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ORIGINAL INVESTIGATION

H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study

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Abstract

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

Key words: *Transcranial magnetic stimulation (TMS), major depressive disorder, medication resistance, continuation treatment, neuromodulation*

Introduction

Major depressive disorder (MDD) is a common disorder that presents a clinical challenge in terms of both acute and long term treatment (Greden 2001; Ustun et al. 2004; Lopez et al. 2006). Residual symptoms are common and lead to high relapse rates in the short term and disability in the longer term (Frank et al. 1991; Rush et al. 2006; Fekadu et al. 2009).

Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a novel tool for the treatment of MDD (Fitzgerald et al. 2003). A large body of research suggests that rTMS has clinically meaningful anti-depressive effects (Holtzheimer et al. 2001; Burt et al. 2002; Kozel and George 2002; Martin et al. 2002; Couturier 2005; Herwig et al. 2007; O'Reardon et al. 2007; Schutter 2009; George et al. 2010). Surprisingly, only limited data have been published that describe the possible role of rTMS in maintaining a therapeutic effect beyond an acute course of treatment for MDD. With the recognition that mood disorders are chronic relapsing illnesses, and in light of the high-standard continuation studies for ECT and pharmacological therapies (e.g., Kellner et al. 2006), the thorough investigation of rTMS as a continuation treatment is much needed. The first published case

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report to describe a successful continuation treatment of unipolar depression with rTMS (administered over a four month period) was that of a 45-year-old woman with medication-resistant depression (Abraham and O'Brien 2002). Another study showed beneficial effects in eight out of 11 patients with refractory depression, who maintained response over a period of 3 months after receiving 4 weeks of rTMS treatment administered at 10 Hz over the left prefrontal cortex (Benadhira et al. 2005). An additional study examined the effects of long term rTMS in ten subjects who had responded to acute rTMS treatment. Seven of the ten participants showed sustained response rates after receiving one to two rTMS sessions per week for periods ranging from 6 months to 6 years. No serious adverse events were reported by any of the participants (O'Reardon et al. 2005).

Standard rTMS coils induce an effective depth of approximately 1 cm (Roth et al. 2002). One hypothesis suggests that deeper stimulation could improve results (Blumberger et al. 2010). Recently, a novel *deep-TMS* H-Coil was introduced, inducing a magnetic field with greater depth and distribution (Roth et al. 2002; Zangen et al. 2005). It reaches up to 3 cm beneath the surface without a significant increase of electric fields induced in superficial cortical regions (Roth et al. 2007). The H-coil was found to be safe and showed an acute anti-depressive effect in MDD patients (Levkovitz et al. 2007, 2009; Isserles et al. 2011). Safety of *Deep-TMS* H-coil as a continuation treatment has not been previously assessed. The purpose of the present study was to assess the safety and feasibility of *Deep-TMS* H-coil rTMS, given as an add-on treatment for MDD, over a period of 22 weeks that included both acute and continuation phases.

Methods

Subjects

Potential candidates were recruited from the outpatient program at the Shalvata Mental Health Center (affiliated with Tel-Aviv University). The inclusion criteria were: (a) 18–65 years old; (b) DSM-IV diagnosis of a major depression episode, unipolar type, established by two senior psychiatrists using the Structured Clinical Interview for DSM-4 (SCID) (Spitzer et al. 1992); (c) a score of >20 in the Hamilton Depression Rating Scale (21 items) at screening; (d) treatment-resistance (i.e. failure of at least one adequate pharmacological trial during the current episode, or intolerance to two antidepressants) according to the subject's medical chart and ATHF (antidepressant treatment history form) instruction guidelines.

Exclusion criteria included: (a) other axis-I psychopathology; (b) a current depressive episode related to borderline personality disorder; (c) electroconvulsive therapy (ECT) less than 9 months prior to study entry; (d) unsuccessful treatment with more than four antidepressants in the past year; (e) high suicide risk or a suicide attempt in the past year; (f) any risk factors for seizures; (g) substance abuse during the past year.

Procedure

The 22-week study was divided into three distinct phases: (1) Acute Phase: 4 weeks, in which daily rTMS sessions were conducted five times per week, for a total of 20 sessions. (2) Continuation Treatment I (CT-I): 8 weeks, in which rTMS sessions were conducted twice a week for a total of 16 sessions. (3) Continuation Treatment II (CT-II): 10 weeks, during which rTMS sessions were conducted once a week.

