ELSEVIER

Deep transcranial magnetic stimulation over the prefrontal cortex: Evaluation of antidepressant and cognitive effects in depressive patients

Yechiel Levkovitz, MD[a], Eiran V. Harel, MD[a], Yiftach Roth, PhD[b],
Yoram Braw, PhD[a], Dana Most, BSc[b], Leor N. Katz, BSc[b],
Aharon Sheer, MSc[b], Roman Gersner, PhD[b], Abraham Zangen, PhD[b]

[a]Shalvata Mental Health Care Center, Cognitive and Emotional Laboratory, Hod-Hasharon, Israel
[b]Neurobiology Department, Weizmann Institute of Science, Rehovot, Israel

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
We 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. Herein, we 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
We have studied the antidepressant and cognitive effects induced by 4 weeks of high-frequency (20 Hz) repeated deep TMS (DTMS) over the prefrontal cortex (PFC) of 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

DTMS over the PFC was found safe and effective in alleviating depression. The results accentuate the significance of deep, high-intensity stimulation over low, and serve as the first study to indicate the potential of DTMS in psychiatric and neurologic disorders.

Major depressive disorder (MDD) is a highly prevalent and disabling condition associated with significant morbidity and mortality. As established by converging neuropsychologic, biochemical, neuroimaging, and postmortem evidence, depression is unlikely to be a disease of a single brain region or neurotransmitter system. Rather, it is now generally viewed as a system level disorder affecting integrated pathways.[1-5] A system that has gained increasing focus in the study of MDD is the reward circuit. The main component of the reward system is the mesolimbic dopaminergic pathway consisting of the nucleus accumbens (NAc) and the ventral tegmentum area (VTA), both interconnected with the dorsal and ventral lateral prefrontal cortices (DLPFC and VLPFC).[4,6] Previous studies indicate that the NAc and VTA contribute significantly to the pathophysiology and symptomatology of depression.[7] Interestingly, several studies indicate that the role of the PFC in depression is asymmetric, with relative hypoactivity in the left DLPFC, along with relative hyperactivity in the right.[8]

Notwithstanding the therapeutic armament available for clinicians treating MDD, approximately 30% remain symptomatic despite standard interventions; this group is considered to have treatment-resistant depression (TRD).[9,10] Electroconvulsive therapy (ECT) is considered an effective alternative for such patients, but necessitates administering general anesthetic, induces a seizure, and causes significant memory[11] and learning[12] impairments. Transcranial magnetic stimulation (TMS) has been proposed as a refined alternative. TMS is a noninvasive technique used to apply magnetic pulses to the brain through an electromagnetic coil placed above the patient's scalp, inducing electrical activity in the underlying cortical tissue that can result in localized neuronal depolarization.[13]

Differences between the functional state of the left and right DLPFC are reflected in the therapeutic effects of repetitive TMS (rTMS). Patients with MDD have been found to benefit from excitatory high-frequency rTMS over the left DLPFC and inhibitory low-frequency rTMS over the right DLPFC.[14,15] These rTMS results, together with neuroimaging studies, have led to the imbalance hypothesis of MDD, which postulates prefrontal asymmetry with relative hypoactivity in the left DLPFC, along with relative hyperactivity in the right DLPFC.[16,17]

Although TMS treatment for depression has improved over the last years,[18] current TMS methodologies do not yet yield the desired results. Standard TMS techniques enable direct stimulation of superficial cortical areas to a maximum depth of roughly 1 cm.[19,20] Whereas for treating depression, direct stimulation of deeper regions may prove to be superior because deeper layers of the PFC are interconnected with reward-related brain sites such as the ventral striatum and the VTA.[6,21-23] To stimulate deeper neuronal regions such as reward-related pathways directly, much higher stimulation intensities are needed, as the electric field decreases rapidly as a function of tissue depth. However, even if stimulation intensities could be highly increased at the source, the use of standard TMS coils (such as the figure-8 coil) at such high stimulation intensities does not allow safe stimulation and can lead to undesirable side effects.[24] These limitations have led to the development of the H-coil, a novel coil allowing direct stimulation of much larger and deeper brain regions by significant reduction of the decay rate, but at the expense of reduced focality.[19,20,25] In a safety study conducted on healthy volunteers, the stimulation of the H-coils was found to be well tolerated, and neither serious adverse effects nor cognitive deterioration occurred.[25]

In the current study, we tested the effectiveness of deep TMS (DTMS) and the suggested asymmetry of the PFC in major depression. We studied 65 treatment-resistant depressive patients treated by three different DTMS H-coils (H1, H2, and H1L) with four distinct paradigms (Figure 1A and the Method section for differential stimulation profile of the treatment groups). Three groups differed in stimulation laterality (H2-coil, induces bilateral stimulation; H1-coil, induces greater stimulation over the left PFC; and H1L-coil, induces stimulation exclusively over the left PFC), whereas a fourth group differed solely in stimulation intensity. The coil chosen for this fourth group was the H1L-coil due to its unilateral properties, and was used in both high and low stimulation intensities.

