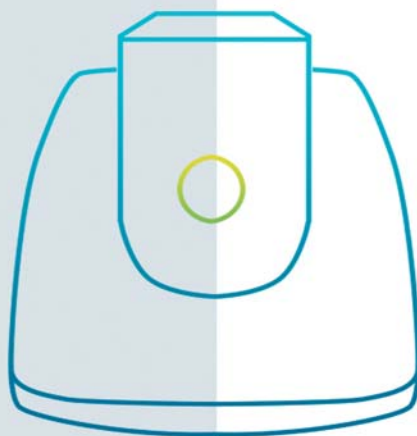


# An In-Depth Look at BrainsWay Technology (Deep TMS)



**BrainsWay**



# TABLE OF CONTENTS

## Section 1

Design Principles: The Art of Deep.....1

## Section 2

The Math of Deep.....3

## Section 3

The Importance of Deep.....5

## Section 4

The Myth of Precision Targeting.....7

## Section 5

The Proof is in the Pudding.....10

**Reality Check-List** .....14

**References** .....15

## Section 1 *Design Principles: The Art of Deep*

Deep Transcranial Magnetic Stimulation (Deep TMS) using BrainsWay's H-coils is a novel development in non-invasive neuromodulation.

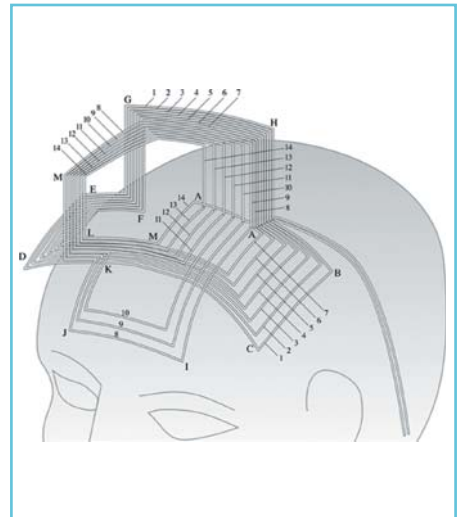
The ability to stimulate deeper neuronal structures than any other commercially available TMS system is based on science and engineering.

BrainsWay holds the exclusive rights to the Deep TMS technology, which was originally patented by the NIH, with subsequent patents by BrainsWay. Deep TMS H-coils feature a complex coil geometry designed to enhance the depth penetration of TMS.

Transcranial magnetic stimulation (TMS) is delivered using an electromagnetic coil placed against the scalp surface. The coil generates brief but powerful magnetic field pulses, which pass unimpeded through the scalp and skull and induce an electric field in the brain. Electric currents are induced by TMS at points where the coil is tangential to the scalp. Non-tangential coil elements cause the accumulation of surface charge, which counteracts the induced field resulting in faster dissipation.<sup>1,2</sup>

TMS is typically delivered using a rigid figure-8-shaped coil. BrainsWay's Deep TMS H-coils feature a unique design in which multiple coil elements are oriented tangentially with respect to the scalp surface, and non-tangential coil elements are minimized (Figure 1). A flexible base allows the coil to conform to the curvature of the scalp for maximal magnetic coupling. When the coil is discharged, various elements act in concert, and locally induced fields combine to form a deeper and broader total electric field whose rate of decay is considerably slower compared to other TMS coils.<sup>3-5</sup>

*What is the significance of the rate of decay of the induced electric field?*

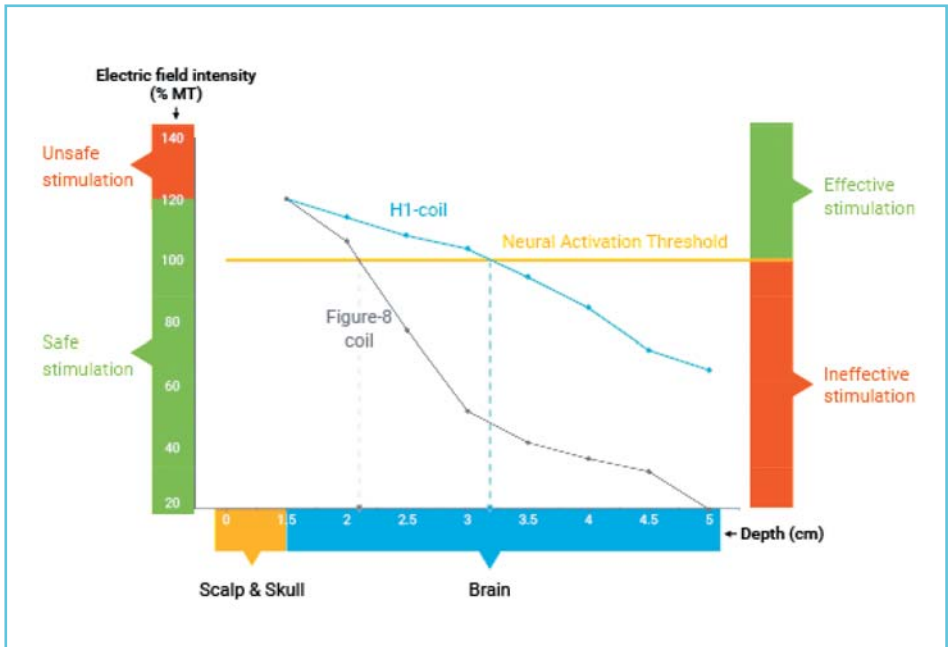


**FIGURE 1.** Sketch of the H1-coil near a human head. The coil position and orientation shown in the figure are designed for activation of deep neuronal targets in lateral and medial prefrontal regions, with left hemispheric preference. Figure taken from [5].

