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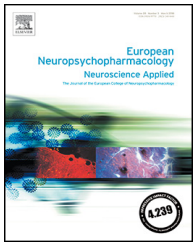

# Application of transcranial magnetic stimulation for major depression: Coil design and neuroanatomical variability considerations

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**Abstract**
High-frequency repeated transcranial magnetic stimulation (rTMS) as a treatment for major depressive disorder (MDD) has received FDA clearance for both the figure-of-8 coil (figure-8 coil) and the H1 coil. The FDA-cleared MDD protocols for both coils include high frequency (10–18 Hz) stimulation targeting the dorsolateral prefrontal cortex (dlPFC) at an intensity that is 120% of the right-hand resting motor threshold. Despite these similar parameters, the two coils generate distinct electrical fields (e-fields) which result in differences in the cortical stimulation they produce. Due to the differences in coil designs, the H1 coil induces a stimulation e-field that is broader and deeper than the one induced by the figure-8 coil.
In this paper we review theoretical and clinical implications of these differences between the two coils and compare evidence of their safety and efficacy in treating MDD. We present the design principles of the coils, the challenges of identifying, finding, and stimulating the optimal brain target of each individual (both from functional and connectivity perspectives), and the possible implication of stimulating outside that target. There is only one study that performed a direct comparison between clinical effectiveness of the two coils, using the standard FDA-approved protocols in MDD patients. This study indicated clinical superiority of the H1 coil but did not measure long-term effects. Post-marketing data suggest that both coils have a similar safety profile in clinical practice, whereas effect size comparisons of the two

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respective FDA pivotal trials suggests that the H1 coil may have an advantage in efficacy. We conclude that further head-to-head experiments are needed, especially ones that will compare long-term effects and usage of similar temporal stimulation parameters and similar number of pulses.


## 1. Introduction

Despite the high prevalence of major depressive disorder (MDD), treatment options are often lacking. Depression is the fourth leading source of disease burden (Ferrari et al., 2013; Murray et al., 2015; Üstün et al., 2004), and that is only projected to increase over the next 15 years, particularly in high-income countries (Mathers and Loncar, 2006). Of those with MDD, only a small fraction receive adequate treatment (Ebmeier et al., 2006), and the situation is worse for those with treatment resistant depression (TRD), which describes 20–30% of depressed patients (Berlim et al., 2008a; Mathew, 2008). For such patients, pharmacological interventions are not an option, and even for those who do respond, current medications often come with significant side effects (Lam et al., 2009).

Over the past decade, repetitive transcranial magnetic stimulation (rTMS) has become a promising, noninvasive and safe (Rossi et al., 2009) alternative to medication for the treatment of MDD (Berlim et al., 2008b; M.T. 2014; George, 2010; Perera et al., 2016a; Voigt et al., 2017). TMS is performed by passing an electric current through a coil placed on the scalp. This current generates a temporary magnetic field that passes through the scalp, skull and intermediate layers of the cortex, such that a suprathreshold (>100 V/m) electrical field (e-field) is generated within the cortex and activates local neuronal activity.

Clinically, in its most common form, high-frequency (≥10 Hz) rTMS is applied above the left dorsolateral prefrontal cortex (dlPFC) over the course of several weeks (George et al., 2013a; Perera et al., 2016a) with response and remission rates of about 30% and 20% respectively, according to the most recent meta-analysis of randomized controlled trials (RCT) (Berlim et al., 2014). Rates reported in non multi-center RCTs and those observed in the clinics are higher and at least as robust as antidepressant medication (George et al., 2013a; Mutz et al., 2018). However, there is potential for rTMS to improve its efficacy even further if it can overcome its high inter-individual variability in response strength and effect duration (Daskalakis et al., 2008; De Raedt et al., 2015; Fitzgerald, 2009; George et al., 2013a).

High-frequency rTMS over the dlPFC as a treatment for MDD first received FDA clearance in 2008 using a focal iron core figure-8 coil (Neuronetics Inc., Malvern, PA, USA) followed by, in 2013, a second device using the H1 coil (Brainsway, Jerusalem, Israel) (Perera et al., 2016a). While similar in application, the two coils differ greatly in approach, with radically different design principles that affects the depth and breadth of the induced e-field. Here we review these design differences and how each design relates to and possibly addresses the many issues and challenges of rTMS treatment of MDD.

## 2. Design principles of the figure-8 coil

The figure-8 coil (Fig. 1a and b) consists of two adjacent wings, with an identical number of turns, such that the current orientation is clockwise in one loop and anti-clockwise in the other. This alignment creates a superimposition of the currents which induces direct stimulation focally in superficial cortical regions underneath the central segment. As such, neuronal fibers oriented parallel to the central segment are most likely to be stimulated (Basser and Roth, 1991; Chen et al., 2003; Roth and Basser, 1990). The relative angle between the wings affects the efficiency and focality of the coil, such that coil elements which are non-tangential to the scalp induce accumulation of surface charge that reduces coil efficiency and depth penetration (Eaton, 1992; Roth et al., 2002; Tofts, 1990; Tofts and Branston, 1991). For example, when the angle is smaller than 180° the wings are more tangential to the scalp and the efficiency increases (Thielscher and Kammer, 2004), but the coil is less convenient for fine localization over the head.

## 3. Design principles of the H1 coil

The H1 coil (Fig. 1c and d) has a flexible base that allows the coil to conform to the curvature of the scalp of the individual patient for maximal magnetic coupling at the required position and orientation. The coil includes base elements carrying “forward” stimulating currents aligned along a common direction tangential to the scalp, and coil elements carrying “return” current paths positioned away from the base. As such, non-tangential electric field components are minimized over the targeted area and accumulation of electrostatic charge on the brain surface is reduced, thereby improving field depth penetration (Eaton, 1992; Roth et al., 2002; Tofts, 1990; Tofts and Branston, 1991). Optimal and effective field summation in depth requires that coil elements in the base are dispersed rather than forming a dense organization, as in a figure-8 coil (Roth et al., 2013; Tendler et al., 2016). The various elements induce a summation of the electric field in the targeted deep brain region, with a sufficiently high e-field intensity relative to the maximal field located at the brain’s surface (Heller and van Hulsteyn, 1992).