Materials and Methods

Subjects and study design

The study was registered (clinicaltrials.gov, NCT00445237), approved by institutional and national review boards (IRB) committees, and was conducted at the Shalvata Mental Health Center in Israel. Active enrollment ran from April 2006 through May 2008 in which all subjects signed
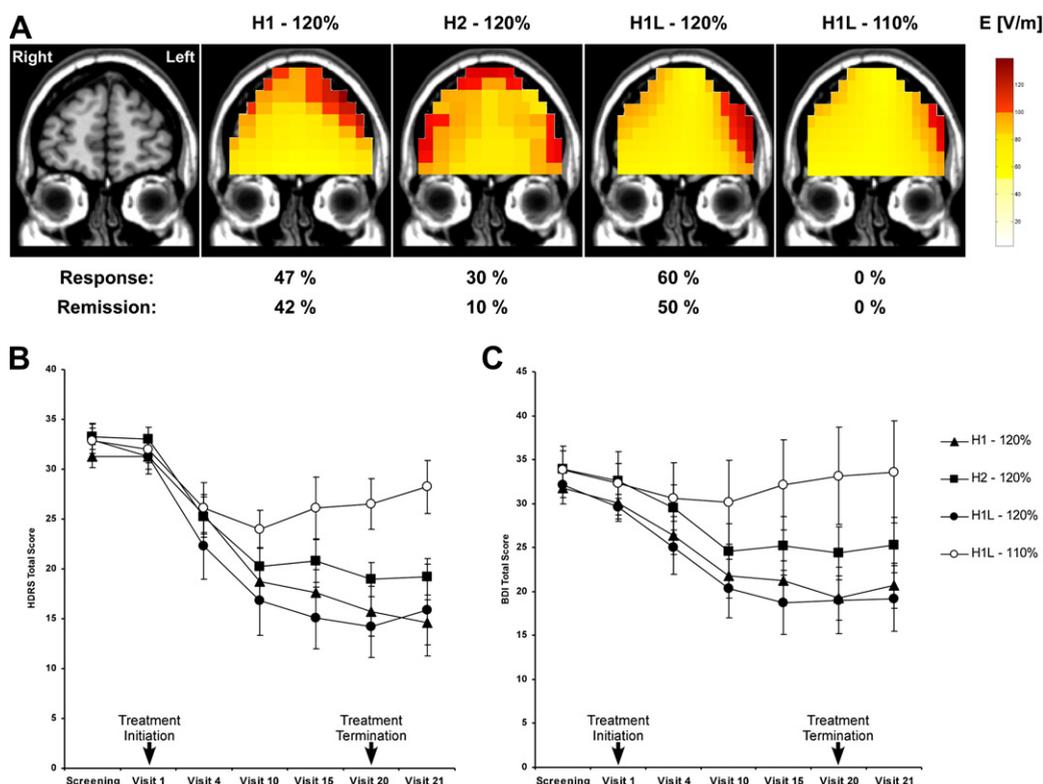
Figure 1 Differential effects of various DTMS treatments on depression scores. (**A**) Response and remission rates relative to stimulation site based on phantom brain measurements. The distribution of the electric field induced by the various coils were measured in a phantom brain (Roth et al.[19]) and presented here in a representative coronal slice that includes the prefrontal cortex. The red colors indicate a field magnitude above the threshold for neuronal activation (set to 100 V/m). All coils were similar in stimulation parameters, yet differed in laterality: The H1-coil stimulates the PFC bilaterally, but gives distinct preferential stimulation to the deep layers of the left PFC. The H2-coil stimulates the PFC bilaterally, with no lateral preference. The H1L-coil provides left unilateral stimulation of the dorsolateral and ventrolateral PFC. The full distribution of the electric field presented on 10 coronal slices is presented in Figure S1. The response and remission rates induced in the various experimental groups, are presented. (**B**) Effect of DTMS on HDRS scores over time are presented for each treatment group (mean ± SE). There was no significant change in HDRS score between screening and baseline (t_{57} = 1.54; P = .1281, paired t test), or were there significant differences in the total HDRS score between the groups at baseline (F(3,54) = 0.43; P = .7337, ANOVA). The change from baseline over time was significantly different between the groups, as determined by the treatment × visit interaction (F(3,58) = 6.42; P = .0008; RMANOVA). The mean change over 5 weeks per treatment group was estimated from the model as −12.30 points (SE = 1.92) in the H1 group, −6.78 (SE = 1.89) in the H2 group, −7.60 (SE = 2.68) in the H1L-120% group, and +3.20 (SE = 2.9) in the H1L-110% group. (**C**) Effect of DTMS on BDI-II scores over time are presented for each treatment group (mean ± SE). There were no significant differences in the BDI score between the groups at baseline (F(3,53) = 0.44; P = .7245, ANOVA). By visit 21, the improvement rates were 31%, 22%, 35%, and −4% in the H1, H2, H1L-120%, and H1L-110% groups, respectively. A statistically significant difference among the treatment groups was found in the change from baseline over time as determined by the treatment × visit interaction (F(3,57) = 3.27; P = .0277). The mean change over 5 weeks per treatment group was estimated from the model as −6.99 points (SE = 2.02) on average in the H1 group, −4.17 (SE = 2.01) in the H2 group, −7.02 (SE = 2.84) in the H1L-120% group, and 4.82 (SE = 3.39) in the H1L-110% group. TMS = transcranial magnetic stimulation; PFC = prefrontal cortex; HDRS = Hamilton Depression Rating Scale; SE = standard error; ANOVA = analysis of variance; RMANOVA = repeated measures analysis of variance; BDI-II = Beck Depression Inventory-II.

informed consent forms before study entry and were free to withdraw at any time without prejudice. Healthy control subjects (CS) without a current or historical major medical/psychiatric illness were also recruited for the study to evaluate the normal performance in the cognitive assessments battery, but did not receive treatment.

The screening procedure included a medical interview and physical examinations to determine suitability as fully detailed in the Inclusion and Exclusion criteria section (Supplementary Material). Right-handed, unipolar MDD

patients, aged between 18-65 years who did not respond to at least two antidepressant medications in the current episode were randomly assigned to DTMS treatment in one of the four H-coil paradigms. Each patient received a random number generated by a simple randomization scheme via computer program that assigned him/her to one of the four treatment groups using a 2:2:1:1 ratio for the H1, H2, and H1L (110% or 120%) groups, respectively.

The lead-in phase, in which antidepressants were tapered down, lasted 2 weeks (from Screening to visit 1).

Thereafter, 20 daily DTMS sessions (visits 1-20) were conducted during 4 consecutive weeks, with five sessions per week. Depressive symptoms were assessed every week by the 24-item Hamilton Depression Rating Scale (HDRS-24), including the last visit (visit 20). The primary efficacy time point was defined as 1 week after the end of active treatment, that is, visit 21, after which antidepressant resumption was permitted. This evaluation time point was chosen to reduce the acute effects of treatment and to evaluate lasting effects, before the resumption of various medications that may confound interpretation of results collected at later time points. The primary efficacy outcome measure was the response rate, defined as a reduction in HDRS-24 score of at least 50% from baseline to visit 21. Patients were evaluated in a later follow-up meeting, 3 months after active treatment termination, visit 22.

Evaluations conducted

Throughout the course of the study, all DTMS sessions were administered by one of two trained physicians, and a third physician who was blinded to the treatment arm performed all physical and psychiatric evaluations. Patients were under direct monitoring, and any adverse effects or subjective complaints were immediately recorded and treated. Safety measures and appropriate emotional tests were administered, as well as a battery of computerized cognitive tests that were sensitive to cognitive changes caused by a wide range of central nervous system disorders and medication effects.[26,27] Safety measures were chosen according to the safety guidelines for TMS studies[28] and in accord with our previous studies using the H-coils.[20,25] The antidepressant outcome was assessed by the HDRS-24 score and several secondary outcome measures as detailed in Figure 2.

Materials

DTMS device
The DTMS stimuli were delivered by a Magstim Super Rapid stimulator (Magstim Company, Ltd, Carmarthenshire, Wales, UK) with the H-coils. The H-coil was positioned on the patient's scalp over the prefrontal cortex as detailed later in the text. The inner rim frame of the coil is flexible to fit the variability in the human scalp shape (for theoretical considerations and design principles[20,29,30]). Each subject was treated with one of three versions of the H-coil (H1, H2, and H1L), similar in external appearance and acoustic properties when actively pulsed. The H1-coil is designed to stimulate deep prefrontal brain regions, preferentially in the left hemisphere.[19] The H2-coil is designed to stimulate deep prefrontal brain regions bilaterally, with no lateral preference.[19] The H1L-coil is designed to stimulate deep prefrontal brain regions unilaterally, exclusively in the left hemisphere. The shape of the various coils and

distribution of electric fields induced are presented in Figure S1, Supplementary Material.

CANTAB
The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computer-administered set of neuropsychologic tests developed to rapidly assess specific components of cognition. It consists of a custom computer with a touch screen and a paddle, all from Cambridge Cognition Ltd, Cambridge, England.