## Slow and Steady Wins the Race

All TMS protocols are bound by the same safety guidelines, permitting the same maximal field strengths to be produced at the cortical surface (in depression protocols, this is equal to 120% of the patient's individual's resting hand motor threshold [MT]).<sup>6</sup> The magnitude of the induced electric field is always strongest at the scalp and it diminishes with increasing distance from the coil.<sup>1,2,7-9</sup> The threshold intensity required to achieve neural stimulation in the motor cortex is on the order of 100 V/m.<sup>10</sup> The depth of effective stimulation depends on the rate at which the electric field decreases with distance.

This rate of decay was measured (see Section 2: The Math of Deep) for the BrainsWay H1-coil and the figure-8 TMS coil.<sup>5,11</sup> The H1-coil was found to have a much slower rate of attenuation, allowing the stimulation to penetrate deeper into the brain at the same safe stimulation levels (Figure 2). To reach similar depths with the figure-8 coil, stimulator output would have to be increased beyond safety limits, causing pain and increasing risk of seizure.



**FIGURE 2.** Decay profiles of the electric fields produced by the H1-coil and figure-8 coil. The maximal depth of effective penetration can be read off the graph at the points of intersection of the decay curves with the threshold for neuronal activation. Thanks to its slower rate of decay, the field induced by the H1-coil remains above this threshold at greater distances from the coil. Figure based on data from [11].

## Section 2 The Math of Deep

The H1-coil was designed for effective and tolerable stimulation of prefrontal regions associated with depression.<sup>5,12</sup> Deep TMS using this coil was cleared by the FDA for the treatment of resistant major depressive disorder (MDD) in 2013.<sup>13,14</sup>

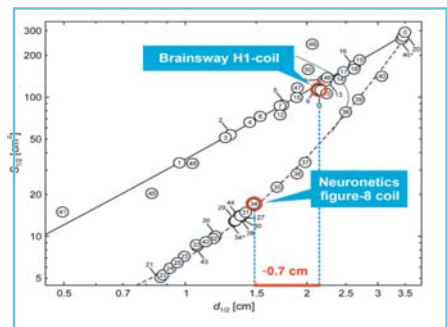
Converging evidence from a number of studies using different measuring methodologies points toward a consistent depth advantage to the H1-coil relative to figure-8 coils,<sup>5,11,15-19</sup> with a more pronounced difference suggested by field measurements in phantom heads and by realistic anatomical modelling.

The electric field induced by TMS cannot be easily measured in the living brain, but it can be estimated using numerical, analytical or experimental approaches. Irrespective of the method used, every comparison of depth penetration favors the H1-coil over the figure-8 coil. The following methods all defined depth as the distance along a radial direction passing through the brain center.

»»»The spatial properties of the electric fields produced by TMS coils were analyzed using a spherical head model.<sup>15</sup> The analysis found a deeper penetration of the BrainsWay H1-coil compared to an iron-core figure-8 coil, with a corresponding difference of approximately 0.7 cm in their respective half-distance values (the distance at which the fields decay to half their maximal value at the cortical surface) (Figure 3). Since TMS is thought to exert its effects by induction of long-lasting changes in synaptic transmission,<sup>20,21</sup> a more clinically relevant metric of depth penetration would be the spatial distribution of supra-threshold fields sufficient to trigger action potentials. Even though the half-distance metric is not very useful for comparing maximal depth of effective stimulation, it still demonstrates the slower decay of the field produced by the H1-coil. Since this reductive model fails to capture the full complexities of human brain geometry and skull curvature, its results are best interpreted only qualitatively.

»»»Among other limitations, computational models may not be able to reproduce the characteristics of real TMS coils. One way to overcome this limitation is to perform actual measurements of the electric field induced by TMS in a realistic head model filled with physiological saline solution, which mimics the conductive properties of neural tissue.

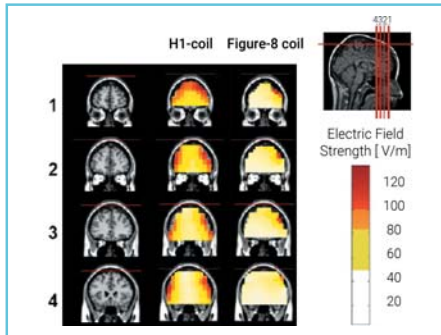
Unlike a spherical model, this method accounts for the complex shape of the skull. However, it suffers from the limitation of treating the brain as a homogeneous conductive medium, without distinguishing between its various constituent elements.