Clinical measures

Clinical evaluations were performed at baseline and every week throughout the duration of the study. Evaluations consisted of the 21-item version of the Hamilton Depression Rating Scale (HDRS), the Clinical Global Impression Scale (CGI) including CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) subscales, the Beck Depression Inventory II (BDI-II) and the Hamilton Anxiety Rating Scale (HARS). All evaluations were performed by clinically trained raters.

Response was defined as $>50\%$ decrease from baseline in HDRS score, remission defined as ≤ 10 score on the HDRS, and relapse as ≥ 18 score on the HDRS for two consecutive weeks.

The primary outcome measure for the study was probability of response.

Secondary outcome measures were: probability of remission, probability of relapse after response, probability of relapse after remission, percent (and standard error) of response and remission at 4 weeks and at end of study and median response and remission times, and symptomatic improvement at the end of each phase as measured using HARS, BDI-II and the CGI-S and CGI-I questionnaires.

Safety was assessed using a medical assessment interview in which subjects were asked to report any kind of physical changes related to the rTMS treatment at the end of each treatment session. Inspection of the scalp near the locus of stimulation was performed before and immediately after each stimulation session. Weekly measurements of blood pressure and heart rate were taken.

Cognitive performance was assessed at baseline and at the end of the study (week 22), using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The tasks evaluated four different

cognitive domains and were presented in a semi-randomized order in a controlled environment. The four domains and their subset of tasks included: psychomotor speed (reaction time (RTI)); visuo-spatial memory (pattern recognition memory (PRM), spatial recognition memory (SRM)); sustained attention (rapid visual information processing (RVP)); and frontal lobe related/executive function (stockings of Cambridge (SOC), spatial working memory (SWM), and spatial span (SSP)).

Study device and procedure

rTMS sessions were conducted using a Magstim Super Rapid stimulator (Magstim, UK) with the novel *Deep-TMS* H-coil, which is positioned on the patient's scalp. Prior to stimulation, subjects 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 by delivering single stimulations to the motor cortex.

MT was defined as the lowest intensity of stimulation that produced motor evoked potentials of at least 50 μV in five of 10 trials. MT was determined by gradually increasing the stimulation intensity using single pulse mode in a 5-s interval and recording electrical activity in the APB using surface electrodes. Next, the coil was placed 6 cm anterior to the motor spot (i.e. the prefrontal cortex) and spatial coordinates were marked on a cap placed on the subject's head each session to ensure placement reproducibility. The MT was measured daily before each session. Each rTMS session consisted of 42 trains (2 s per train, 20-s inter-train interval) delivered at a frequency of 20 Hz and an intensity of 120% of the measured MT, for a total of 1680 magnetic pulses per session (Levkovitz et al. 2009; Isserles et al. 2011).

Statistical analyses

All analyses were performed using SAS version 9.2. A P value of 0.05 or less was considered statistically significant.

Kaplan–Meier Survival analysis was performed for probability of response, time to remission, probability of relapse after response and probability of relapse after remission. The Kaplan–Meier estimates of the percent (and standard error) with response and remission at 4 weeks and at end of study are presented, the median response and remission times are presented as well.

The change from baseline in clinical rating scales was estimated from repeated measures analysis of covariance models (SAS PROC MIXED). For each rating scale, the change from baseline was modeled as a function of the time (in weeks) and the baseline value. Linearity was assessed by comparing the –2log likelihood of two models, one in which "week" was entered as a continuous variable and the other in which "week" was entered as a categorical variable. The difference for the HDRS-21 score was found to be statistically significant, thus it was assumed that the change from baseline follows a non-linear pattern and therefore the models chosen were those with "week" entered as a categorical variable. Adjusted mean of the change from baseline (Δ) at each visit were estimated (null hypothesis: $\Delta = 0$) and presented. For each CANTAB test, the measurements at baseline and at the last treatment were compared using paired t-tests.

Results

Subjects

Forty-seven MDD patients were referred for a screening meeting. Twenty-nine met admission criteria, and were enrolled in the study (see CONSORT diagram for full patient disposition). The mean age of participants (15 men, 14 women) was 40.97 ($\pm$ 10.51). Full demographic data, medical history and a list of medications taken during the study are presented in Table I. Twenty-six (89.65%) subjects

Table I. Demographic and clinical measures.