## 4. E-field characteristics

While the influence of the e-fields induced by TMS cannot be easily measured in the living brain, there are numerical, analytical and experimental approaches to estimate depth (defined as the distance along a radial direction

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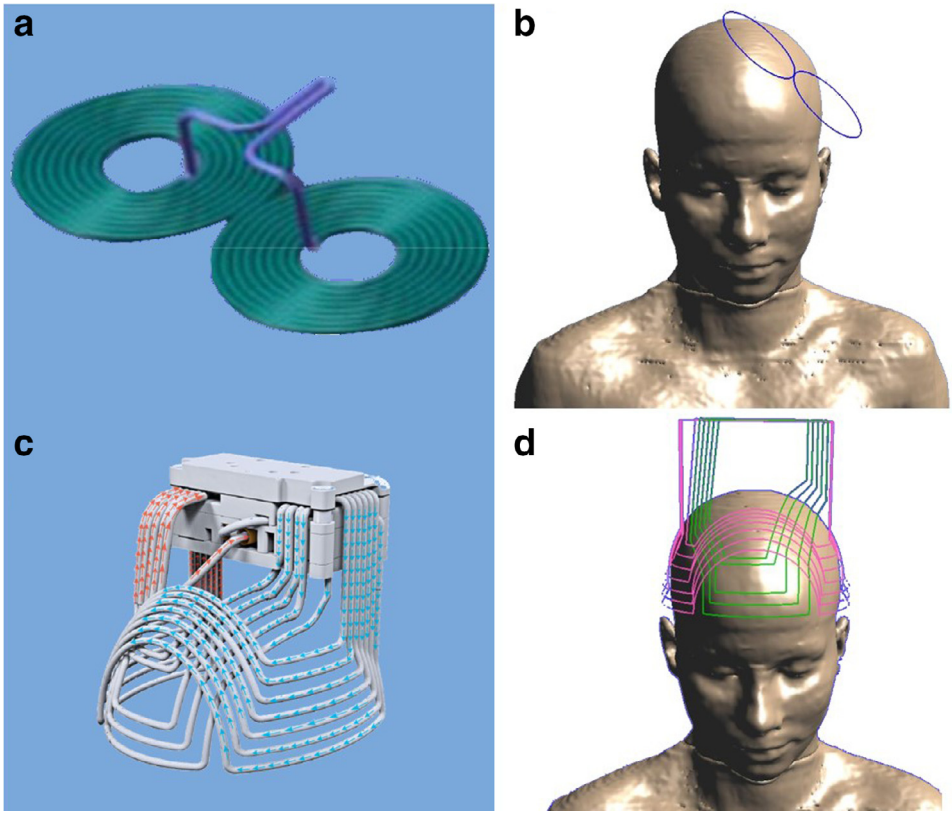


**Fig. 1 Coil Designs of the figure-8 coil (a,b) and H1 coil (c,d).** Schematic of the figure-8 coil (a) and its placement on the head targeting the left dlPFC (b); adapted with permission from (Parazzini et al., 2017b). Schematic of the H1 coil (c) and its placement on the head targeting the left dlPFC (d); adapted with permission from (Parazzini et al., 2017b).

passing through the brain center), the rate of decay, and the spatial distribution of the e-field.

An analysis using a spherical, single shell head model (Deng et al., 2013) found a deeper penetration of the H1 coil compared to the figure-8 coil, with a 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; Fig. 2a). In addition, in studies that measure the rates of decay in a phantom head model filled with a saline solution (Rosenberg et al., 2010; Roth et al., 2007) the H1 coil was found to have a more gradual drop in e-field intensity that allowed deeper penetration at safe stimulation levels (Fig. 2b). Safety guidelines of rTMS suggest limiting stimulation intensities to 120% of the motor threshold (Rossi et al., 2009). To reach similar depths with the figure-8 coil, the stimulation intensity would have to be increased beyond the safety limits, which can cause pain and increase the risk of seizure.

In recent years, realistic computational models based on high-resolution anatomical magnetic resonance imaging (MRI) have emerged. These models faithfully reproduce not only the variable curvature of the skull surface and its non-uniformity, but also the characteristics and properties of brain tissues (such as cerebrospinal fluid, gray matter, white matter, etc.). As such, these models allow investigation of the possible role of complex anatomical structures on electric field distributions, and may provide more realistic estimations of depth penetration (Christ et al., 2010). Currently, only one study of TMS induced e-fields (Guadagnin et al., 2016) includes a head to head comparison of the H1 coil and figure-8 coil with a clinical relevant value. This study examined the depth below the cortical surface for which the stimulation intensity remains suprathreshold when stimulating with the common treatment protocols for depression (Levkovitz et al., 2015; O'Reardon et al., 2007). This intensity of 120% of MT is considered the maximal intensity for rTMS in the safety guidelines (Rossi et al., 2009). The results showed that when measured with the coils positioned over the Cz electrode, the H1 coil has a depth penetration of 1.8 cm from the cortical surface compared to 1.1 cm for the figure-8 coil. Parazzini et al. also compared the H1 coil and the figure-8 coil head to head with the coils positioned over the more clinically relevant target of the dlPFC (Fig. 3) but did not quantify the results with clinically relevant values (Parazzini et al., 2017b). Another distinction between the generated fields apparent from Fig. 3 is that the H1 coil, while preferentially stimulating the left hemisphere, produces a bilateral supra-threshold field. Finally, deeper stimulation comes at the expense of focality (Deng et al., 2013), which can be assessed using a realistic head model filled with physiological saline solution. Using this approach, which mimics the conductive properties of neural tissue, the field maps generated by each coil when set to a stimulus intensity of 120% MT revealed a total