**FIGURE 3.** In a simple spherical head model, the half-distance value of the H1-coil was found to be approximately 0.7 cm greater than that of the iron core figure-8 coil. Figure adapted from [15].

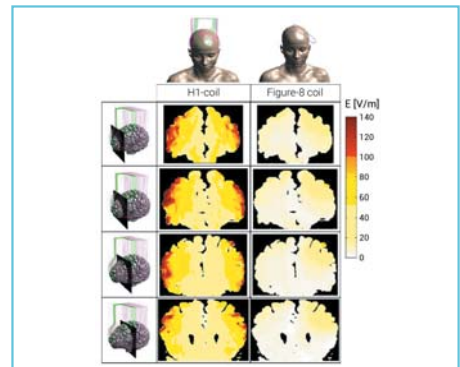
Field maps were generated from measurements in a head model to which TMS was applied using either a figure-8 coil or the BrainsWay H1-coil.<sup>5,11</sup> At stimulation intensity of 120% MT (the standard intensity for the treatment of depression) the H1-coil induces supra-threshold fields at depths of 1.8 cm beneath the cortical surface, compared to 0.7 cm for the figure-8 coil. The total stimulated brain volume at 120% MT is 17 cm<sup>3</sup> for the H1-coil compared to just 3 cm<sup>3</sup> for the figure-8 coil (Figure 4).<sup>11,19</sup>

»»» The geometry of the human brain is very different from an ideal sphere, due to the variable curvature of the skull surface and different tissue types and orientation. Calculations obtained from a spherical model may be inadequate to inform clinical applications of TMS. In recent years, realistic computational models based on high-resolution anatomical MRI (magnetic resonance imaging) images have emerged.



**FIGURE 4.** Maps of electric field distributions induced by the H1-coil and a figure-8 coil, based on measurements in a phantom head filled with physiological saline solution. The field maps are adjusted for stimulator power output levels required to obtain 120% of the hand motor threshold. The absolute magnitude of the induced electric field is indicated in 4 coronal slices 1 cm apart. Red pixels indicate field magnitudes above the threshold for neuronal activation (100 V/m). The H1-coil was found to induce supra-threshold fields at depths of 1.8 cm, compared to 0.7 cm for the figure-8 coil. Figure adapted from [11].

These models, which faithfully reproduce the characteristics and properties of brain tissues (such as cerebrospinal fluid, gray matter, white matter, etc.), allow investigation of the possible role of complex anatomical structures on electric field distributions, and may provide more realistic estimations of depth penetration. Simulations of the electric field induced in an anatomically realistic head model confirm that the decrease in field intensity with distance is slower for the H1-coil.<sup>16</sup> Consistent with this, stimulation at 120% MT with the H1-coil was found to induce an effective electric field at depths ranging from 1.8 to 2.8 cm beneath the cortical surface,<sup>16-18</sup> whereas 120% MT stimulation with a figure-8 coil was found to extend no deeper than 1.1 cm beneath the cortical surface (Figure 5).<sup>16,18</sup> found to extend no deeper than 1.1 cm beneath the cortical surface (Figure 5).<sup>16,18</sup>



**FIGURE 5.** Coronal maps of electric field distributions induced by the H1-coil and a figure-8 coil, based on simulations in an anatomically realistic computational head model, which accounts for the structural and physiological complexities of the skull and brain. In this model, it is shown clearly that stimulation at 120% MT with the H1-coil induces a deeper and wider spread of supra-threshold fields (indicated by red shades) than with a figure-8 coil. Figure adapted from [18].

## Section 3 *The Importance of Deep*

The prefrontal cortex (PFC) has rich interconnectivity with subcortical limbic and reward system structures involved in mood regulation,<sup>22-25</sup> which cannot be directly stimulated with TMS. The interaction of the prefrontal cortical signal induced by TMS with these subcortical regions is thought to contribute to its antidepressant effect.<sup>26,27</sup>

Cortical folding, which is a hallmark of the human brain, may play a role in shaping the cortical response to TMS. Recent evidence suggests that the main activation by TMS may occur in sulci, which are situated deeper beneath the surface.<sup>28-31</sup>

Deeper electric fields are better able to engage prefrontal circuitry, and may enhance the antidepressant effects of TMS.

In an animal model of depression, TMS-like electrical stimulation of the frontal cortex was shown to relieve depressive symptoms. Symptom relief correlated with neurochemical modulation of the reward system, and was critically dependent on the depth of stimulation.<sup>32</sup>