Parametric measures		**Mean ± SD**
Age (years)		40.97 ± 10.51
Education level (years)		13.76 ± 2.28
Psychiatric history	Age at first episode	24.03 ± 11.58
	Number of depressive episodes	4.21 ± 2.22
	Current episode duration in months	25.79 ± 16.84
	Number of hospitalizations	0.72 ± 1.58
Non-parametric measures		**Number**
Gender	Male	15 (51.72%)
	Female	14 (48.28%)
Family Status	Single	15 (51.72%)
	Married	9 (31.03%)
	Divorced	5 (17.24%)
Birth Country	Israel	24 (82.76%)
	Other	5 (17.24%)
Occupation	Full employment	16 (55.17%)
	Unemployed	13 (44.83%)
Medications		
Current Anti-depressants	SSRI's	11
	SNRI's	4
	Tricyclics	1
	Neuroapenifrin reuptake inhibitors	1
	None	11

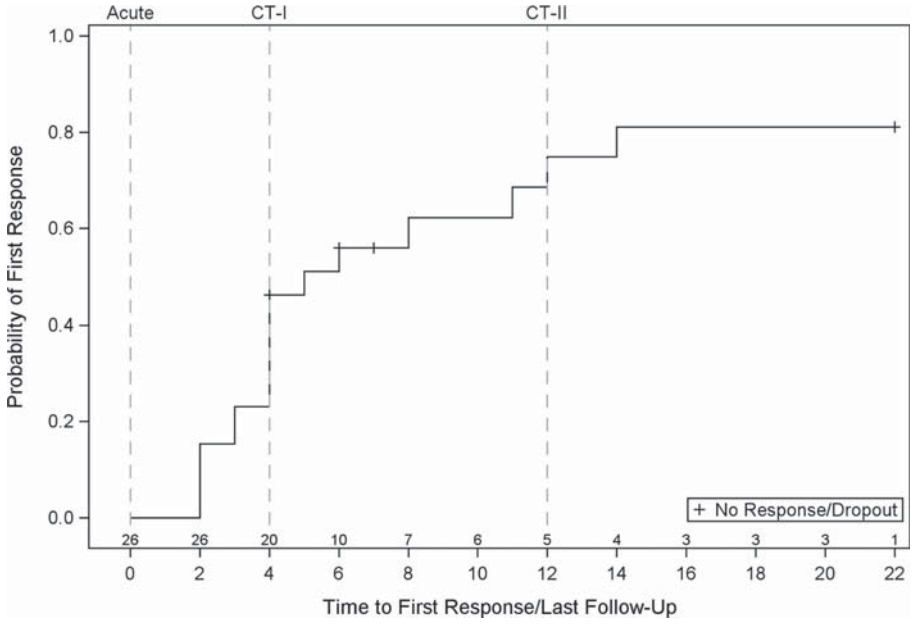


Figure 1. Kaplan–Meier curve of the probability of response.

completed the acute phase (4 weeks). Three subjects were excluded from the study within the first week of the treatment: one subject was excluded for safety reasons before receiving the first treatment and two subjects were excluded due to non-compliance with the study protocol (one had changed his medication, the other was absent from too many treatment sessions). Twelve (46.2%) of the subjects that completed the acute treatment phase showed a significant response. The average HDRS scores at baseline and at the end of the acute treatment were 23.38 (± 4.25) and 11.71 (± 7.28), respectively. Twenty six participants entered CT-1 (12 responders, 14 non-responders). Ten subjects dropped out by the end of the phase: Four (33.33%) of the 12 responders, and six (42.85%) of the 14 non-responders. Of the 16 subjects who entered CT-II (10 responders, six non-responders), one non-responder was excluded due to non-compliance with study protocol, and 15 completed the full length of the continuation phase. No statistically significant differences were found in baseline characteristics (demographic and clinical), between completers and early drop outs, at all phases. No adverse events or major discomfort with the procedure were reported.

Table II. Adjusted means of the change from baseline in HDRS score.