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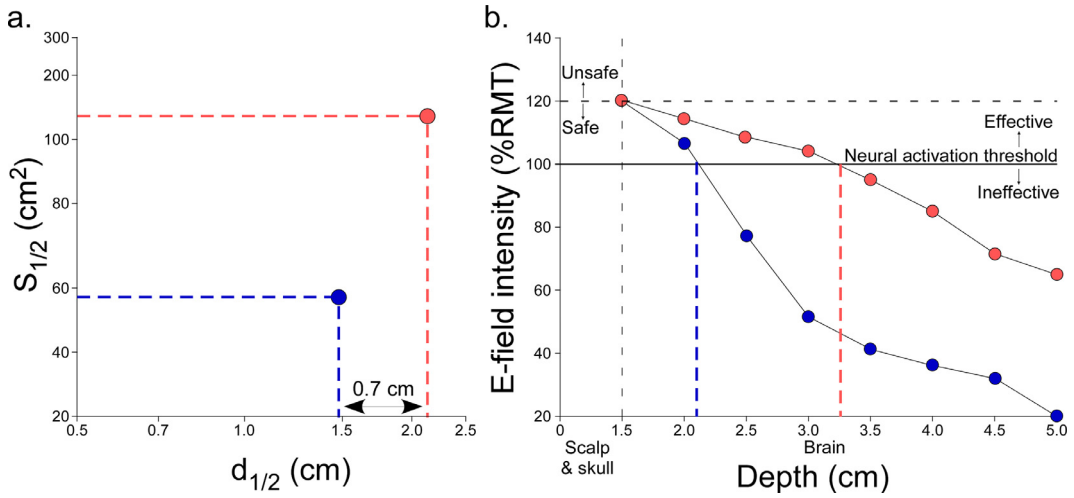


**Fig. 2 E-field depth and decay as a function of stimulation intensity.** (a) Electric field focality quantified by the half-value spread, $S_{½}$, as a function of the half-value depth, $d_{½}$, in a simple spherical model for the H1 coil (red) and the figure-8 coil (blue), as modified from (Deng et al., 2013). (b) Decay profiles of the electric fields produced by the H1 coil (red) and figure-8 coil (blue). 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 (based on data from (Roth et al., 2007)) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

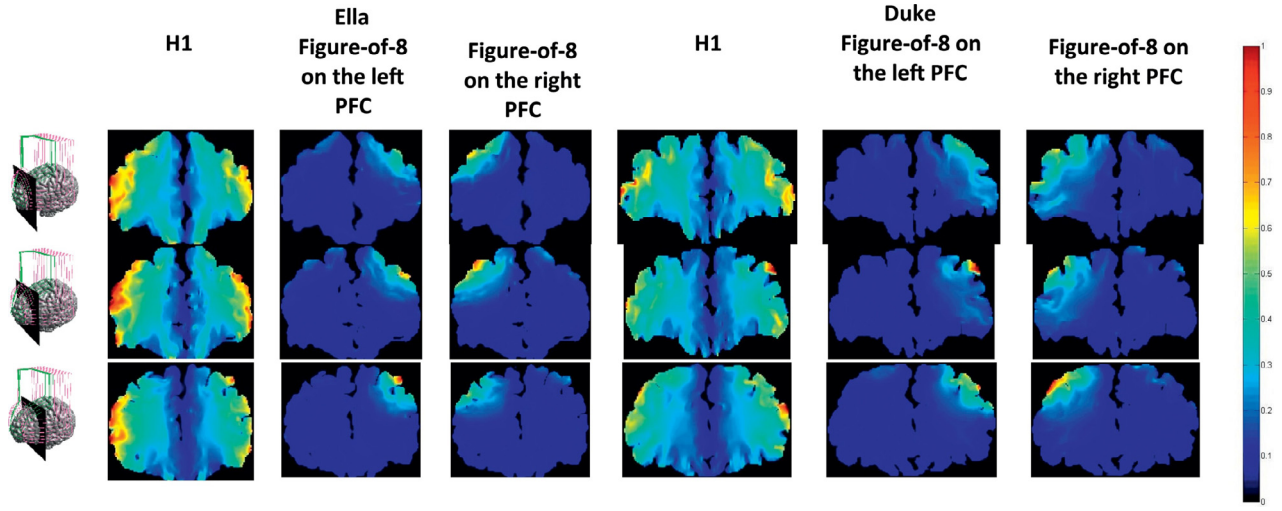


**Fig. 3 Distribution of the e-field.** Coronal maps of e-field distributions, normalized to the maximal e-field at the cortex, based on simulations in an anatomically realistic computational head model with coils positioned to target the dlPFC; reproduced from (Parazzini et al., 2017b).

stimulated brain volume of 18 cm$^3$ for the H1 coil compared to 3 cm$^3$ for the figure-8 coil (Ginou et al., 2014; Rosenberg et al., 2010).

Taken together, these methods verify that the two coils differently interact with the brain tissue, with a focal and superficial e-field induced by the figure-8 coil, and a deeper and more distributed e-field induced by the H1 coil.

## 5. Stimulating the target

The choice of the left dlPFC as the target for rTMS is based on associations between depression and impaired left dlPFC activity, but primarily on the empirical success of a large number of rTMS trials (Downar and Daskalakis, 2013). As the average thickness of the cortical gray matter strip is just 2 mm (Fischl and Dale, 2000), and the coil-to-cortex distance is usually less than 1.5 cm in most subjects (Haeussinger et al., 2011), neither clinically used coil has a problem with inducing a direct stimulation of the cortex. However, stimulation depth may still play an important role. As much as two thirds of the surface area of the cortex forms the walls of sulci, and is hidden from surface view (Rogers et al., 2010). In addition, the favorable field orientation for neuronal stimulation is along the neuronal axis (Day et al., 1989; Rushton, 1927). Therefore, it has been