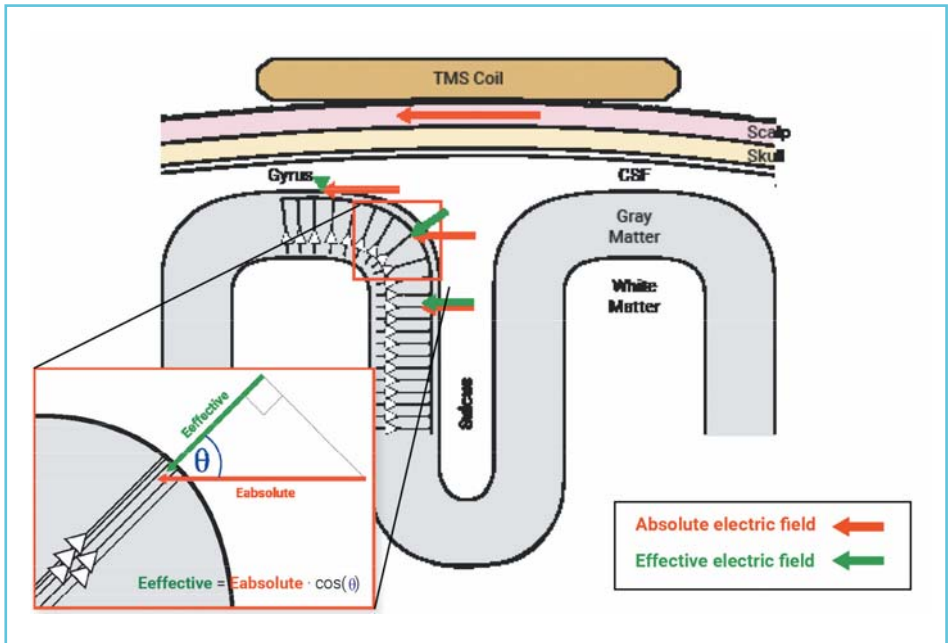
Although the human brain is very different, stimulation depth may likewise play an important role. The human cerebral cortex is a complex anatomical structure. Although the average thickness of the cortical gray matter strip is just 2 mm,<sup>33</sup> it is organized into a highly convoluted pattern of bumps and grooves, called gyri and sulci. As much as two thirds of the surface area of the cortex forms the walls of sulci, and is hidden from surface view.<sup>34</sup> Notably, the degree of folding is among the highest in the prefrontal cortex.<sup>35-37</sup> Since the field induced by the H1-coil extends deeper into the PFC, it is more likely to stimulate neurons residing within the sulcal folds. This advantage may be of particular importance in the lateral PFC, where both sulcal depth,<sup>38</sup> and the inter-

individual variability in sulcal depth<sup>39</sup> are among the greatest of any area in the brain.

Cortical pyramidal neurons are organized into mini-columns oriented perpendicular to the cortical surface.<sup>40</sup> It has been proposed that a major factor in TMS-induced brain activation is the orientation of the cortical columns in relation to the direction of the induced electric field.<sup>28,29</sup> TMS involves the induction of tangential, but not radial currents.<sup>2</sup> Since the favorable field orientation for neuronal stimulation is along the neuronal axis,<sup>41,42</sup> it has been proposed that stimulation is more efficient along sulcal banks than at gyral crowns since at these locations, cortical pyramidal neurons are aligned with the induced electric field vector (Figure 6). The preferential activation of sulcal targets by TMS is supported by volume conducting modelling<sup>30</sup> and functional neuroimaging.<sup>31</sup> If we accept the evidence that the principal site of action of TMS is within the depths of the sulci, the advantage of penetrating deeper becomes even more apparent.



The deeper field induced in the PFC using the H1-coil encompasses a significantly larger volume of cortical gray matter than does the field induced by a figure-8 coil. This field is likely to maximize stimulation of cortical neurons, especially along sulcal banks, where activation by TMS is thought to predominate. Prefrontal TMS is thought to exert its antidepressant effect by way of interaction with subcortical regions involved in mood regulation.<sup>26,27</sup> The recruitment of larger prefrontal cortical networks may therefore be expected to augment the antidepressant response to TMS.



**FIGURE 6.** Evidence suggests that stimulation is more efficient as the cortical column becomes perpendicular to the surface (i.e. along sulcal banks) rather than parallel to it (i.e. at the gyrus crown). The Cortical Column Cosine (C3) model<sup>28</sup> proposes a mechanism which relates differences in activation to the relative angle of the neuronal axis with respect to the angle of the externally applied electric field. The more the neuron and current are aligned, the greater the activation. Thus, activation occurs primarily along sulcal banks, despite the fact that larger absolute fields are usually produced at the gyrus crowns. Adapted from [28].

## Section 4 *The Myth of Precision Targeting*

The broader field produced by Deep TMS may also be clinically advantageous in the treatment of depression. The probabilistic nature of coil positioning and the high individual variability of putative TMS prefrontal targets render the highly focal field induced by figure-8 coils woefully prone to targeting errors, perhaps even with the aid of MRI-based neuro-navigation. These limitations favor the use of coils that produce more widespread electric fields.

Furthermore, the electric field of the H1-coil also extends to ventrolateral and ventromedial prefrontal cortices. These areas are richly interconnected with subcortical brain reward structures,<sup>22-25</sup> and are known to be associated with reward processes and motivation.<sup>43-45</sup> Stimulation impinging upon these areas may thus serve to enhance the antidepressant effect of TMS.