Procedure

Before stimulation, patients were instructed to insert earplugs to lessen any possible adverse effects on hearing. Next, the optimal spot on the scalp for stimulation of the right abductor pollicis brevis (APB) muscle was located, and the motor threshold (MT) was established.[25] To localize the optimal placement, suprathreshold intensities were applied around the hand motor area (tested at increments of 1 cm) and the spot inducing the greatest motor response was marked. To refine the "hot" spot for APB activation, the intensity was reduced until the motor-evoked potential (MEP) was less than 100 µV and motor responses were tested around the marked spot searching for placement for inducing the maximal response. Although the H2-coil could induce activation of the left APB during the search for the "hot" spot, the placement and MT were based only on the right ABP. The MT was measured by using single-pulse mode, applying one pulse every 5-10 seconds and recording electrical activity in the APB by using surface electrodes. MT was defined before each daily session as the lowest intensity of stimulation able to produce MEPs of at least 50 µV in three of six trials. Next, the coil was placed 5.5 cm anterior to the motor spot (over the prefrontal cortex). Although in many previous studies evaluating the antidepressant effects of rTMS, the standard coils were placed 5 cm anterior to the hand motor cortex, we have placed the coil a little more anteriorly, because the 5 cm was shown in many cases to result in placement over the premotor cortex rather than the relevant areas over the prefrontal cortex.[31] The treatment was delivered in trains of 20 Hz at either 120% or 110% of the measured MT, similar to studies that used relatively intensive parameters with standard coils.[18,32,33] Three of the groups were treated with a stimulation intensity of 120% MT (each group receiving one of the three coils), whereas the additional group was treated with a lower intensity of 110% MT (tested only for the H1L-coil). Although differing in stimulation intensity, all four groups were assessed by the same methodologies and received the same number of treatments with an identical stimulation frequency. The patients and the raters did not know to which stimulation group they were assigned. Each TMS session consisted of 42 two-second trains, with an
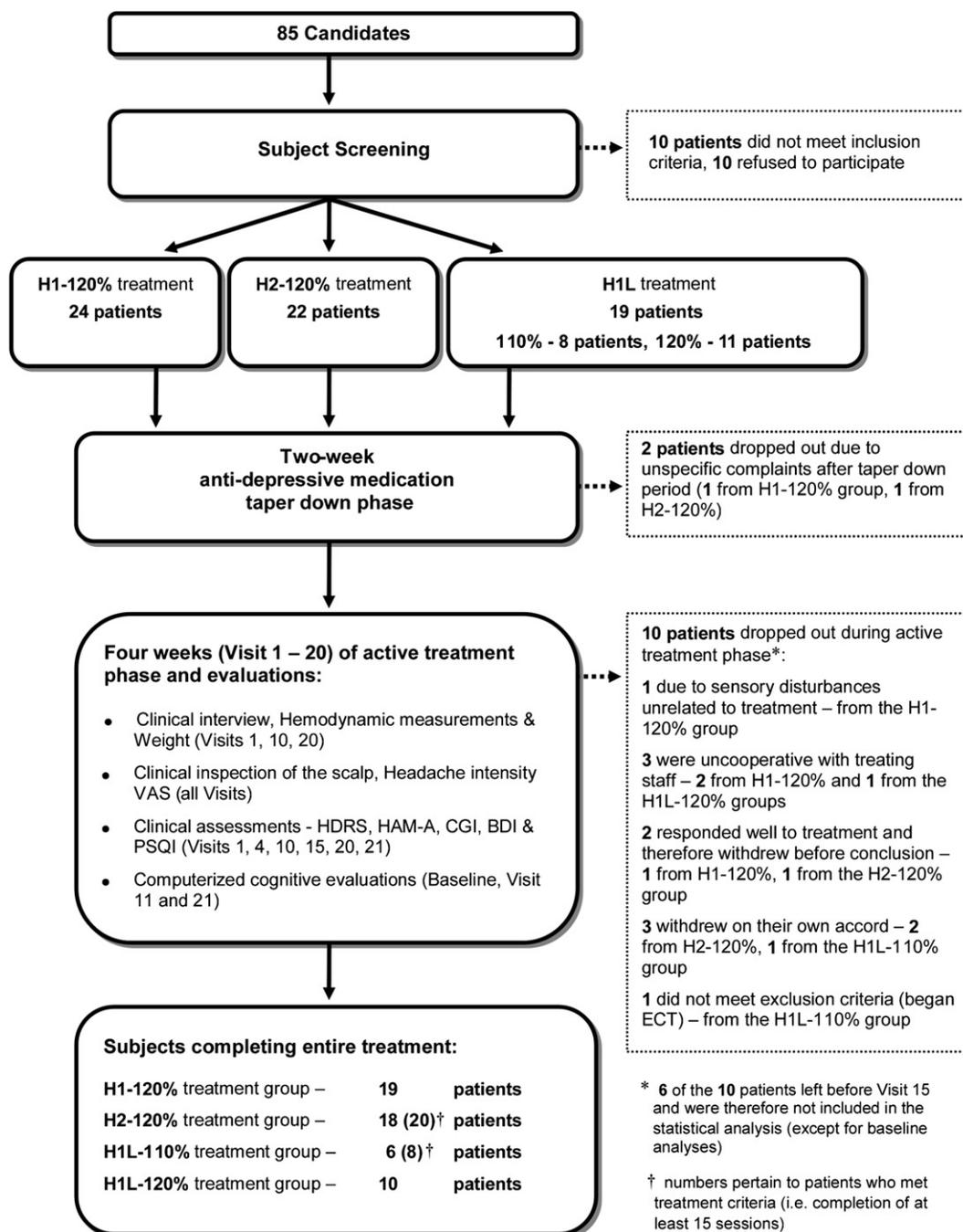
Figure 2 Study progression and evaluations conducted. The entire course of treatment undertaken by the MDD patients, evaluations conducted, accountability and reasons for withdrawal are presented. No baseline demographic or clinical data differed between the study dropouts and the patients left in treatment, and no systematic differences among treatment groups regarding reasons for discontinuation were seen. Evaluations conducted: A medical assessment interview by a trained psychiatrist in which the subject was asked to report any physical changes related to treatment. Hemodynamics and weight were measured coincident with the medical interview (conducted on visits 1, 10, and 20). Inspection of the scalp was performed before and after each stimulation session to assess possible skin lesions. After each visit, the patients were asked to rate their current headache intensity on a self-graded questionnaire by marking an "X" on a 10-cm visual analogue scale (graded 0-100 afterward) within 5 minutes poststimulation. A trained psychiatrist performed extensive psychiatric status examinations: the 24-item Hamilton depression rating scale (HDRS-24), the Hamilton anxiety rating scale (HAM-A), the clinical global impression severity (CGI-S), and improvement questionnaires (CGI-I), all administered at screening, visits 1, 4, 10, 15, 20, 21, and on the follow-up (visit 22). During these visits, the patients further filled in the self-graded Beck Depression Inventory-II (BDI-II), and the Pittsburgh sleep quality index (PSQI). Finally, a comprehensive battery of cognitive tests using the Cambridge neuropsychologic test automated battery (CANTAB) was administered at baseline, visit 11, and visit 21, to assess any changes in cognitive performance. MDD = major depressive disorder.

intertrain interval of 20 seconds (i.e., a total of 1680 pulses delivered during a 15-minute daily session).