End of phase	*Adjusted decrease*	*Standard Error*	*p-value*	*95% CI*
Acute (4 weeks)	−9.48	1.067	<.0001	[−11.58–−7.38]
CT-1 (8 weeks)	−9.92	1.232	<.0001	[−12.35–−7.50]
CT-2 (10 weeks)	−10.12	1.283	<.0001	[−12.64–−7.59]

Primary outcome measure–probability of response

Figure 1 shows the Kaplan–Meier plot for the probability of response over 22 weeks (as well as the number of subjects without response). The median time to response was 5 weeks. The Kaplan–Meier estimated probability of response at 4 weeks was 46.15% (SE = 9.78%) and at the end of the study (22 weeks) this probability was 81.12% (SE = 9.32%).

Secondary outcome measure

Average decrease from baseline in HDRS score. The mean change from baseline in HDRS, adjusted for baseline HDRS, at the end of each phase, are presented in Table II along with their respective *P* values. A statistically significant average decrease from baseline in HDRS score was found at the end of each phase (adjusted mean change: acute phase $\Delta = -9.48 \pm 1.067$; CT-I$\Delta = -9.92 \pm 1.232$ $P < 0.0001$; CT-II$\Delta = -10.12 \pm 1.283$ $P < 0.0001$)). No statistically significant differences were found between the changes at the end of each of the phases, i.e. the reduction observed at week 4 was maintained (in average) until week 22. The average decrease in HDRS score, across the 22 weekly evaluations, is presented in Figure 2.

Time to remission. Kaplan–Meier plot for the probability of first remission (HAMD ≤ 10) over 22 weeks,

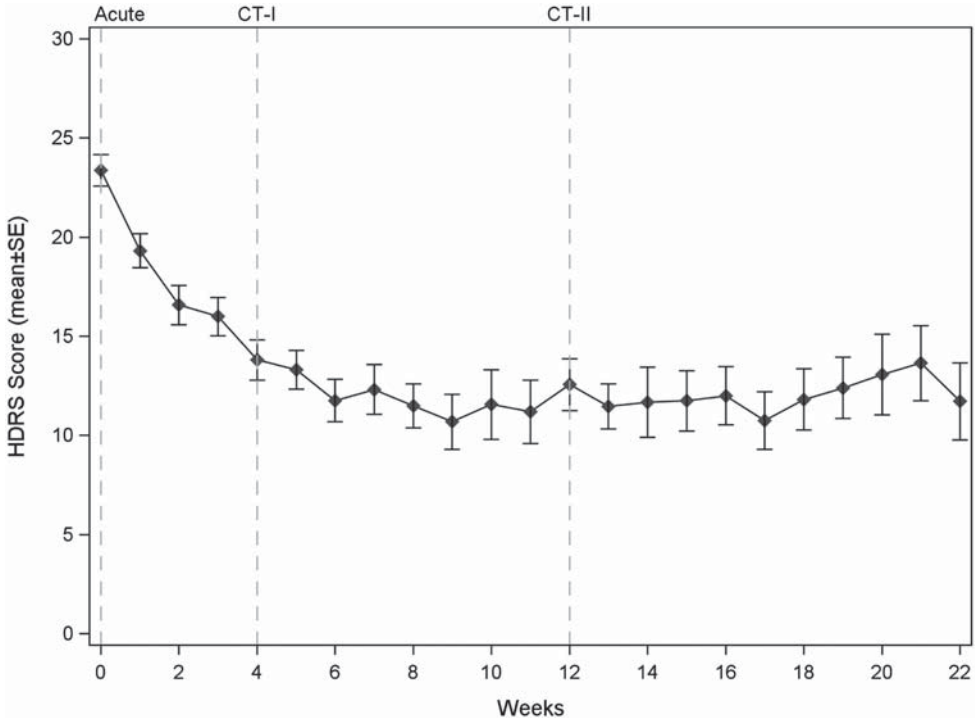


Figure 2. HDRS change from baseline throughout the study. Hamilton Depression Rating Scale (HDRS) total score (± SE) including all subjects that were enrolled in the study at different points (Baseline $n = 29$, week 1 $n = 26$, week 5 $n = 23$, week 6 $n = 21$, week 7 $n = 19$, week 8 $n = 8$, week 9 $n = 16$, week 19 $n = 16$, week 22 $n = 15$).

as well as the number of subjects without remission are presented in Figure 3. The median time to remission was 6 weeks. The Kaplan–Meier estimated probability of remission at 4 weeks was 26.92% (SE = 8.70%) and at the end of the study (22 weeks) this probability was 71.45% (SE = 10.99%).