The putative target area for TMS depression therapy is the left dorsolateral prefrontal cortex (DLPFC).<sup>46-48.</sup>

The “5-cm rule” is an empiric method used for probabilistic targeting of the DLPFC based on its relative location to the hand area of the motor cortex. Although this method is used in most clinical trials and in routine practice, it may be suboptimal.

The “5-cm rule” neither accounts for differences in skull size or variations in prefrontal anatomy relative to motor cortex location, nor for inherent procedural variability in application of the rule. In fact, evidence shows that application of this standard targeting procedure with a figure-8 coil places stimulation outside the DLPFC target area in as many as two thirds of clinical trial subjects (Figure 7).<sup>49</sup> Herbsman et al. found that figure-8 TMS coil placement correlated with treatment efficacy,<sup>50</sup> which is not surprising given that the cortical area excited by figure-8 TMS is smaller than 1 cm in diameter.<sup>51</sup> In a recent prospective clinical trial comparing the “5-cm rule” to a more anatomically precise stereotactically guided and MRI-based figure-8 rTMS targeting procedure,

figure-8 rTMS targeting procedure, Fitzgerald et al. found that the latter method produced greater clinical improvement,<sup>52</sup> although this has not been confirmed in a large sample. Finally, in a large sham-controlled trial of figure-8 TMS,<sup>53</sup> treatment location was verified in advance of treatment based on neuroimaging guided visual inspection, and relocated 1 cm anteriorly in cases where targeting had failed to reach the prefrontal target area. Without this correction procedure, which is not employed in routine practice, TMS would have been administered outside the target area entirely in 33.2% of patients.

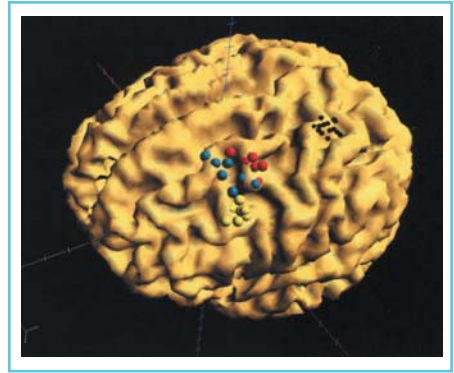
Fox et al. investigated whether differences in the clinical efficacy of reported left DLPFC TMS sites was related to differences in their functional connectivity to deeper limbic areas. Using functional connectivity MRI, a strong correlation was found between the efficacy of TMS sites and intrinsic functional connectivity with the subgenual cingulate cortex. The authors suggest these results can be translated into a connectivity-based targeting strategy for focal brain stimulation that might be used to optimize clinical response.<sup>54</sup> However, in a subsequent study, the same group demonstrated

that there is substantial inter-individual variability in the precise location of putative optimized targets identified by this strategy, which argues against the efficacy of population-based targeting approaches (Figure 8).<sup>55</sup> Thus, even within the general anatomical prefrontal area targeted by the “5-cm rule”, the efficacy of different TMS sites may vary considerably between individuals.

These findings are not surprising. As mentioned previously, the prefrontal cortex contains a high degree of folding.<sup>35-37</sup> The specific pattern of folding varies considerably across individuals, with the gyrification pattern of each human brain appearing as an individual ‘fingerprint’.<sup>56</sup> Moreover, the regions presenting maximum folding coincide with the regions of highest variability in measures of network connectivity.<sup>35</sup> For these reasons, targeting characteristics appropriate for one subject could be completely inappropriate for another.

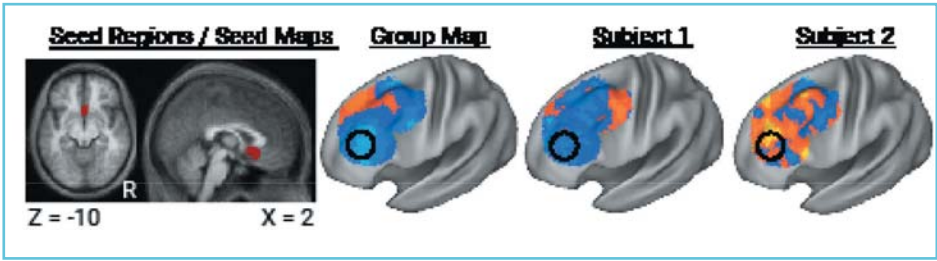
The lack of anatomical precision of TMS targeting, as well as the inherent variability of TMS targets between subjects, both suggest the possibility that many subjects, to whom TMS is administered in depression clinical trials and in clinical practice settings using figure-8 coils, may be receiving stimulation in areas that are unlikely to be involved in the pathophysiology of depression. The significant variability in prefrontal functional network architecture means that neuronavigation based on cranial or cortical landmarks alone may be inadequate for accurate detection of depression TMS targets for focal stimulation. Functional connectivity-based targeting may represent the best strategy for focal TMS using figure-8 coils, yet it is impractical in routine psychiatric care. It is clear that figure-8 coils, with their highly focal stimulation zones, are highly prone to missing the target. By contrast, the electric field induced by the H1-coil is sufficiently broad to avoid the

pitfalls of empiric coil targeting and to overcome the inherent non generalizability of stimulation target selection. Deep TMS is assured to stimulate the relevant prefrontal TMS target areas consistently.