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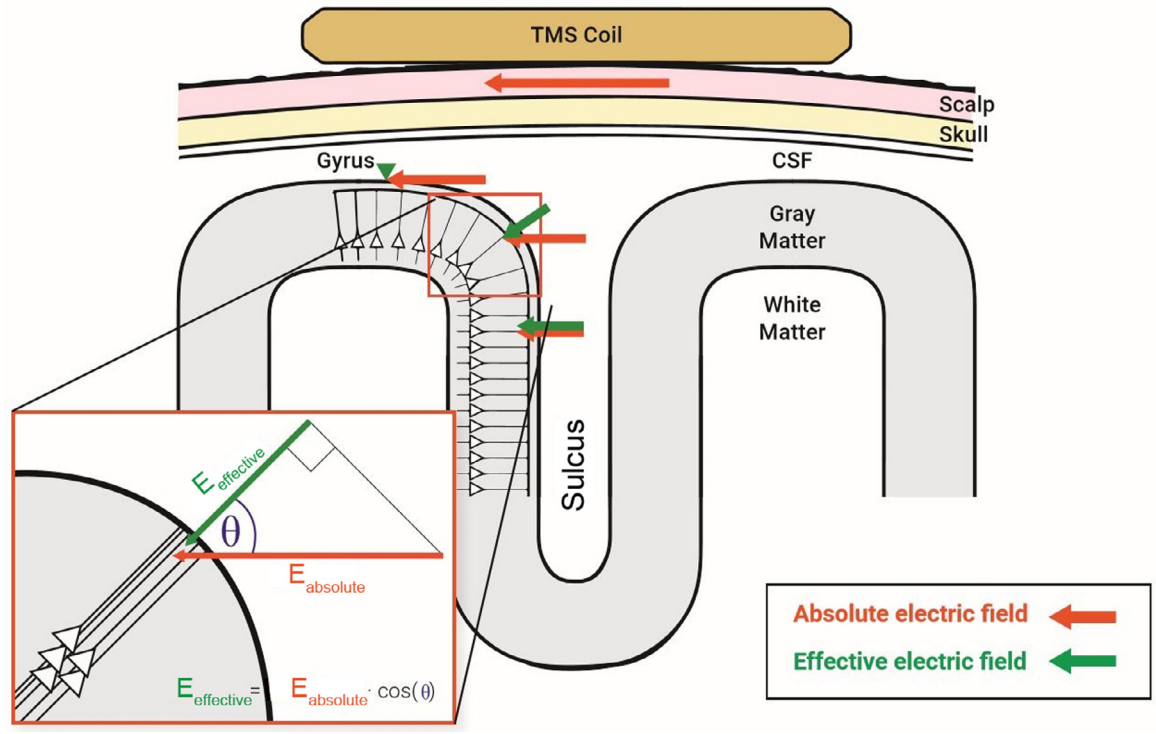


**Fig. 4 Model of the cortical columns.** Evidence suggests that stimulation is more efficient as the cortical column becomes perpendicular to the surface (i.e. along sulcal banks) rather than parallel to it (i.e. at the gyral crown). The Cortical Column Cosine (C3) model (Fox et al., 2004) proposes 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 gyral crowns.

proposed (Fox et al., 2004) that stimulation is more efficient along the sulcal banks than at the gyral crowns, since, at these locations, cortical pyramidal neurons are aligned with the induced electric field vector. This is due to the organization of cortical pyramidal neurons into mini-columns oriented perpendicular to the cortical surface (Buxhoeveden and Casanova, 2002) and the fact that TMS involves the induction of tangential, but not radial currents (Tofts and Branston, 1991; Fig. 4). This preferential activation of sulcal targets by TMS is supported by volume conducting modelling (Janssen et al., 2015; Laakso et al., 2018; I. 2014; Nummenmaa et al., 2014; Parazzini et al., 2017a; Silva et al., 2008) and functional neuroimaging (Krieg et al., 2015; T.D. 2013). If indeed the principal site of action of TMS is within the depths of the sulci, there is advantage of penetrating deeper. This advantage may be of particular importance in the lateral PFC, where both sulcal depth (Jones et al., 2000), and the inter-individual variability in sulcal depth (Hill et al., 2010) are among the highest of any area in the brain.

It has been recently suggested that the success of the dlPFC as a target for MDD treatment is due not to induced changes to local activity in the dlPFC but rather to its connectivity to subcortical regions of the reward network (De Raedt et al., 2015). Since subcortical regions are not directly accessible to TMS stimulation, the dlPFC acts as a gatekeeper. Stimulation over the dlPFC results in the activation of projection fibers which leads to the propagation of the evoked activity down to the subcortical regions. Realistic computational models based on high-resolution anatomical MRI images have recently begun to include diffusion tensor images (DTI) with reconstructed white matter fiber tracts and simulated neuronal activity to explore how TMS activation propagates down to deeper structures (Seo and Jun, 2017). Based on these simulations, direct stimulation of the white matter is initiated at sharp bends in the fibers which occur at different depths for different tracts (De Geeter et al., 2016; N. 2015). This is of particular relevance since rTMS of the dlPFC has been shown to induce changes in activity of the subgenual anterior cingulate (Dowdle et al., 2018; Kimbrell et al., 2002; Li et al., 2004; Narushima et al., 2010). While deeper stimulation is not necessary in order to induce such indirect activity changes, as is evident empirically from these studies as well as by simulation studies using the figure-8 coil (De Geeter et al., 2016), inducing a deeper field would be expected to result in a greater recruitment of white matter tracts due to its ability to recruit fibers with deeper bends. This in turn will result in stronger propagation to the subcortical targets and therefore may augment the antidepressant response to TMS. In addition, while the depth of suprathreshold stimulation for the H1 coil is well short of the subgenual nucleus, it still generates there stimulation with intensities as high as 42% of the maximal field at the surface of the brain, as opposed to the figure-8 coil which generate only 6% of the maximal field at these depths (Parazzini et al., 2017a). While subthreshold,

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the direct stimulation would be expected to have an additive effect, boosting the secondary stimulation via the white matter tracts. This is of greater importance when considering that depression represents a "disconnection syndrome" characterized by disconnections in pathways between the frontal cortical and subcortical limbic regions due to abnormalities in white matter microstructures (Liao et al., 2013; Sexton et al., 2009). For example, Avissar and colleagues showed that the baseline connectivity between the dlPFC and subgenual nucleus correlates with the efficacy of the treatment with a figure-8 coil (Avissar et al., 2017). Therefore, patients with more severe connectivity deficiencies should theoretically benefit from the greater recruitment of pyramidal tracts by the H1 coil (Avissar et al., 2017).