Probability of relapse after response. Kaplan–Meier plot for the probability of relapse after response over 22 weeks (as well as the number of subjects with response but without relapse) is presented in Figure 4. A relapse is defined as two consecutive weeks with HDRS ≥ 18. The median time to relapse in the responders was 8 weeks. The Kaplan–Meier estimated probability of relapse free survival at the end of the study (22 weeks) was 60.34% (SE = 12.91%).

Probability of relapse after remission. Figure 5 below shows the Kaplan–Meier plot for the probability of relapse after remission (HAMD ≤ 10) over 22 weeks, as well as the number of subjects with first remission but without relapse. The median time from remission to relapse was 10 weeks. The Kaplan–Meier estimate of relapse free survival rate at 22 weeks was 68.10% (SE = 13.29%).

Average decrease from baseline in CGI-S HARS and BDI-II score. A significant reduction from baseline in the CGI-S, HARS and BDI-II scores was also found at the end of each phase:

-*Acute phase:* CGI-S $\Delta = -1.1771 \pm 0.2263$, $P < 0.0001$; HARS $\Delta = -5.3074 \pm 0.8565$, $P < 0.0001$; BDI-II $\Delta = -8.5844 \pm 1.3579$, $P < 0.0001$;

-*CT-I:* CGI-S $\Delta = -1.6045 \pm 0.2549$, $P < 0.0001$; HARS $\Delta = -6.4369 \pm 1.0116$, $P < 0.0001$; BDI-II $\Delta = -9.7563 \pm 1.5059$, $P < 0.0001$.

-*CT-II:* CGI-S $\Delta = -1.5745 \pm 0.2640$, $P < 0.0001$; HARS $\Delta = -5.6567 \pm 1.0596$, $P < 0.0001$; BDI-II $\Delta = -9.2109 \pm 1.5558$, $P < 0.0001$.

Responders vs. non-responders. Based on the response in the acute phase we divided the subjects into two sub-groups: responders ($N = 12$) and non-responders ($N = 14$). Eight responders and seven non-responders completed the full study protocol. A significant difference was found in the HDRS (primary outcome measure) between responders and non-responders in CT-I ($P = 0.0009$) and CT-II ($P = 0.013$). Moreover, six of the 12 responders achieved remission at the end of the study, as compared to only one of the 14 non-responders.

Safety measures

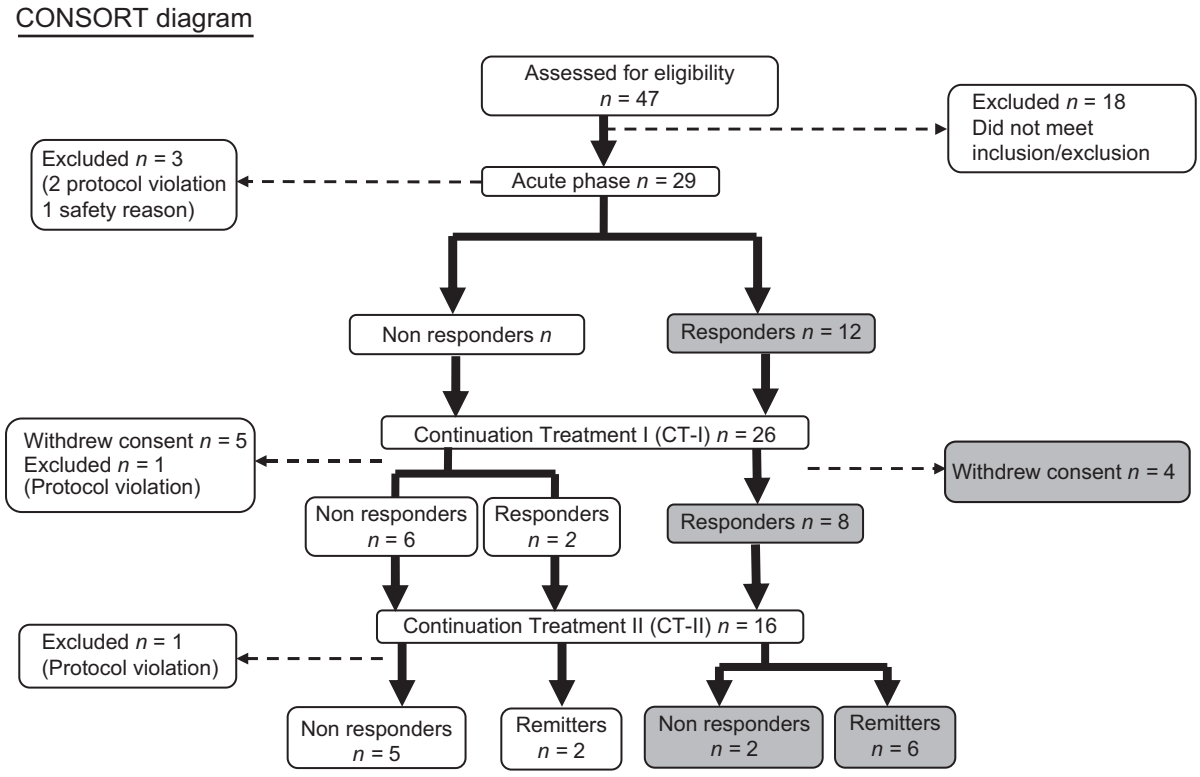
The major safety concern in rTMS studies is induction of seizures. Out of 971 daily rTMS sessions within the protocol, no seizures occurred nor were any