**FIGURE 7.** Evaluation of the fidelity of the “5-cm rule”. The individual coordinates before and after standard positioning of a figure-8 coil using the “5-cm rule” are visualized on an image of the brain (view onto the left frontal cortex). The small black dots indicate the optimal sites for stimulation of the hand motor area. The larger dots indicate the coil positions arrived at by application of the “5-cm rule”. The DLPFC was targeted correctly in just 7/22 of subjects (yellow dots). Figure taken from [49].

Targeting is not the only unreliable aspect of TMS using a figure-8 coil. The focality of the figure-8 field makes it highly sensitive to small displacements of the coil during treatment. This may be partially remedied with the aid of sophisticated sensor systems used with figure-8 coils, which ensure continuous contact with the scalp. Yet, such sensors do not replace the need for accurate target detection and coil positioning. The H1-coil is insensitive to slight changes in position thanks to its deeper and broader field distribution. Moreover, the H1-coil is fitted into a helmet with adjustable straps to fasten the coil securely to the patient’s head. This maximizes magnetic coupling and prevents coil movement and loss of contact during treatment.



**FIGURE 8.** Identification of connectivity-based TMS targets in the left DLPFC at the group and single subject level. Resting state functional connectivity maps are shown for the population (group) and two individual subjects (subjects 1 and 2) for a seed region in the subgenual cingulate. TMS targets are identified on the basis of maximal anti-correlation (indicated by blue shades) with the subgenual cingulate.<sup>54</sup> Surface-based maps are masked to show only voxels in the left DLPFC. The black circles identify a potential stimulation site at the group level that is different between subjects 1 and 2, indicating the inadequacy of population-based approaches for detection of individual targets. Figure adapted from [55].

## Section 5 *The Proof is in the Pudding*

There are many reasons to assume that the deeper and broader field induced with Deep TMS are advantageous in the treatment of MDD. However, the true test of efficacy is patient response in adequately powered randomized clinical trials.

Deep TMS and figure-8 TMS have not been compared directly in head-to-head studies, each intervention was cleared by the FDA based on results from large-scale pivotal clinical trials, which compared active to sham TMS.<sup>13,57</sup> Although the two studies employed somewhat different designs, they enrolled MDD patients that presented with roughly similar baseline clinical and demographic characteristics, and both assessed clinical response using well-validated clinician-administered rating scales for depression. Notably, dropout rates in both trials were similar, suggesting no substantial difference in treatment tolerability.

Remission is considered the preferred endpoint for treatment of major depression, as it is associated with the best prognosis for recovery.<sup>58-61</sup> In the multicenter randomized controlled trial of Deep TMS, which led to FDA clearance of the BrainsWay device, 1 in 3 patients achieved remission after 4 weeks of active Deep TMS treatment.

While the results of the two trials are not strictly comparable, they provide an idea of the general degree of response seen with each intervention. The reader is encouraged to examine these published studies closely. A summary of the results is provided in this section.

The randomized double-blind sham-controlled multicenter trial leading to FDA clearance of the BrainsWay TMS device was conducted globally at 20 sites in the U.S., Israel, Germany and Canada. The study included 212 medication-free patients with major depressive disorder who had not received benefit from 1 to 4 antidepressant trials (mean=1.70).

Patients were randomly assigned to monotherapy with either active Deep TMS with the H1-coil or sham TMS for a 4-week acute treatment phase followed by a 12-week continuation

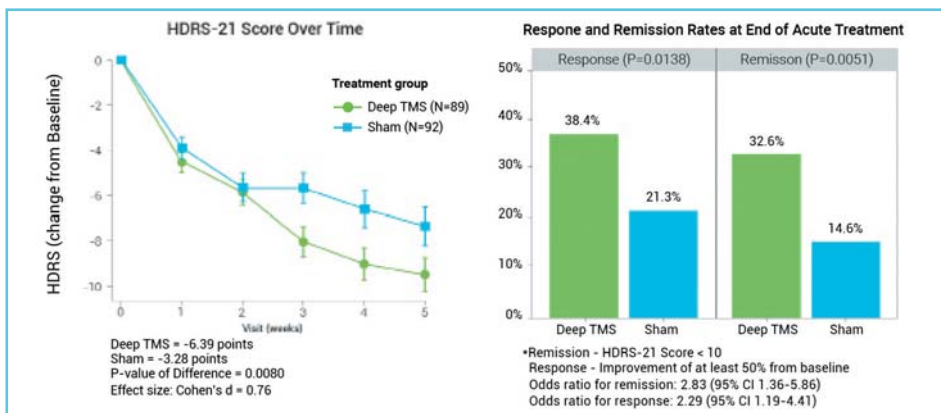
maintenance phase of bi-weekly treatment. During the acute phase, Deep TMS was administered 5 times per week. Deep TMS was administered using the H1-coil, intensity, 18-Hz pulse frequency.