## 6. Finding the target

Along with the challenge of effective stimulation of the target, there is the challenge of locating the target. The routine practice used in most clinical trials is the "5-cm rule" (Perera et al., 2016b), an empiric method used for probabilistic targeting of the dlPFC based on its relative location to the hand area of the motor cortex (5 or 6 cm anteriorly). In the latest survey of members of the clinical TMS society, 77.6% of responders still use a 5 or 6 cm rule in their clinics for targeting the dlPFC (Perera et al., 2016b), and a recent review of 81 randomized controlled trials found that 79% used either the 5 or 6 cm rules (Brunoni et al., 2017). However, the "5-cm rule" may be suboptimal as it neither accounts for differences in skull size or variations in prefrontal anatomy relative to motor cortex location (Rajkowska and Goldman-Rakic, 1995), 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 (Herwig et al., 2001). For example, in a large sham-controlled trial with the figure-8 coil (George et al., 2010), 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, TMS would have been administered outside the target area entirely in 33.2% of patients. In addition, a prospective clinical trial comparing the "5-cm rule" to a more anatomically precise stereotaxically guided and MRI-based figure-8 coil rTMS targeting procedure found that the latter method produced greater clinical improvement (Fitzgerald et al., 2009; also see Ayache et al., 2016), although this has not been confirmed in a large sample (McClintock et al., 2017).

The challenge of targeting is even greater when considering that the optimal target may not be anatomical but rather functional. Fox et al. (2012) 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 figure-8 TMS sites within the dlPFC and intrinsic functional connectivity with the subgenual cingulate cortex. The authors suggest that these results can be translated into a connectivity-based targeting strategy for focal brain stimulation to optimize the clinical response. However, in a subsequent study, the same group demonstrated that there is substantial inter-individual variability in the precise location of the putative optimized targets identified by this strategy, which argues against the efficacy of population-based targeting approaches (Fox et al., 2013; Weigand et al., 2018). Thus, even within the general anatomical prefrontal area, the efficacy of different TMS sites may vary considerably between individuals. As mentioned previously, the PFC contains a high degree of folding (Mueller et al., 2013; Toro et al., 2008; Zilles et al., 1988), with specific patterns of folding that varies considerably across individuals such that the gyrification pattern of each human brain appearing as an individual 'fingerprint' (Toga, 2015). Moreover, the regions presenting maximum folding coincide with the regions of highest variability in measures of network connectivity (Mueller et al., 2013). For these reasons and taking into account that the cortical area excited by the figure-8 coil is focal and relatively small (Ginou et al., 2014; Rosenberg et al., 2010), structural anatomy based navigation 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 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 neuro-navigation 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 these coils, yet it is impractical in routine psychiatric care (McClintock et al., 2017). By contrast, the electric field induced by the H1 coil is sufficiently broad to include the wider lateral PFC, hence this concern is less relevant for the H1 coil. However, as neuronavigation techniques improve in time and decrease in cost, the concern for missing targets with a figure-8 coil in the clinical setting will likely diminish.

A further source of variability in TMS treatment is the possibility of other targets within the PFC (i.e. other than the dlPFC) for rTMS in depression. Evidence regarding the emotional function of the frontal lobe (not available 25 years ago when the dlPFC was first suggested as the target for rTMS in depression treatment) points to the various advantages of the dorsomedial prefrontal cortex (dmPFC), frontopolar cortex (FPC), ventromedial prefrontal cortex (vmPFC), and ventrolateral prefrontal cortex (vlPFC) (Anderson et al., 2016; Downar and Daskalakis, 2013). These regions are not directly activated by the figure-8 coil when placed over the dlPFC, but structures in these regions may be stimulated by the broader field of the H1 coil. Here too, the optimal target may differ between individuals (Dubin et al., 2017). For example, a recent study by Drysdale and colleagues used resting state connectivity to differentiate between 4 subtypes of depression and found that rTMS targeted to the dmFPC was most effective for one of the subtypes (Drysdale et al., 2017).

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## 7. Stimulating outside the target

TMS stimulation is never restricted to the targeted area and, due to the interconnectivity of the brain, the stimulation reaches even areas far from the coil (Li et al., 2004; Vink et al., 2018). This is a major concern when considering the broader e-field of the H1 coil, which theoretically may affect neuronal populations whose stimulation produces unwanted or interfering effects (Dubin, 2017; Dubin et al., 2017). The focal stimulation of the figure-8 coil, on the other hand, likely minimizes this issue, assuming the correct coil placement and localization of the target (see previous section).

The concern of stimulating non-pathological tissue is particularly relevant due to the preferentially left but bilateral stimulation of the H1 coil. The motivation for bilateral high frequency stimulation was the clear evidence that bilateral ECT is superior to unilateral ECT (Daskalakis et al., 2008, but see Hermida et al., 2018 for a more current review). However, initial studies investigating bilateral high frequency rTMS compared to sham were unsuccessful (Loo et al., 2003). In fact, more recent evidence points to the beneficial effect of low frequency rTMS over the right dlPFC (Cao et al., 2018) and bilateral stimulation protocols therefore tend to consist of sequential stimulation of high and low frequency stimulation over the left and right dlPFC respectively (Daskalakis et al., 2008; Lee et al., 2012). Nonetheless, it is worth noting a preliminary study (Levkovitz et al., 2009), in which the efficacy of the H1 coil in treating subjects with depression was compared to the more bilaterally symmetric H2-coil and the H1L-coil which exclusively stimulates the left PFC. In this study, stimulation with all three coils demonstrated a significant reduction is depression scores without a significant difference between the coils. Yet the effect of stimulation with the H1 coil (42% remission rate) or the H1L coil (60% remission rate) were both higher than the effect with the H2 coil (10% remission rate). This suggests that like the figure-8 coil, the main mechanism of treatment for the H1 coil is stimulation of the left dlPFC.