Computerized cognitive assessments using the CANTAB tests were conducted on baseline and visits 11 and 21. Each subject was administered the tests in a pseudo-randomized fashion and in a controlled environment. A description of the cognitive tasks is presented in the Supplementary Material.

Statistical analyses

As this was an exploratory study being the first one to assess various effects of the new stimulation method, we could not estimate in advance what differences in treatment effect may be found among the groups, and thus no formal calculation of sample size was performed. Nevertheless, it was decided to attempt to evaluate the effectiveness in 20 patients for each coil. Baseline evaluations were performed on all subjects in the intent-to-treat cohort including healthy controls. Efficacy analyses were performed on the per protocol sample of all assessable patients, defined in the protocol as those patients with a baseline measurement and at least 3 weeks of assessment (n = 58) (because otherwise patients did not have data available for efficacy analysis). Baseline demographic and depression-related data were compared among the study groups. Continuous variables are summarized by a mean and standard deviation and compared with univariate analysis of variance (ANOVA) comparing either four or five (four coils and CS) groups. Discrete data were summarized by a count and percentage and compared among all groups (four treatment groups and CS) with a chi-squared test or Fisher exact test, where relevant. The change from baseline over time in rating scale data was modeled via repeated measures ANOVA (RMANOVA) methodology (PROC MIXED in SAS v9.1 (SAS institute, Cary, NC). The change from baseline for each rating scale was modeled as a function of treatment group (treatment), treatment progression (visit), and the treatment × visit interaction as fixed effects, and with baseline rating scale values as covariates in the models, assuming an unstructured covariance matrix. If the treatment × visit interaction was found statistically significant, select pairs of treatment groups were compared by using t tests performed using the ESTIMATE command. Adjusted mean changes (least-squares [LS] means) from baseline were estimated from the models as well. Pearson's correlation coefficient was calculated between the HDRS and Beck Depression Inventory II (BDI-II) scores at 5 weeks. Neuropsychologic variables of the treatment groups and CS were compared at baseline, and at week 5 as the change from baseline to week 5, with univariate ANOVA, pairwise t tests and LS means (with 95% confidence interval [CI]) were performed and estimated as well. As this is an exploratory study assessing various effects of the new stimulation method, only nominal P-values are presented and no adjustments were made for multiple testing. All statistical tests were two-sided and tested at a 5% level of significance.

Results

Patient disposition

The study included 65 treatment-resistant depressive patients randomly assigned to four treatment groups, and 20 healthy volunteers who served as a control group for the battery of computerized cognitive tests. No significant differences were found among groups regarding disorder-related parameters, or the degree of treatment resistance in the current episode of depression. In addition, no significant differences were found among groups regarding demographic parameters, except for years of education (that was higher in the H1L-120% group). Finally, no significant difference was found between the CS and the depressive patients in terms of either age or education level (Table S1).

Clinical measures

The primary outcome measure used in this study was the HDRS-24, and standard criteria for antidepressant response and remission were applied.[34] Response was defined as a decrease of 50% or more in the HDRS-24 score from baseline (visit 1) to visit 21; remission was defined as an absolute HDRS-24 score of 10 or less.

By the primary efficacy time point of 5 weeks (visit 21), 47% (9/19) of the patients treated with the H1-coil, 30% (6/20) of the patients treated with the H2-coil, 60% (6/10) of the patients treated with the H1L-120% coil, and none (0/8) of the patients treated with the H1L-110% coil reached the defined response criteria. These differences were statistically significant (P = .0331, Fisher exact test). Remission rates at 5 weeks for the H1, H2, and H1L-120% treatment groups were 42% (8/19), 10% (2/20), and 50% (5/10), whereas in the H1L-110% treatment group no (0/8) patients remitted. These differences were statistically significant (P = .0092, Fisher exact test), showing evidence of the superior efficacy of the higher intensity treatments (H1, H2, and H1L-120%) over the more superficial stimulation induced by the H1L-110% coil, in which no patients responded or remitted, and the tendency for greater response rates and remission rates induced by left rather than bilateral stimulation (Figure 1A and Supplementary Material for field distribution of each coil). Indeed, when we grouped together all patients receiving greater stimulation over the left PFC (the H1 and H1L-120% groups) and compared them with those receiving the bilateral stimulation with the H2-coil, response and remission rates were 52% (15/29) versus 30% (6/20) (P = .1541, Fisher exact test) and 45% (13/29) versus 10% (2/20) (P = .0121, Fisher exact test), respectively.

Throughout the entire course of treatment, patients in all groups exhibited clinical improvements, evident in the significant decrease of HDRS scores. A significant treatment × visit interaction effect was found (F(3,58) = 6.42; P = 0.0008; RMANOVA), expressing differences in the slopes of change over time between treatment groups. Although the H1-coil produced the highest mean reduction from baseline, the patients treated with the H2-coil, although not greatly differing from those treated with the H1-coil and H1L-120% coil, displayed a reduced level of improvement (Figure 1B). Mean percentage HDRS improvement of patients from the four treatment groups were 52%, 42%, 49%, and 12% for the H1, H2, H1L-120% and H1L-110%, respectively. Thus, it was concluded that patients treated with the H1L-110% coil had a notably reduced benefit from treatment compared with the other groups. Furthermore, several standardized HDRS subscale scores were derived that mostly substantiate these findings (Table 1). Apart from the lesser efficacy of the superficial H1L-110% treatment (evident in most subscales), analysis of both the Maier and Gibbons subscales also showed that treatment with the H1-coil was significantly superior to that of the bilateral H2-coil (Table 1) supporting the asymmetry of the PFC in depression. Both these scales measure depression and are similar to the HDRS in sensitivity to change, but are unidimensional, whereas HDRS is a multidimensional measure.[35]

The self-rated BDI-II was used to assess the subjective evaluation of patients. Analysis of these scores revealed a similar pattern to that obtained by the HDRS scores; the three high-intensity treatments (H1, H2, and H1L-120%) yielded significant improvements, whereas the low-intensity H1L-110% treatment did not (Figure 1C). This subjective report of patients is corroborated by that of the psychiatrist, apparent by the significant positive correlation between the BDI-II and HDRS scores (r = 0.6416; P < .0001).

The clinical global impression severity (CGI-S) and Hamilton anxiety rating scale (HAM-A) scores showed no significant differences among the treatment groups at baseline, but a significant treatment × visit interaction (F(1,56.6) = 42.13; P < .0001 and F(3,56.9) = 3.45; P = .0225, respectively, Table S2). Mean percent improvements by visit 21 were 40%, 26%, 39%, and 7% in the CGI-S, and 52%, 39%, 52%, and 14% in the HAM-A for the H1, H2, H1L-120%, and H1L-110% groups, respectively.

No significant baseline differences among groups or treatment × visit interaction were found in the Pittsburgh sleep quality index (PSQI) scores. However, PSQI scores tended to decrease over time (Table S2, Supplementary Material).