serious adverse events recorded. An inspection of the scalp following each treatment session did not reveal skin lesions in any of the subjects. No significant changes in blood pressure were found throughout the study (systolic BP (baseline: 121.83 ± 12.66; at the end of the study: 122.0 ± 11.25), diastolic BP (baseline: 81.76 ± 10.03; study end: 84.25 ± 9.87); pulse: (baseline: 71.59 ± 9.73; study end: $74.50 \pm$ SD = 13.16)). Finally, none of the subjects reported hearing loss or any specific adverse consequences.

Ten subjects completed all cognitive evaluations (at baseline and at the end of the study). No significant differences were found between the two assessments.

Discussion

This open study examined the safety and feasibility of using *Deep-TMS* H-coil stimulation of the prefrontal cortex as an add-on treatment for MDD. As most studies utilizing rTMS for MDD examine its acute therapeutic effect, the importance of this study lies in its exploration of using rTMS as a continuation treatment. Moreover, in contrast to several MDD treatment studies that evaluated response in a single assessment, subjects in the current study were evaluated weekly throughout the 22 weeks of the study allowing for a stronger assessment of response and its course and stability throughout the



Drop out

[1]Out of 29 participants three were excluded during the acute phase for the following reasons:

- One patient was excluded from the study for safety reasons before receiving the first treatment.
- Two patients were excluded from the study during week 2 due to non-compliance with study protocol.

[2]Out of 12 responders, four dropped out during CT-I for the following reasons:

- One patient withdrew from the study during week 6. She felt a vast improvement and wished to return home overseas.
- One patient withdrew from the study during week 7 as she could not keep up with the study schedule.
- Two patients withdrew from the study during weeks 8 and 10 as they felt no improvement. It should be noted that a significant improvement in HDRS score was seen.

[3]Out of 14 non-responders, six dropped out during CT-I for the following reasons:
Withdrew from study; $n = 5$

- Three patients withdrew from the study during week 5 as they felt no improvement.
- One patient withdrew from the study during week 6 as he felt no improvement. Some improvement although not significant was seen.
- One patient withdrew from the study during week 8 as he felt no improvement.

Excluded from study; $n = 1$

- One patient was excluded from the study for using medication against study protocol.

[4]Out of six non-responders, one was excluded during CT-II for the following reasons:

- One patient was excluded from the study during week 18 due to non-compliance with study protocol