Whether stimulation beyond the target modifies the activity of non-pathological tissue and, if so, in fact leads to undesirable behavioural side effects is yet unknown. There is almost no research on unintended behavioural effects of stimulation beyond the primary measures of the study. However, cognitive performance has been tested following treatment with TMS in subjects with depression. While the literature contains many reports of negative results showing no reduction in depression related cognitive deficits, and even some reports of cognitive improvement, there are no instances of treatment-induced deterioration with either the figure-8 coil (Serafini et al., 2015) or the H1 coil (Kaster et al., 2018; Kedzior et al., 2016; Levkovitz et al., 2009).

## 8. Clinical findings

Much of the above discussion is theoretical, suggesting possible benefits and drawbacks of the two coil designs but which have not been sufficiently explored empirically. However, as with any clinical intervention, the best test of efficacy is patient response in adequately powered RCTs, and particularly in large multicenter studies.

Each intervention was cleared by the FDA based on results from separate large-scale pivotal, multicenter RCTs, which compared active and sham rTMS (Y. Levkovitz et al., 2015; O'Reardon et al., 2007). The two studies 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. However, due to differences in design and stimulation parameters (e.g. stimulation frequency and number of pulses), it can be difficult to determine the relative efficacy of the two techniques. Therefore, in this section, we limit our analysis to the data clearly presented in the studies that can be used to determine an effect size and present only results from each study's primary endpoint (Table 1). Another large RCT using the figure-8 coil was designed to determine optimal session number (George et al., 2010). This study is notable as it is the only academic, non-industry sponsored, multicenter RCT exploring rTMS treatment of MDD. However, unlike the above studies, this study had a dynamic design in which subjects received daily rTMS treatment for different durations, many completing their participation before the primary endpoint. Hence, the results of this study are more difficult to compare to the two pivotal studies with fixed primary endpoints.

Table 1 summarizes the features and results of both pivotal multicenter RCTs. The limitations of each study and the differences between them are discussed below. Importantly, since much of the above discussion regarding differences between coils relates to the variability between subjects, we focus on the categorical measures of response and remission, which are also considered the preferred endpoints for treatment of major depression (Rush et al., 2006), and associated with the best prognosis for recovery (Fava, 2003; Keller, 2003; Sobocki et al., 2006; Trivedi et al., 2009).

As seen in Table 1, both trials tested high-frequency rTMS against a sham control but differed in the exact protocol, including higher frequency but lower pulse number and session length in the H1 coil study. In both studies the primary outcome, measured at the end of 4 weeks, did not pass the 0.05 threshold of significance for the reported intent to treat (ITT) population. O'Reardon achieved significance only after removing subjects with low baseline MADRS scores, and Levkovitz showed a significant effect for the per-protocol population, removing subjects who did not receive the rTMS at the full 120% intensity (based on a previous study that showed stimulation intensity to significantly affect the response (Levkovitz et al., 2009)).

Although these studies used different continuous outcome measures, quantitative comparisons between their results may be made using standardized effect size. 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 0.29 for the figure-8 coil. It should be noted that Levkovitz et al. used the adjusted slopes of the changes in HDRS-21 scores between study arms. To make a more direct comparison, we use the raw values for the end point in the PP population, 13.9 (7.62) and 15.6 (7.05) for the active and sham arms respectively, which yield an effect size of 0.52. In addition, the O'Reardon study emphasized results achieved following an

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**Table 1** Studies characteristics.

| Coil type/Reference | Figure-8 coil (O'Reardon et al., 2007) | | | | H1-coil (Levkovitz et al., 2015) | | | |
|---|---|---|---|---|---|---|---|---|
| **Study design** | | | | | | | | |
| Sessions/weeks | 20/4 | | | | 20/4 | | | |
| Session duration (min) | 37.5 | | | | 20 | | | |
| Pulse/session | 3000 | | | | 1980 | | | |
| Frequency (Hz) | 10 | | | | 18 | | | |
| Intensity (% of RMT) | 120 | | | | 120 | | | |
| Scale used for the primary outcome | MADRS | | | | HAMD-21 | | | |
| Randomized (n) | 325 | | | | 212 | | | |
| **Clinical outcomes** | | | | | | | | |
| Population | mITT | | Supplementary Analysis | | mITT | | PP | |
| Group | Active | Sham | Active | Sham | Active | Sham | Active | Sham |
| n | 155 | 146 | 151 | 144 | 101 | 111 | 89 | 92 |
| Baseline score Mean (SD) | 32.8 (6.0) | 33.9 (5.7) | NR | | 23.5 (4.3) | 23.4 (3.7) | NR | NR |
| Endpoint Mean (SD) | 27.0 (11.1) | 29.8 (10.1) | NR | | Slope of −6.1 | Slope of −3.9 | Slope of −6.3* | Slope of −3.2 |
| p-value | 0.057 | | 0.038 | | 0.058 | | 0.008 | |
| Cohen's d | 0.29 | | NR | | | | 0.76 | |
| % Response | 18.1* | 11.1 | NR | | 37* | 27.8 | 38.4* | 21.4 |
| Odds Ratio | 1.79 | | NR | | 1.52 | | 2.29 | |
| % Remission | 7.1 | 6.2 | NR | | 30.4* | 15.8 | 32.6* | 14.6 |
| Odds Ratio | 1.16 | | NR | | 2.33 | | 2.83 | |
| **Safety and subjective experience (Active groups) – n (%)** | | | | | | | | |
| Serious adverse events | 9 (5.4) | | | | | | 4 (4.0) | |
| Application site discomfort | 18 (10.9) | | | | | | 3 (3.0) | |
| Application site pain | 59 (35.8) | | | | | | 5 (5.0) | |
| Muscle twitching | 34 (20.6) | | | | | | 2 (2.0) | |
| Headache | NR | | | | | | 27 (26.7) | |
| Back pain | NR | | | | | | 2 (2.0) | |
| Eye pain | 10 (6.1) | | | | | | NR | |
| Facial pain | 11 (6.7) | | | | | | NR | |
| Pain of skin | 14 (8.5) | | | | | | NR | |