Safety and tolerability

The treatment was well tolerated and there was no neuropsychologic deterioration or physical adverse events, aside from minor headaches. Ten patients reported a headache (assessed as > 50 of 100 in the headache intensity visual analogue scale [VAS]) in the first week of treatment (visits 1-5), whereas in the subsequent 3 weeks, only three patients reported a headache. Headaches were resolved by standard pain relief medication and did not exacerbate. Scalp discomfort, reported to be a reason for withdrawal in previous rTMS studies,[33] was not related to drop-out in the current study. Inspection of the scalp (conducted before and immediately after each stimulation session) revealed no skin lesions. No differential treatment effect was found for these reports. Finally, none of the following adverse outcomes occurred: accidental seizure induction, hearing loss, transient hypotension, visual disturbances, weakness, paresthesia, instability, vertigo, tinnitus, or other bodily sensations. Although there were no seizures in this study, in which antidepressant medications were not allowed, in a separate ongoing study that evaluates the safety and effectiveness of DTMS in patients who continue to receive antidepressant medications, there was one case of a seizure in a patient receiving extremely high doses of several antidepressant drugs.

Three-month follow-up—visit 22

Three months posttreatment termination, 61%, 57%, 40%, and 50% of patients from the H1, H2, H1L-120%, and H1L-110% groups, respectively, participated in the follow-up visit (visit 22). Patients who participated in visit 21 but not in visit 22 failed to arrive on their own accord, and not because of adverse effects. No significant differences in demographic or disorder-related measures were found between patients who participated in the follow-up visit and those who did not. By this time point, 41% of subjects had resumed antidepressant medication. The response rates among patients who participated in visit 22 were 63%, 50%, 60%, and 37%, and remission rates among these patients were 52%, 25%, 50%, and 25%, for the H1, H2, H1L-120%, and H1L-110% groups, respectively.

Neuropsychologic findings

The neuropsychologic battery was designed to differentiate dorsolateral, superior medial, and ventrolateral functions potentially affected by DTMS treatment. The performance of the four treatment groups, together with the healthy CS was assessed in cognitive domains including sustained attention, visuospatial memory, and executive functions (divided into cognitive planning and spatial working memory). Overall, no negative impact on cognition was observed (Figure 3). In fact, many cognitive domains in which depressive patients were significantly impaired at baseline improved over time and normalized, especially in the groups receiving deep left-lateralized treatments (the H1 and H1L-120% treatment groups). A subset of tests is presented in Figure 3 (statistical analyses are detailed in the Supplementary Material). In addition, no negative

Table 1 HDRS Subscales

HDRS Subscales by Treatment and Visit		Visit					
		Baseline		Visit 10		Visit 21	
		Mean	SD	Mean	SD	Mean	SD
Depression Core Factor	H1 – 120%	1.99	0.40	1.22	0.70	0.61	0.54
(Items: 1, 2, 3, 7, 8)	H2 – 120%	1.95	0.40	1.33	0.67	0.73	0.51
	H1L – 120%	1.86	0.41	1.14	0.81	0.66	0.71
	H1L – 110%	2.14	0.30	1.86	0.38	1.23	0.65
Maier Subscale	H1 – 120%	2.04	0.41	1.28	0.69	0.64	0.53
(Items: 1, 2, 7, 8, 9, 10)	H2 – 120%	1.98	0.37	1.33	0.57	0.86	0.52
	H1L – 120%	1.87	0.47	1.18	0.87	0.70	0.67
	H1L – 110%	2.05	0.23	1.74	0.27	1.50	0.69
Gibbons Subscale	H1 – 120%	1.89	0.34	1.19	0.54	0.59	0.42
(Items 1, 2, 3, 7, 9, 10, 11, 14)	H2 – 120%	1.88	0.26	1.23	0.47	0.75	0.46
	H1L – 120%	1.71	0.35	1.05	0.75	0.65	0.76
	H1L – 110%	1.97	0.14	1.63	0.27	1.33	0.69
Anxiety / Somatization Factor	H1 – 120%	1.09	0.39	0.63	0.29	0.51	0.42
(Items 10, 11, 12, 13, 15, 17)	H2 – 120%	1.18	0.36	0.68	0.36	0.65	0.29
	H1L – 120%	1.17	0.27	0.60	0.39	0.56	0.47
	H1L – 110%	1.26	0.25	0.88	0.28	1.14	0.28
Retardation Factor (Items 1, 7, 8, 14)	H1 – 120%	2.26	0.35	1.47	0.75	0.53	0.49
	H2 – 120%	2.13	0.51	1.53	0.70	0.69	0.48
	H1L – 120%	1.95	0.33	1.23	0.90	0.68	0.61
	H1L – 110%	2.14	0.45	1.96	0.49	1.13	0.95
Sleep Factor (items 4, 5, 6)	H1 – 120%	1.27	0.50	0.68	0.55	1.07	0.77
	H2 – 120%	1.25	0.58	0.68	0.58	1.25	0.76
	H1L – 120%	1.07	0.58	0.50	0.36	0.73	0.78
	H1L – 110%	0.95	0.65	0.71	0.56	1.43	0.42

Standardized Hamilton depression rating scale (HDRS) subscale scores are presented for each treatment group. The various HDRS items which constitute each subscale are presented in the above table. Repeated measures analysis of variance models were used for comparing the change from baseline over time, between the four treatment groups, per subscale. Significance of the treatment*visit interaction is presented as a primary evaluation. **Depression Core factor:** No significant differences were found, $F_{(3,57)}=1.45$; p=0.2381. **Maier:** Significant differences were found, $F_{(3,57)}=3.44$; p=0.0226. Pair-wise comparisons between the groups show that the H1 group had a significantly faster decrease (greater slope) in the subscale score than the H2 group ($t_{57}=-2.02$, p=0.0303), and that the H1L-110% group had a significantly lower reduction than all three other groups ($t_{57}=-2.32$, p=0.0239). **Gibbons factor:** Significant differences were found, $F_{(3,57)}=3.79$; p=0.0151. Post hoc pair-wise comparisons between the groups show that the H1 group had a significantly faster decrease (greater slope) in the subscale score than the H2 group ($t_{57}=-2.32$, p=0.0237), and that the H1L-110% group had a significantly lower reduction than all other groups ($t_{57}=-2.28$, p=0.0264). **Anxiety/Somatization:** Significant differences were found, $F_{(3,57)}=3.16$; p=0.0316. Post hoc pair-wise comparisons between the groups show that the H1L-110% group had a significantly lower reduction than all three other groups ($t_{57}=-2.52$, p=0.0147). **Retardation:** No significant differences were found, $F_{(3,57)}=2.65$; p=0.0572. **Sleep:** Significant differences were found, $F_{(3,57)}=2.89$; p=0.0432. Post hoc pair-wise comparisons between the groups show that the H1L-110% had a significantly lower reduction than all other groups ($t_{57}=-2.86$, p=0.0059).

impact was observed on psychomotor speed either (Table S3, Supplementary Material).