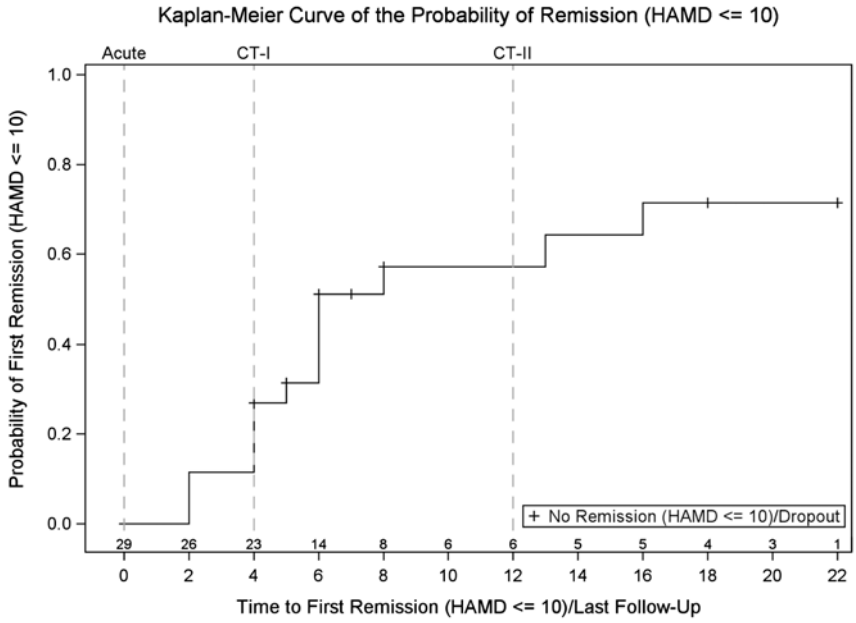


Figure 3. Kaplan–Meier curve of the probability of remission.

continuation treatment. We observed a positive acute therapeutic effect on depressive symptoms in MDD as evidenced by the 46.2% response rate at the end of the acute phase and a significant average decrease in the HDRS score. Importantly, we found that continuing rTMS treatments following the acute treatment twice a week for 8 weeks, and once a week for 10 more weeks maintained response rate throughout the study. By the end of the study the Kaplan–Meier estimated probability of response was 81.12%, and 71.45% for remission.

A significant reduction from baseline in anxiety, clinical global impression, and an additional depression rating scale (BDI-II) scores were also found at the end of each phase. Nevertheless, the possibility of a placebo effect, therapeutic effects of meeting daily with study personnel and the natural course of the depressive episode, remain possible factors in the

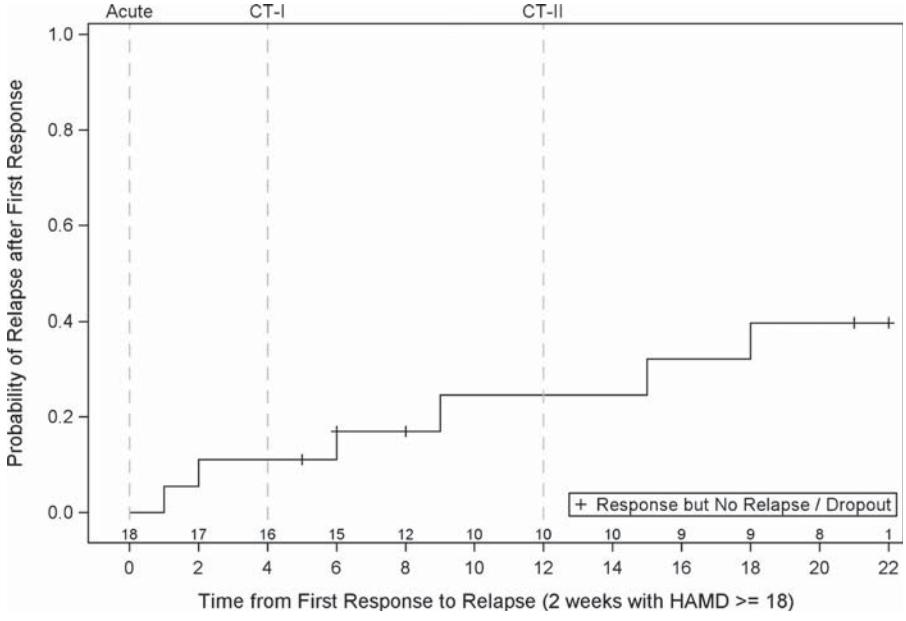


Figure 4. Kaplan–Meier plot for the probability of relapse after response.