Treatment sessions lasted for 20 minutes for a total of 1,980 magnetic pulses delivered per session. Blinding was achieved using an advanced sham methodology, in which electronically switchable active and sham coils were incorporated into the same helmet. The sham coil was designed to mimic the scalp sensations and acoustic artifact of

the real H1-coil, without inducing neuronal activation. The primary efficacy measure was the change in depressive symptom scores as assessed after 4 weeks of acute treatment with the 21-item Hamilton Depression Rating Scale (HDRS-21). Secondary efficacy measures were response and remission rates with the HDRS-21 after 4 weeks. The treatment was well-tolerated, with a relatively low discontinuation rate of 8.1% in the active Deep TMS arm.

Per-protocol analysis revealed a statistically and clinically significant improvement relative to sham on all primary and secondary outcome measures. Active Deep TMS induced a 6.39 point improvement in HDRS-21 scores, while a 3.28 point improvement was observed in the sham group (difference  $p=0.008$ ; Effect size=0.76). A statistically significant benefit relative to sham was also apparent in response rate (38.4% vs. 21.4%,  $p=0.013$ ) and in remission rate (32.6% vs. 14.6%,  $p=0.005$ ). The odds ratio for response was 2.29 (95% confidence interval [CI] 1.19- 4.41), and the odds ratio for remission was 2.83 (95% CI 1.36-5.86) (Figure 9).

The FDA clearance for the NeuroStar TMS System, which features an iron-core figure-8 coil, was based on the first randomized controlled multicenter trial of rTMS for MDD, which was conducted at 23 centers in the U.S., Australia, and Canada. The study included 301 medication-free MDD patients who had failed between 1 and 4 adequate antidepressant treatments (mean=1.6) during the current or most recent episode of depression. The study consisted of a 1-week lead-in phase followed by a 4-6-week acute treatment phase, during which TMS was administered 5 times weekly. TMS was administered to the left DLPFC, at 120% MT, 10-Hz pulse frequency. Treatment sessions lasted for 37.5 minutes for a total of 3,000 magnetic pulses delivered per session. Sham TMS was delivered using to the left DLPFC, at 120% MT field intensity, 10-Hz pulse frequency. Treatment sessions lasted for 37.5 minutes for a total of 3,000 magnetic pulses delivered per session.



**FIGURE 9.** Continuous and categorical outcomes in the Brainsway multicenter trial.<sup>13</sup>

Treatment sessions lasted for 37.5 minutes for a total of 3,000 magnetic pulses delivered per session. Sham TMS was delivered using a sham coil similar to the active coil in weight, appearance and acoustic properties, but which contained an embedded magnetic shield.

In a subsequent clinical trial of this device,<sup>53</sup> the sham condition was improved by the addition of scalp electrodes designed to mimic somatosensory sensations of TMS as well. The primary efficacy measure in this study was the change in depressive symptom scores after 4 weeks of treatment with the Montgomery–Asberg Depression Rating Scale (MADRS). Secondary efficacy measures included changes on the 17- and 24-item HDRS, as well as categorical endpoints (response and remission) with the MADRS and HDRS at weeks 4 and 6. The treatment was welltolerated, with an overall dropout rate of 7.7% reported for the active TMS arm.

This trial employed a duration adaptive design for antidepressant trials,<sup>62</sup> which enforces dropout of patients failing to improve after 4 weeks of acute treatment. Randomization was thus only truly present up to the primary efficacy time-point at week 4. Scores for 49% (148/301) of subjects who dropped out at week 4 were carried forward from prior visits, confounding interpretation of the 6-week results.

At week 4, both groups experienced improvement in MADRS scores: 5.8 points in the active TMS group versus 4.1 points in the sham group, but the difference did not reach significance (difference  $p=0.057$ ; Effect size=0.355). Statistically significant differences were observed on the HDRS-17 and HDRS-24. Remission rates were generally low

depending on the scale, but better with active TMS (7.1% to 9.0% vs. 6.2% to 8.2% with sham) and the difference relative to sham was not statistically significant in any of the scales. The continuous and categorical outcomes on all three depression rating scales are summarized in Table 1. The reported 6-week results are included for completeness. These trials represent the strongest class of evidence for the antidepressant efficacy of left prefrontal TMS using the NeuroStar system and Deep TMS using the H1-coil. Despite using different sham methodologies, stimulation parameters, and rating scales for depression, the trials share certain important commonalities. The patient populations of the two studies overlap with regard to demographics, clinical diagnosis, symptom severity and prior treatment failure (See Table 2). Both trials applied TMS as a monotherapy in medication-free patients, and compared it to sham stimulation. Finally, both studies followed a similar design up to the primary efficacy time-point after 4 weeks of treatment, which corresponds to a treatment course of 20 TMS sessions. While no direct quantitative comparisons may be made between the respective outcomes of the two studies, general comparisons are appropriate, and are most relevant at the primary efficacy endpoint of each study.