Factors associated with response

An important exploratory goal of this study was to examine and perhaps identify potential factors associated with successful outcome of brain stimulation that used the DTMS treatment. Baseline demographic and disorder-related characteristics of a patient were considered for this evaluation, and in light of the observed inefficacy of the H1L-110% treatment, the analysis was applied on the H1, H2, and H1L-120% groups alone.

The patient's age was found to be associated with treatment efficacy. Surprisingly, DTMS seemed to enhance responsiveness in somewhat older patients, the mean age of the responders was 48 years (standard deviation [SD] = 11.4) versus 44 (SD = 12.6) for the nonresponders. We found that of the 21 responders 67% were aged 49-65 versus 33% who were aged 18-48 years ($P = .0320$, chi-squared test). In addition, the mean number of antidepressants used in the current episode (before DTMS treatment) was 2.6 (SD = 1.5) medications in subjects who responded and 3.6 (SD = 2.4) in subjects who did not respond. However, this apparent difference is not statistically significant ($t_{43.3} = 1.77$; $P = .835$, t test [Satterthwaite]). Lastly, the baseline cognitive performance of responders was found to be similar or even tended to be inferior to that of the nonresponders in various tasks (Figure S2, Supplementary Material). Over time, however,
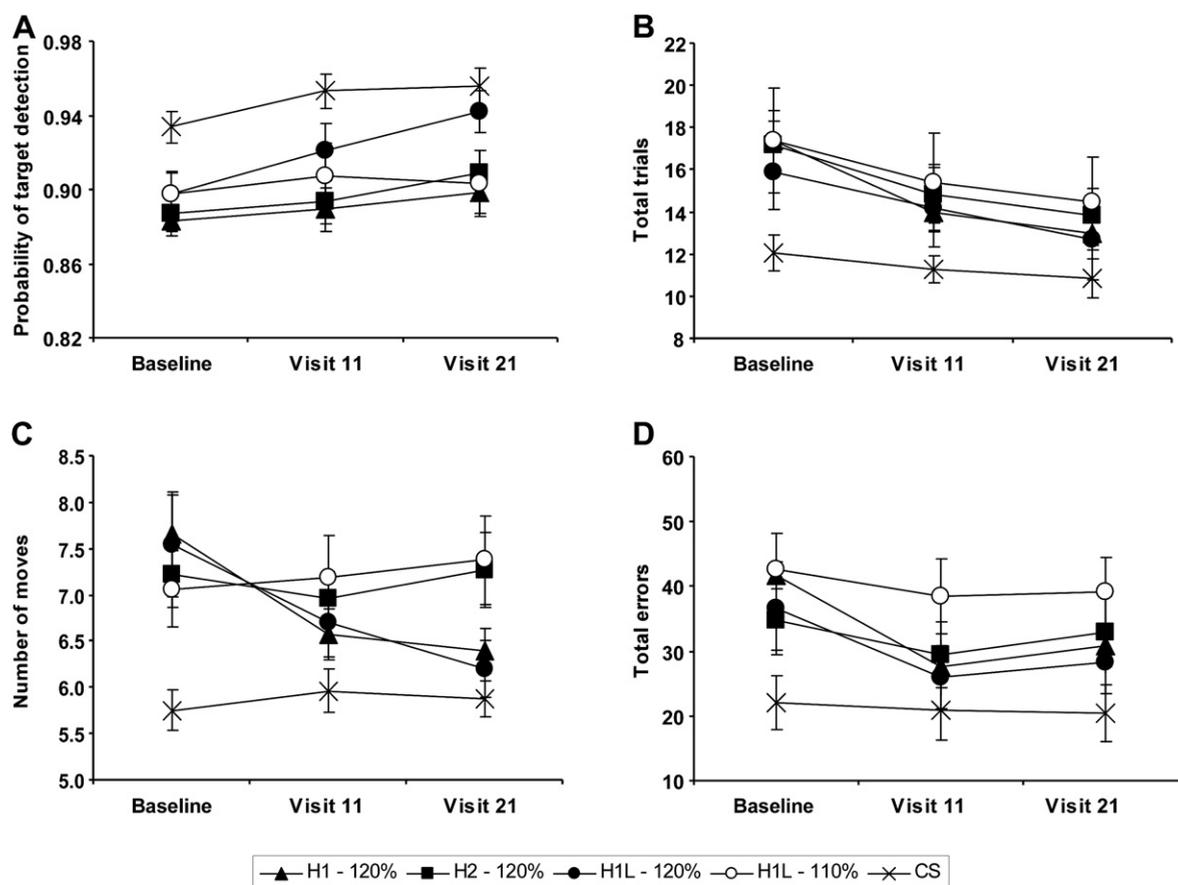
Figure 3 Differential effects of various deep transcranial magnetic stimulation (DTMS) coils on cognitive performance. Cognitive changes from baseline to visit 21 were measured by various tasks. In all tasks, performance of all four treatment groups was significantly worse than the control subjects (CS) at baseline, and performance of the CS did not change significantly throughout the study. For the detailed statistical analysis, see Supplementary Material. (**A**) Changes in sustained attention as measured by the Rapid Visual Processing (RVP) task (selected measure was A'; probability to detect a target). Although no treatment × visit interaction effect was found, a significant increase in performance was found in the three high-intensity treatments (i.e., H1, H2, and H1L-120%), but not in the low-intensity treatment, H1L-110%. The H1L-120% treatment group yielded the largest rate of improvement, and reached performance similar to that of the CS group by visit 21. (**B**) Changes in visuospatial memory as measured by the Paired Associated Learning (PAL) task. Although no treatment × visit interaction effect was found, a significant increase in performance was found in the H1 treatment group. (**C**) Changes in cognitive planning as measured by the Stockings of Cambridge task (SOC) task. A treatment × visit interaction effect was found. The difference was caused mainly because of the significantly increased performance found in the two unilateral treatments groups (i.e., H1 and H1L-120%), which reached values of the CS group by visit 21. (**D**) Changes in spatial memory as measured by the Spatial Working Memory (SWM) task. Although no treatment × visit interaction effect was found, a significant increase in performance was found in the three high-intensity treatments (i.e., H1, H2, and H1L-120%), but not in the low-intensity treatment, H1L-110%. The two unilateral treatments groups (i.e., H1 and H1L-120%) yielded the largest rate of improvement, and reached values of the CS group by visit 21.

executive performance of responders significantly exceeded that of nonresponders in the executive functioning task, Stockings of Cambridge (SOC). In the other tasks, no significant differences between responders and nonresponders over time were found (Figure S2, Supplementary Material).

Discussion

This is the first study in which DTMS, using the novel H-coils, was tested as a therapeutic apparatus for depressive patients who have failed to receive sufficient benefit from

prior antidepressant treatment. We have examined the differential effect of three versions of the H-coil in four different paradigms, and observed the clinical benefit this novel tool holds.