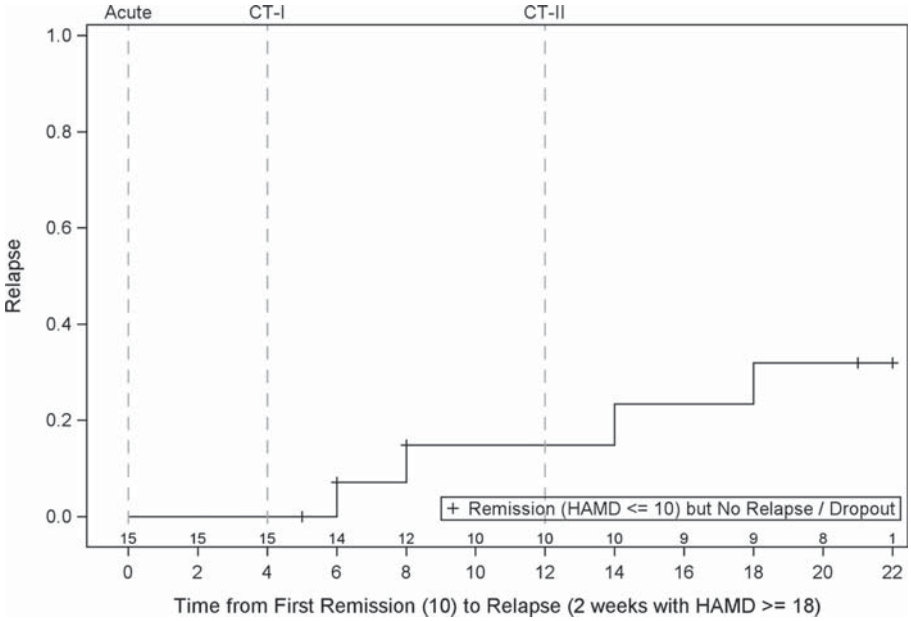


Figure 5. Kaplan–Meier plot for the probability of relapse after remission.

antidepressant benefit in addition to the inherent neurobiologic activity of TMS.

It is interesting to note that the median time to response was 5 weeks, indicating that half of the patients took 5 weeks or more to achieve response. This point may have significant therapeutic consequences, since all acute treatment studies that we are aware of have given a maximum of 4 weeks of treatment, thus possibly diminishing the efficacy of the treatment.

Thanks to the weekly evaluations, it was possible to include in our analyses subjects who dropped out of the study by indicating the number of weeks of their participation.

We then divided the subjects into responders and non-responders, in order to explore whether different patterns could be identified during continuation treatment. At the end of the acute phase, the non-responders had a higher dropout rate and a smaller percentage of response. Our data suggests that response in the acute phase is associated with a lower dropout rate and a longer response period during the continuation phases. These results are in accordance with two previous studies that indicate the antidepressive properties of the *Deep-TMS* H-coil rTMS in MDD (Levkovitz et al. 2009; Isserles et al. 2011).

In contrast to previous reports by our group (Levkovitz et al. 2009) no cognitive change was evident throughout the study. However, it should be noted that the small number of participants that completed the cognitive assessment ($N = 10$) limits the ability to draw definitive conclusions and establish the safety of this procedure, and should be the topic of future study.

The treatment was generally well tolerated with no serious adverse events recorded, even though the coil is more powerful than standard coils, and stimulation was delivered at parameters that are above those presented by Rossi et al (2009) as safety guidelines. It should also be noted that patients were receiving antidepressant medications that may have reduced the threshold for a seizure.

The design of the current study has several limitations: as this study was an open study with a small sample size and add-on design, it was not possible to rule out a possible placebo effect and expectancy bias, as well as the possibility of improvement having been the result of other factors, such as the natural course of the illness. Furthermore, our sample included treatment intolerant patients as well as treatment resistant ones. Another limitation is the high dropout rate, probably partly due to the relative length of the study. In addition, the wide variety of antidepressants did not allow us to draw conclusions about the relative efficacy of any given prescribed antidepressant in combination with rTMS. Future studies should use a sham controlled randomized design with a large number of patients to further assess the efficacy of *Deep-TMS* H-coil rTMS in the treatment of MDD, as well as compare the efficacy of rTMS as a continuation treatment to that of other neurostimulation methods.

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Statement of Interest

Professor Levkovitz and Dr Zangen have financial interests in Brainsway, Inc.

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Notice of Correction

The version of this article first published online ahead of print 7 Feb 2012 contained an error in the abstract. The sentence *Deep-TMS* H-coil is a novel tool enabling deeper stimulation than standard coils should read *Deep-TMS* is a novel tool enabling deeper stimulation than standard coils. This error has been corrected in the final version seen here.

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