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Research report

Cognitive–emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) enables non-surgical activation of specific brain areas. TMS over the prefrontal cortex (PFC) is emerging as a significant tool that can augment or replace non/partially effective antidepressant medications. Deep TMS (DTMS) utilizes newly developed coils that enable effective stimulation of deeper cortical layers involved in the pathophysiology of depression.

Objectives: We aimed to assess the H1-DTMS coil as an add-on to antidepressants in treating patients with major depression. We also intended to evaluate whether the antidepressant outcome of DTMS treatment is affected by a cognitive–emotional procedure performed during stimulation.

Methods: 57 patients were enrolled in the study that included 4 weeks of daily 20 Hz stimulation sessions and additional 4 weekly sessions as a short maintenance phase. Two subgroups of patients received either positive or negative cognitive–emotional reactivation along with the stimulation sessions.

Results: 21 of 46 patients (46%) who received at least 10 stimulation sessions achieved response (improvement of ≥50% in the Hamilton Depression Rating Scale (HDRS)) and 13 of them (28%) achieved remission (HDRS-24 ≤ 10) by the end of the daily treatment phase. Improvements were smaller in the negatively reactivated group and Beck Depression Inventory scores were not significantly improved in this group.

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

1. Introduction

Major Depressive disorder (MDD) is a common, highly disabling disorder with a life-time prevalence of about 16% in the western world (Kessler et al., 2005). Aproximately 30% of patients remain symptomatic despite treatment (Rush et al., 2006) and are considered to have treatment resistant depression (TRD) (Berlim and Turecki, 2007; Fava, 2003), posing a significant challenge to clinicians. Transcranial magnetic stimulation (TMS), which enables non-invasive modulation of brain activity, has been proposed as a novel

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treatment alternative for major depression and even treatment resistant depression. A recent placebo-controlled multicenter study (O'Reardon et al., 2007) led the FDA to approve TMS treatment of adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication. In that study, the remission rate after 6 weeks of daily active treatment was 17.4% (while the sham treatment induced remission rate was 8.2%, $p<0.05$). Although these results show evidence that TMS achieves a therapeutic effect, most of these resistant patients still failed to achieve remission.

Numerous lines of evidence deriving from different research and clinical methodologies attest that depression involves integrated neural pathways linking select cortical, subcortical, and limbic sites and their related molecular mediators (Manji et al., 2001; Mayberg, 1997; Nemeroff, 2002; Nestler et al., 2002; Vaidya and Duman, 2001). Hence, it is reasonable to assume a potential benefit of stimulating targets in relatively deep brain regions. These regions cannot be effectively stimulated utilizing standard TMS technology (Nadeem et al., 2003). The development of H-coils was meant to overcome this obstacle and to allow safe stimulation of deeper brain regions (Roth et al., 2002; Zangen et al., 2005). H-coils induce an effective field at a depth of approximately 3 cm below the skull compared to less than 1 cm for the standard figure-8 TMS coil (Zangen et al., 2005; Roth et al., 2007a,b). In safety studies conducted on healthy volunteers, motor or prefrontal cortex (PFC) stimulation using H-coils was found to be well tolerated, and no serious adverse events or cognitive impairment occurred (Zangen et al., 2005; Levkovitz et al., 2007). The first feasibility study with H-coils performed on 65 resistant, unipolar, depressed patients demonstrated safety and effectiveness of repeated high frequency deep stimulation of the left PFC (Levkovitz et al., 2009). Moreover, when a more superficial stimulation was applied (using lower intensity) the antidepressant effect was dramatically diminished. In addition, bilateral PFC stimulation was found less effective than left sided stimulation supporting the asymmetric hypothesis of depression (Garcia-Toro, et al., 2001).

While the previous study assessed the efficacy of deep TMS (DTMS) as a monotherapy, the present study was designed to further assess the safety and efficacy of the H1-coil as an add-on in treating resistant unipolar depressed patients. In addition, the effect of cognitive–emotional reactivation on the outcome of DTMS treatment was evaluated. Administering DTMS in conjunction with antidepressants that proved partially effective or ineffective can simulate a typical real-life clinical scenario where the clinician prefers not to expose the patients to the risks of medication wash-out. Combining DTMS and antidepressants can however raise safety and efficacy concerns (e.g. increasing the risk of inducing a seizure).