Treatment with the three H-coil designs administered over the PFC at a high-stimulation intensity of 120% MT (H1, H2, and H1L-120%) was found to produce a significant amelioration of depression symptoms. This was revealed by response and remission rates, HDRS, and CGI scores, as well as by self-rated measures (i.e., BDI) and most secondary clinical and cognitive outcome measures. The clinical response was sustained, as evident in the 3-month follow-up (visit 22). The left (H1L) or preferentially left

(H1) stimulation induced larger response and remission rates than those induced by the bilateral H2-coil. Furthermore, a substantial portion of the responders from the H1 and H1L-120% groups achieved remission, 88% and 83%, respectively; whereas in the H2 group, only 33% of the responders reached remission. The importance of the degree of stimulation intensity was accentuated by the inefficacy of the low-intensity H1L-110% coil that produced no significant improvement in HDRS scores, HDRS subscales, or other secondary measures over time. It is important to note that according to the phantom brain measurements (Figure S1, Supplementary Material) that althogh the H1L coil at 110% MT stimulation intensity induces direct effective stimulation up to 1 cm in depth, the same coil at 120% induces direct effective stimulation up to 3 cm in depth, because of the slow decay of the electric field as a function of distance.[19,20,25]

Although other interventions for the treatment of drug-resistant depression (e.g., electroconvulsive therapy) may result in severe cognitive defects or require brain surgery, neither serious adverse events (SAEs) nor cognitive deterioration were observed in either of the stimulation paradigms. Both clinical and cognitive findings indicated that administration of DTMS at the abovementioned parameters is safe and effective in the treatment of depression.

Stimulation intensity and laterality

The intensity of stimulation was found to be a critical factor in the therapeutic effect of DTMS. Studies questioning the efficacy of standard TMS in the treatment of depression concluded that among other factors, higher intensities are needed to reach clinical significance.[15,32] In the current study, direct stimulation of deeper brain regions by the H-coils resulted in very high response and remission rates. Specifically, the striking difference in both response and remission rates and the sustained effect in the H1 and H1L-120% groups relative to the H1L-110% group, emphasizes the importance of higher stimulation intensities in TMS studies.

Although standard TMS does not directly excite deep brain regions such as the reward system, it does induce an antidepressant effect, which could be accounted for by the brain's abundant interconnectivity. Though the DLPFC is strongly linked to the dorsal-posterior caudate, the VLPFC is mainly interconnected to the ventral caudate and the NAc.[6,21,23] Studies that mapped these connections in primates indicated that although the connections of VLPFC to the ventral striatum (i.e., NAc) are indeed related to reward, the connections of DLPFC to the dorsal caudate are mainly related to cognitive functions.[22] On the basis of the phantom brain measurements, the distribution of the electric field induced by the high intensity may very well reach the VLPFC, thus affecting reward pathways directly. Stimulation exerted at 110% does not reach

such depths directly (Figure S1, Supplementary Material). Although this inference has not yet been empirically substantiated, it may serve as one explanation as to how DTMS alleviates depressive symptoms so effectively, even in drug-resistant patients.

The laterality of stimulation was also found to play an important role. Although no difference in efficacy was observed between the H1L-120% and the H1-coil groups, these treatments tended to induce greater improvement than that induced by bilateral stimulation using the H2-coil. The apparent differences between the effects of the H1-coil or H1L-120% coil and that of the H2-coil on remission rates and BDI scores were not statistically significant, but in two of the six HDRS subscales analyzed, a significant superiority was found for the H1-coil and H1L-120% coil over the bilateral H2-coil. Overall, these data suggest that high-frequency stimulation over the left PFC is more effective than over both hemispheres in depressive patients. Indeed, high-frequency stimulation over the right hemisphere might interfere with the positive effect of left PFC stimulation, or perhaps even, contribute directly to a dysphoric effect. Further work is required to assess the implications of the imbalance hypothesis[16,17] in brain stimulation treatments for depression.

Cognitive findings

Overall, DTMS did not have a discernable negative impact on cognitive functioning. Although no significant correlation was found between baseline cognitive performance of depressive patients and their baseline HDRS score, the performance of depressive patients was significantly lower than that of the CS group in various cognitive domains: sustained attention, visuospatial memory, working memory, and psychomotor speed, suggesting dysfunctions in frontostriatal systems, medial temporal lobe systems, and the posterior parietal cortex.[36-39] By the primary efficacy time point, a significant cognitive amelioration was found in most of the previously mentioned tasks. In accord with the clinical results, coils exerting greater stimulation over the left PFC, that is, H1 and H1L-120%, were most prominent in producing cognitive improvement. Therefore, it is possible that the alleviation of depressive symptoms was the cause for cognitive improvements, rather than the stimulation per se. However, there was no significant correlation between depressive and cognitive improvements, and the highest cognitive improvements were observed in frontostriatal circuitry-related tasks (SOC and Spatial Working Memory) (Figure 3). Indeed, extensive evidence from neuroimaging studies has found PFC circuitry to be a key neural substrate of cognitive control, executive functions, and attention.[40-43] This contributes to the proposition that the cognitive amelioration was perhaps induced by direct stimulation of the left DLPFC and VLPFC rather than by the depressive alleviation, though this inference warrants further research.

Limitations

Despite the encouraging results presented in this study, there are limitations that should be addressed. The ability of the H-coils to effectively stimulate deeper neuronal structures is obtained at the cost of a wider distribution of the electrical field in the brain, and thus a loss of focality.[19,20] It is possible that the high rates of response result from the larger volume receiving direct stimulation, and not merely the depth of stimulation. Indeed, Schutter et al.[44] reported that parietal stimulation also results in treatment efficacy in depression. However, it is important to note that the H1L-coil at 110% also induces a relatively broad volume of direct stimulation (Figures 1A and S1), but was much less effective, possibly because of the reduced depth in the PFC relative to the other groups (Figure 1A). Future imaging studies may address this issue.

In the current study, the effectiveness of different versions of the H-coil were compared in depressive patients; however, to establish DTMS as an effective treatment for depression, a double-blind sham-controlled study with a larger sample size is required. Although a sham DTMS treatment was not incorporated in this study, the lower intensity group (H1L-110%) showed an important contrast, despite its small sample size (n = 8). However, it is important to note that the choice of 110% MT rather than lower was not to form a pseudo control group, but rather to obtain insight regarding the efficacy of direct effective stimulation depths of 1 cm (induced by H1L at 110% MT) as opposed to 3 cm (at 120%; Figures 1A and S1).

Patients treated by the H1L-coil at 110% MT improved only mildly, considerably less than expected according to previous rTMS literature using standard coils in depressive patients.[18,32,33] This finding might reflect the severity of the disease and drug resistance in the patients of this study, as response rates to standard TMS were shown to be reduced in such patients.[32,33] In addition, it is possible that the low response in the H1L-110% group relative to that of standard coils results from the differential coil shape and placement, or the small sample size (n = 8). Nevertheless, this treatment was not deleterious, for HDRS scores of this group 3 months postactive treatment termination (visit 22) show that two of the six patients who remained in the study remitted, one responded, and the remaining three maintained a similar HDRS score to that at visit 21, which is lower than that of baseline.

DTMS—what's next?