*Note* Both studies used the Medical Dictionary for Regulatory Activities when reported adverse events, but O'Reardon et al. (2007) reported only events that occurred at a rate ≥5% and at least twice the rate for the sham group. MADRS - Montgomery-Asberg depression rating scale; HAMD-21 - Hamilton depression scale (21 items); mITT- modified intention-to-treat; PP – per protocol; NR – not reported;.

* - significant difference compared to the relevant control group.

additional 2 weeks of daily treatment (at week 6, rather than the primary endpoint of week 4). The effect size at this later time point in the O'Reardon study based on the MADRS scale was 0.36.

As opposed to the continuous outcomes, both pivotal multicenter RCTs achieved significant differences between active and sham treatment both in response and remission rates for the fully reported mITT population, making these results the most easily comparable. This is even more true for response rate since both studies use the same definition of 50% reduction in the symptoms although using different scales. The response percentage of the H1 coil of 37% is noticeably higher than that of 18.1% achieved for the figure-8 coil. The definitions of remission used in the two pivotal studies are summarized in Table 2. Although different scales were used, the remission definitions seem comparable and are the most important practical clinical endpoint of any antidepressant therapy. Here, the remission percentage of the H1 coil of 30.4% is noticeably higher than that of 7.1% achieved for the figure-8 coil. This difference is noticeable even when looking at the best remission rates obtained in the pivotal figure-8 coil study of 17.4% after 6 weeks of treatment, 2 weeks after the primary time endpoint (O'Reardon et al., 2007). Continued treatment was associated with increased rates of response also in the H1 coil pivotal study. 60.6% of patients who did not respond during 4 weeks of daily treatments, achieved response after additional 4 weeks of twice-weekly sessions (Yip et al., 2017). However, for comparisons of categorical outcomes (such as remission) where the sham response rates vary between studies (as in these trials in which the higher active rates with the H1 coil are accompanied by higher sham rates as well (Table 1)), odds ratios are more appropriate. At the primary endpoint, after 4 weeks of acute treatment, the

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**Table 2** Definitions of remission.

| Coil type/ Reference | Figure-8 coil (O'Reardon et al., 2007) | | | H1-coil (Levkovitz et al., 2015) |
|---|---|---|---|---|
| Scale | MADRS | HAMD-17 | HAMD-24 | HAMD-21 |
| Definition of remission | MADRS Total Score<10 | HAMD-17 Total Score<8 | HAMD-24 Total Score<11 | HAMD-21 Total Score<10 |

odds ratio for remission was found to be 2.33 for the H1 coil, compared to 1.16 with the figure-8 coil. With additional two weeks of daily treatment with the figure-8 coil (following the primary time point) the odds ratio increased to 2.84. These results suggest that many initial non-responders may benefit from additional rTMS treatments, regardless of the stimulation e-field generated by the coil. The preferential outcomes of the H1 coil compared to those of the figure-8 coil are supported by a recent publication of the first RCT to include both coils with their respective FDA approved protocols in 228 MDD patients (Filipčić et al., 2019). The authors reported clinical superiority for the H1 coil standard protocol (i.e. 20 min, 1980 pulses/day) over that of the figure-8 coil standard protocol (i.e. 40 min, 3000 pulses/day) showing significant differences in symptoms reduction and response rates and a trend for differences between remission rates.

Often, metanalyses provide a higher odds ratio for treatment with the figure-8 coil by including the higher remission odds ratio of 3.09 of George et al. (2010) (Berlim et al., 2014; Mutz et al., 2018). However, as mentioned above, this result cannot easily be interpreted due to the flexible endpoint in the study design. The remission results reported include total responders or remitters at the end of the 6-week phase 1, despite all remitters and non-improvers being removed after 3 weeks and improvers being removed once achieving stable remission. The presented results may therefore be more comparable to the results of the double-blinded maintenance phase of the Levkovitz study which also showed a significant effect of four additional weeks of twice-weekly stimulation with the H1 coil even for non-responders after the initial four weeks (Yip et al., 2017). Looking at the results at the three week point in George et al., which include all subjects, only 6% of the HF-rTMS and 2% of the SHAM group achieved remission. Finally, it should be noted that response and remission rates reported in open-labeled or naturalistic studies or in single-site RCTs (which in most cases did not include a sham control but compared different stimulation or patterns or anatomical locations) are often much higher than those obtained in the pivotal multicenter studies discussed above (Carpenter et al., 2012; Perera et al., 2016b).

## 9. Safety

The greatest safety concern associated with TMS is the risk of seizures, and it has been suggested that the greater stimulation volume of the H1 coil would potentially increase this risk (Carpenter et al., 2017; Ziemann, 2017). The most recently available numbers reveal similar seizures rate of ~1 in 1000 and 6 in 5000 patient exposures with the NeuroStar figure-8 coil and the Brainsway H1 coil, respectively (Guo et al., 2017). The current risk is even lower with adherence to recommendations endorsed by the International Federation for Clinical Neurophysiology (Perera et al., 2016b; Rossi et al., 2009), and is lower than the comparable seizure rates associated with antidepressant medications (Alper et al., 2007; Pisani et al., 2002). In addition, all TMS seizures have occurred during stimulation in the presence of medical personnel and were self-limiting, lasting between 20 and 120 s with highly varied post ictal periods (George et al., 2013b).

