motor impairment, bilateral high-frequency rTMS of motor/premotor areas, following motor training, was associated with greater and more sustained motor improvement compared with motor training followed by sham. Such improvement was clinically relevant (FM-UE 6 point) for 70% of subjects in the real group (vs 10% of the sham group). Interestingly, the investigators found that bilateral stimulation of motor/premotor areas was associated with a greater FM-UE improvement in more severely impaired patients, opposite to what observed in the sham group.
Conclusions:	It is possible that the wide bilateral, simultaneous stimulation may improve functional intra- and interhemispheric synchronization between motor and premotor areas and promote the unmasking of cortico-cortical and descending pathways.



(A) Change from baseline (D) of FM-UE after real (black) and sham (grey) rTMS at the end of treatment (T1) and 1 month follow-up (T2). (B) Pearson's correlation between baseline upper extremity Fugl-Meyer (FM-UE) score and its change at 1 month follow-up-T2.



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