In addition to a large double-blind sham-controlled study, future studies should characterize the subgroups of patients that are more likely to respond to DTMS. For example, although a recent review concluded that TMS shows no therapeutic effect on depression symptoms in older patients,[45] some studies showed otherwise. Still, these studies and others find age to be negatively correlated to treatment response.[46-48] It has been suggested that the observed inefficacy in older populations may be a result of the progressive shrinking of brain tissue observed with age, which would therefore result in an increased "coil to cortex" distance. In the current study, although patients' ages ranged from 18-65 years (thus excluding geriatric populations), there was no indication that older patients responded less than the younger ones. On the contrary, the percent of reduction in HDRS scores tended to be greater in patients aged 50-65 years than that in patients aged 18-49 years. DTMS may therefore prove to be beneficial in treating depression in older patients who have an increased distance from the skull to the prefrontal cortex (more than 1.7 cm), a distance standard TMS cannot affect directly.[20,49]

Beyond clinical applications, TMS is used in basic studies to produce "virtual lesions"[50,51] to differentiate functional brain mechanisms, map excitatory and inhibitory intracortical circuits, or describe mechanisms of brain plasticity.[52] The ability of the H-coils to affect deeper regions directly may hold great potential for exploring the abovementioned fields, especially when effects are compared with standard TMS coils placed over the same brain region.

Summary

In conclusion, given the extreme treatment refractoriness and well-documented low and poorly sustained placebo response rates of this patient population,[10,53] the potential benefits of DTMS are evident. All DTMS H-coils exhibited adequate safety in the different methodologies used to treat treatment-resistant depression. Treatment with H-coils providing preferential stimulation over deep left PFC regions yielded higher response and remission rates than those induced by deep bilateral stimulation, or superficial stimulation, which was not effective at all. The effect of treatment was further observed in the rehabilitation of impaired cognitive performance. In addition to the potential clinical benefits of the H-coils in various psychopathologic and neurologic conditions, the ability to induce direct stimulation of deeper brain sites in a noninvasive and safe method presents us with an innovative tool to research many fundamental aspects of the human brain.

Acknowledgments

References

1. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001;7:541-547.
2. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9:471-481.
3. Nemeroff CB. Recent advances in the neurobiology of depression. Psychopharmacol Bull 2002;36(Suppl 2):6-23.

4. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34:13-25.

5. Vaidya VA, Duman RS. Depresssion—emerging insights from neurobiology. Br Med Bull 2001;57:61-79.

6. Leh SE, Ptito A, Chakravarty MM, Strafella AP. Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. Neurosci Lett 2007;419:113-118.

7. Nestler EJ, Carlezon WA Jr.. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 2006;59:1151-1159.

8. Garcia-Toro M, Montes JM, Talavera JA. Functional cerebral asymmetry in affective disorders: new facts contributed by transcranial magnetic stimulation. J Affect Disord 2001;66:103-109.

9. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. Eur Neuropsychopharmacol 2007;17:696-707.

10. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53:649-659.

11. Rami-Gonzalez L, Bernado M, Boget T, Salamero M, Gil-Verona JA, Junque C. Subtypes of memory dysfunction associated with ECT: characteristics and neurobiological bases. J ECT 2001;17:129-135.

12. Lukoyanov NV, Sa MJ, Madeira MD, Paula-Barbosa MM. Selective loss of hilar neurons and impairment of initial learning in rats after repeated administration of electroconvulsive shock seizures. Exp Brain Res 2004;154:192-200.

13. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999;56: 300-311.

14. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol 2002;5:73-103.

15. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. Am J Psychiatry 2003;160: 835-845.

16. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry 2000;48:813-829.

17. Grimm S, Beck J, Schuepbach D, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry 2008;63:369-376.

18. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 2007;116: 165-173.

19. Roth Y, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. J Clin Neurophysiol 2007;24:31-38.

20. Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin Neurophysiol 2005;116:775-779.

21. Haber SN, Kim KS, Mailly P, Calzavara R. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J Neurosci 2006;26:8368-8376.

22. Pagnoni G, Zink CF, Montague PR, Berns GS. Activity in human ventral striatum locked to errors of reward prediction. Nat Neurosci 2002;5:97-98.

23. Yeterian EH, Pandya DN. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 1991;312:43-67.

24. Nadeem M, Thorlin T, Gandhi OP, Persson M. Computation of electric and magnetic stimulation in human head using the 3-D impedance method. IEEE Trans Biomed Eng 2003;50:900-907.

25. Levkovitz Y, Roth Y, Harel EV, Braw Y, Sheer A, Zangen A. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin Neurophysiol 2007;118:2730-2744.

26. De Luca CR, Wood SJ, Anderson V, et al. Normative data from the CANTAB. I: development of executive function over the lifespan. J Clin Exp Neuropsychol 2003;25:242-254.

27. Robbins TW, James M, Owen AM, et al. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J Int Neuropsychol Soc 1998;4:474-490.

28. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 1998;108: 1-16.

29. Roth Y, Padberg F, Zangen A. Transcranial stimulation as treatment in mental disorders. In: Marcolin M, Padberg F, editors. Transcranial magnetic stimulation of deep brain regions: principles and methods, vol. 23. Zürich: Karger Publishers; 2007. p. 204-224.

30. Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. J Clin Neurophysiol 2002;19: 361-370.

31. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 2001;50:58-61.

32. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. J Psychiatry Neurosci 2005;30:83-90.

33. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62:1208-1216.

34. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48: 851-855.

35. Ballesteros J, Bobes J, Bulbena A, et al. Sensitivity to change, discriminative performance, and cutoff criteria to define remission for embedded short scales of the Hamilton depression rating scale (HAMD). J Affect Disord 2007;102:93-99.

36. Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. Psychol Med 1996;26:975-989.

37. Sobin Cm Sackeim HA. Psychomotor symptoms of depression. Am J Psychiatry 1997;154:4-17.

38. Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 2000;48:674-684.

39. Sweeney JA, Strojwas MH, Mann JJ, Thase ME. Prefrontal and cerebellar abnormalities in major depression: evidence from oculomotor studies. Biol Psychiatry 1998;43:584-594.

40. Badre D, Wagner AD. Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. Neuron 2004;41:473-487.

41. Duncan J. An adaptive coding model of neural function in prefrontal cortex. Nat Rev Neurosci 2001;2:820-829.

42. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 2000;23: 475-483.

43. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167-202.

44. Schutter DJ, Laman DM, van Honk J, Vergouwen AC, Koerselman GF. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. Int J Neuropsychopharmacol 2009;12:643-650.

45. Frazer CJ, Christensen H, Griffiths KM. Effectiveness of treatments for depression in older people. Med J Aust 2005;182:627-632.

46. Figiel GS, Epstein C, McDonald WM, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 1998;10:20-25.

47. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry 2008;65:268-276.

48. Jorge RE, Robinson RG, Tateno A, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry 2004;55:398-405.

49. Kozel FA, Nahas Z, deBrux C, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 2000;12:376-384.

50. Hilgetag CC, Theoret H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 2001;4:953-957.

51. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 2000;10:232-237.

52. Pascual-Leone A, Tarazona F, Keenan J, Tormos JM, Hamilton R, Catala MD. Transcranial magnetic stimulation and neuroplasticity. Neuropsychologia 1999;37:207-217.

53. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(Suppl. 16):10-17.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brs.2009.08.002