A growing number of studies indicate that brain stimulation effectiveness strongly depends on the state of neuronal activation in the targeted brain region at the time of stimulation (Silvanto and Pascual-Leone, 2008; Amiaz et al., 2009; Stehberg et al., 2009). Many variables may theoretically contribute, alone or in combination, to change the pre-TMS level of neuronal activity, thus changing the resulting TMS effects: menstrual cycle (Smith et al., 1999; Inghilleri et al., 2004), age (Rossini et al., 2007) and theoretically also level of anxiety, mood or sleep deprivation. It probably matters even what subjects and patients do before exposure to TMS, as the effects of the stimulation may be modified. The basal level of neuronal activity, and in turn of brain reactivity to TMS, may be further modified by transcranial direct current stimulation pre-conditioning procedures (i.e., priming) (Lang et al., 2004), making the resulting effect of rTMS different in terms of effect size and even effect direction.

Previous studies showed that the ventrolateral PFC plays a role in reappraisal processes and that dysfunction of this region may be involved in the pathophysiology of depression (Johnstone et al., 2007). Hence, in the present study we evaluated the potential effects of guided positive and negative mood alterations prior and during PFC stimulation, on the outcomes. We hypothesized that neural networks mediating negative or positive emotions may be more strongly affected by DTMS while such networks are activated (Silvanto and Pascual-Leone, 2008; Stehberg et al., 2009) and therefore long-term neuroadaptations in these circuitries, induced by repeated DTMS sessions, may be affected by the type of cognitive–emotional reactivation.

2. Methods

2.1. Patients and recruitment

The study was approved by the Institutional and National Review Boards (IRB) and was conducted simultaneously at the Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel and at Beer Ya'acov Mental Health Center in accordance with the latest version of the Declaration of Helsinki. The study was registered in the NIH clinical trials registry (NCT00460902). Active enrollment of MDD patients took place from May 2007 through August 2009, with candidates recruited via newspaper and radio ads and referrals from collaborations with medical faculties and personnel. These volunteers signed informed consent forms before study entry and were free to withdraw at any time without prejudice.

2.2. Study overview

The screening procedure included a medical interview and a physical examination to determine suitability according to the Inclusion and Exclusion criteria. Main criteria included: a diagnosis of non-psychotic MDD with HDRS-24>21 and treatment failure with at least two antidepressant medications, right handedness, no other DSM-IV axis I or major axis II disorder and absence of known TMS risk factors. Consenting candidates signed a detailed informed consent form. The first ten patients were treated without any cognitive–emotional directives and later on patients were randomly allocated to one of three groups: One group of patients still did not receive any cognitive–emotional directives and two groups were directed to concentrate on their positive or negative thoughts and emotions prior to and during stimulation.

Patients were enrolled after a period of at least 4 weeks of stable antidepressant treatment. During the study no change was made in antidepressant treatment and only limited use of hypnotic or anxiolytic medication was allowed (up to of 2 mg/

day lorazepam or equivalent) for treatment-emergent insomnia or anxiety. During the daily treatment phase, DTMS sessions were scheduled in a 5-day sequence for four consecutive weeks. A total of 20 sessions were conducted at this stage (visits 1 to 20). In the weekly treatment phase that followed, four additional weekly DTMS treatments were administered as a short maintenance and follow-up phase (visits 21–24).

2.3. Evaluations conducted

Throughout the entire course of the study, patients were under the direct follow-up of a physician, and adverse effects or subjective complaints were recorded and treated as necessary. A trained psychiatrist performed psychiatric status examinations on a weekly basis. The Hamilton Depression Rating Scale 24 items (HDRS-24) and the Hamilton Anxiety Rating Scale (HAM-A) were administered at screening and weekly thereafter at the end of each treatment week. During these visits patients also filled in the self graded Beck Depression Inventory II (BDI-II). Lastly, a comprehensive battery of computerized cognitive tests using the Mindstreams cognitive health assessment tool (NeuroTrax Corporation, Newark, NJ) was administered to most patients at screening ($n=31$) and at 4 weeks (the end of the daily treatment phase, $n=26$) in order to assess changes in cognitive performance.