**Table 3** Seizures rates.

| | Figure-8 coil | H1-coil |
|---|---|---|
| Seizures reported in the literature | 25–35 | 8 |
| Seizures in unpublished post-marketing data | No data | 33 |
| # of patients | No data | 48,252* |
| Rate of seizures | No data | 0.085% |

Reference for figure-8 coil seizures: (Dobek et al., 2015; Iorio and Rossini, 2017; Rossi et al., 2009; Wassermann, 1998). References for the H1-coil seizures: (Boes et al., 2016; Cullen et al., 2016; Harel et al., 2011; Isserles et al., 2011; 2013; Levkovitz et al., 2011; 2015; Tendler et al., 2014).
* Based on # of caps until March 2019.

In published literature so far, 25–35 TMS-induced seizure events were reported with the figure-8 coil (Dobek et al., 2015; Iorio and Rossini, 2017; Rossi et al., 2009; Wassermann, 1998) and 9 such events with the H1 coil (Boes et al., 2016; Cullen et al., 2016; Harel et al., 2011; Isserles et al., 2011, 2013; Levkovitz et al., 2011, 2015; Stultz, 2019; Tendler et al., 2014). Seven of the cases with the figure-8 coil preceded the 1998 safety guidelines (Wassermann, 1998), and another 9 were reported in the updated 2009 guidelines (Iorio and Rossini, 2017). Of note, self-limiting seizures are not classified by the FDA as a serious adverse event and are likely under-reported in the literature. A recent admirable effort was made to gather such data through the voluntary completion of surveys by TMS laboratories and clinics. However, as the authors of the study admit, the final sample size was small and the results likely unrepresentative of the true seizure rates (Lerner et al., 2019). In an attempt to provide more accurate statistics, we include all published and manufacturer provided reports of seizure events using the H1 coil as well as, for comparison, available data for the figure-8 coil. (Table 3).

A previous version of the H1 data was recently published (Tendler et al., 2018). Here we present an updated version that includes an additional 6 months. The total number of seizures between 2010 and March 2019 using the H1 coil as reported in the literature and by the manufacturer, spontaneously or in response to active survey is 46 (including 5 pseudo-seizures). During this period, 48,252 personal head

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caps were distributed, which can be used as an approximate number of patients that were treated. This gives an overall crude seizure frequency of 0.00085. Eleven of these seizures occurred in cases where TMS was administered per instructions for use (pIFU) for a frequency of 0.00023. No seizures occurred during the first TMS treatment, and most of the seizures appeared to have had multiple proximal risk factors (Supplementary Table 1). Of a total 46 seizures and pseudo-seizures, 23 occurred when the MT was not checked in the most recent week (perhaps clarifying the fact that no seizures occurred in the first TMS treatment session), and at least six seizures occurred at supra-threshold intensities (above 120% of MT). Increased alcohol intake and withdrawal before the treatment resulted in eight of the seizures, and medication changes without rechecking the MT was a likely cause of eleven of the seizures. Poor sleep was a potential culprit for nine of the seizures, and exaggerated caffeine intake before TMS may have caused one seizure. Three of the seizures may have been induced by voluntary motor activity, which increases cortical excitability and lowers motor threshold (Edwardson et al., 2011; Izumi et al., 2000), immediately before and during the TMS train. There were no reports of seizure related injuries.

As such, seizures induced by therapeutic high-frequency TMS with either coils are very rare, at a rate of 0.085-0.1%, which is consistent with former reports (George et al., 2013b).

## 10. Conclusions and future directions

In this review, we summarized the differences in the design of the two commercially available TMS coils for the treatment of MDD, the figure-8 coil and the H1 coil. We then showed that the H1 coil allows deeper penetration, wider distribution, and a more gradual decay of the e-field compared to the more focal but superficial stimulation of the figure-8 coil. Deeper and larger volumes of e-fields are more likely to engage prefrontal circuitry in sulcal folds, where activation by TMS is thought to dominate. The greater stimulation volume overcomes the high inter-individual variability of the PFC's functional and structural architecture, which makes localization of targets for focal stimulation extremely challenging with any current methodology. While the greater stimulation volume of the H1 coil raised the concerns of stimulating non-pathological tissue and a greater seizure risk, there is currently no evidence for unwanted behavioral effects and a comprehensive reporting of seizures reveals the seizure rate to be comparable to that of the figure-8 coil. More focal stimulation with the figure-8 coil may still minimize behavioral side effects of stimulating additional non-targeted tissue, but evidence of such side effects is lacking in the literature. Finally, we compared clinical results between separate RCTs using the H1 coil or the standard figure-8 coil. While definitive conclusions are difficult due to the difference in the studies and the available results, the H1 coil does provide a higher odds ratio for remission, which is the preferred endpoint for any treatment.

Yet, the challenges remain as there is still a large MDD population that fail to benefit from rTMS and coil design alone is likely insufficient to address all the remaining variability. In that regard, development of new coil designs should be combined with other efforts. For instance, exploring the effects of specific rTMS protocols for treating specific MDD subpopulations as has been attempted with the figure-8 coil (although with a negative outcome) in US veterans (Nemeroff, 2018; Yesavage et al., 2018) and with the H1 coil in late-life depression (Kaster et al., 2018). In addition, effort should be made to deliver an individualized treatment based on biomarkers that can be easily measured in routine clinical practice (Kobayashi et al., 2017; Silverstein et al., 2015).

## 11. Limitations

This review is limited by the availability of experimental results. Many of the arguments regarding stimulation volume and depth come from indirect measures, and there is lack of imaging studies with the H1 coil, including measures of the spatial reach of the stimulation and its interaction with secondary targets.

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## Contributors

All authors helped in the preparation of the manuscript. Samuel Zibman and Gaby Pell designed the structure of the manuscript, Samuel Zibman wrote the manuscript, Noam Barnea-Ygael assisted with the figures.

## Conflict of interest

Prof. Zangen and Dr. Roth are inventors of deep TMS H-coils and have financial interests in Brainsway, a commercial company which produces deep TMS H-coil systems.

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## Supplementary materials

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