Although these studies used different continuous outcome measures, quantitative comparisons between their results may be made using standardized effect sizes. The standardized effect size for the difference in depression scores between active and sham TMS after 4 weeks of treatment was 0.76 for the H1-coil, and ranged between 0.36-0.56 for the figure-8 coil, depending on the scale. For comparisons of categorical outcomes (response and remission)

where the sham response rates vary between groups, odds ratios are appropriate. After 4 weeks of acute treatment, the odds ratio for remission, the ultimate endpoint of any antidepressant therapy, was found to be 2.83 for the H1-coil, compared to 1.11-1.16 with the figure-8 coil, depending on the scale (See Figure 9; Table 1).

**Table 1** *Continuous and categorical outcomes in the NeuroStar multicenter trials<sup>57</sup>*

	4 Weeks					6 Weeks					
	TMS	Sham	Difference	p	Effect Size	TMS	Sham	Difference	p	Effect Size	
Number	155	146				92	98				
Continuous						Cohen's d					
MADRS	27.0	29.8	-2.8	0.057	0.355	26.8	30.0	-3.2	0.058	NR	
HDRS-17	17.4	19.4	-2.0	0.006	0.556	17.1	19.6	-2.5	0.005	NR	
HDRS-24	23.4	25.9	-2.5	0.012	0.481	23.2	26.0	-2.8	0.015	NR	
Categorical						Odds Ratio (95% CI)					
Response %						Odds Ratio (95% CI)					
MADRS	18.1	11.0	7.1	<0.05	1.79 (0.92-3.46)	23.9	12.3	11.6	<0.1	2.24 (1.21-4.15)	
HDRS-17	20.6	11.6	9.0	<0.05	2.00 (1.05-3.79)	24.5	13.7	10.8	<0.05	2.04 (1.13-3.71)	
HDRS-24	19.4	11.6	7.8	<0.05	1.83 (0.96-3.49)	23.9	15.1	8.8	<0.05	1.77 (0.98-3.17)	
Remission %						Odds Ratio (95% CI)					
MADRS	7.1	6.2	0.9	>0.1	1.16 (0.47-2.87)	14.2	5.5	8.7	<0.05	2.84 (1.22-6.60)	
HDRS-17	7.1	6.2	0.9	>0.1	1.16 (0.47-2.87)	15.5	8.9	6.6	0.065	1.88 (0.92-3.84)	
HDRS-24	9.0	8.2	0.8	>0.1	1.11 (0.49-2.48)	17.4	8.2	9.2	<0.05	2.36 (1.15-4.86)	

NR = Not reported

**Table 2** *Baseline clinical and demographic characteristics of the separate study populations of the multicenter trials that led to FDA clearance of the BrainsWay13 and NeuroStar57 devices*

	Levkovitz et al. 2015		O'Reardon et al. 2007	
	TMS	Sham	TMS	Sham
Number	101	111	155	146
Age (years ± SD)	45.1 ± 11.7	47.6 ± 11.6	47.9 ± 11.0	48.7 ± 10.6
Gender (% female)	47.5	47.7	56	51
Failed adequate antidepressant trials (mean ± SD)	1.70 ± 1.32		1.6	
Current episode duration (months ± SD)	21.7 ± 16.3	19.5 ± 15.2	13.6 ± 9.9	13.2 ± 9.5
Baseline depression scores (mean ± SD)				
MADRS	-	-	32.8 ± 6.0	33.9 ± 5.7
HDRS-17	-	-	22.6 ± 3.3	22.9 ± 3.5
HDRS-24	-	-	30.1 ± 5.0	30.5 ± 4.9
HDRS-21	23.5 ± 4.3	23.4 ± 3.7	-	-



# Reality Check-List

- ✓ BrainsWay Deep TMS H-coils possess an irrefutable advantage in terms of attenuated field decay compared to figure-8 coils.
- ✓ Increased depth penetration of the H1-coil is real and proven by evidence from a number of sources including field measurements and realistic simulations.
- ✓ The deeper and broader field distribution of the H1-coil is believed to provide especially strong advantages in the target of depression treatment, the lateral PFC.
- ✓ Cortical folding is prominent in the PFC. Deeper fields are better able to engage prefrontal circuitry in sulcal folds, where activation by TMS is thought to dominate.
- ✓ The functional and structural architecture of the PFC is highly variable across individuals, making localization of TMS depression targets for focal stimulation almost impossible with any current methodology. This strongly favors the use of broader and deeper prefrontal stimulation.
- ✓ BrainsWay's multicenter randomized controlled trial demonstrates the exceptional efficacy of Deep TMS therapy for medication-resistant major depression.

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**BrainsWay System  
with H1 and H7 coils**



**BrainsWay**

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**Indication:**

BrainsWay Deep TMS is indicated by the FDA for the treatment of depressive episodes in adult patients suffering from Major Depressive Disorder, who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode. FDA 510(k) No. K122288.

**Safety Information**

Patients should consult with their doctor before undergoing Deep TMS. The most common side effects include headaches and application site pain or discomfort. There is also a very rare risk of seizure associated with the treatment. Patients with metal in or around the head, such as in metal plates, implants and stents, should not undergo Deep TMS treatment.