3. Materials

3.1. DTMS device

The DTMS stimuli were delivered using the Magstim Super Rapid or Rapid^2 stimulator (Magstim, UK) with the novel H1-coil, an extracorporeal device positioned on the patient's scalp (for theoretical considerations see Roth et al., 2007a,b). The H1-coil is designed to stimulate deep prefrontal brain regions, preferentially in the left hemisphere (Roth et al., 2007a; Levkovitz et al., 2007). The effective part of the coil, in contact with the patient's scalp, includes 14 strips of 7–12 cm long. The frame of the inner rim of the coil is flexible in order to allow optimal fit to individual skull's shape.

3.2. Mindstreams

Mindstreams (NeuroTrax Corporation, Newark, NJ) is a computerized system designed to assess cognitive function. Mindstreams is specially constructed to track cognitive performance over time and meant for use in clinical practice, academic research, and pharmaceutical drug trials. It runs on a standard personal computer (Paleacu et al., 2007; Lavi et al., 2007).

4. Procedure

4.1. Cognitive–emotional reactivation

Prior to treatment subjects were randomly allocated to one of three treatment groups:

a) No cognitive–emotional reactivation group — The stimulation was administered without any directives.
b) Positive cognitive–emotional reactivation group — In this group a short structured questionnaire was administered by the psychiatrist at the receiving session asking the patient to describe factors and emotions causing and accompanying his/her depression and then describe situations when the patient feels better and which positive hopes he/she may have for the future. A short directive paragraph was written based on this questionnaire which was given to the patient to read before and during each treatment, oriented for facilitating positive cognitive–emotional themes throughout the stimulation session.
c) Negative cognitive–emotional reactivation group — In this group a similar process was followed but focused on the negative thoughts and emotions associated with the patient's depression. In this case, the page given to the patient to read before and during each treatment aimed to facilitate negative cognitive–emotional themes throughout the stimulation session.

4.2. DTMS sessions

Prior to stimulation, patients were instructed to insert earplugs to mitigate any possible adverse effects on hearing. Next, the optimal location on the scalp for stimulation of the right abductor Pollicis Brevis muscle was located by a suprathreshold intensity, and the resting motor threshold (MT) was established by gradually decreasing the stimulation intensity (using single pulse mode, applying one pulse every 5 s) while observing the patient's hand. MT was defined as the lowest stimulation intensity producing a motor response in 5 out of 10 trials. Successively, the coil was placed 5.5 cm anterior to the motor spot (i.e., over the prefrontal cortex) and spatial coordinates were recorded with markings on a cap placed on the subject's head to ensure placement reproducibility. Determining the MT was repeated daily, and all treatments were delivered by one of three trained physicians (mainly M.I. or O.R.). Each DTMS session consisted of 42, 2 second trains with a 20 second inter-train interval (a total of 1680 magnetic pulses delivered per session), at 120% of the measured MT. These parameters are similar to previous studies on clinically depressed patients (O'Reardon et al., 2007; Levkovitz et al., 2009).

4.3. Data analysis

Efficacy analyses were performed on the 46 patients with a baseline measurement and at least two additional weekly assessments (i.e. received at least 10 sessions of DTMS treatment). Demographic data and baseline evaluations are presented on these 46 patients. Continuous variables are presented with their mean and standard deviation and compared between the treatment groups with an analysis of variance model (ANOVA). Discrete data are summarized by a count and percentage and compared between the treatment groups with a chi-squared test.

The response rate, defined as a decrease of at least 50% in the HDRS-24 score, and the remission rate, defined as a HDRS-24 score less than or equal to 10, at 4 weeks, were compared between the treatment groups with a Fisher's Exact Test.

The change from baseline to week 4 in rating scale data was analyzed using an analysis of covariance (ANCOVA) model (PROC GLM in SAS v9.1 (SAS institute, Cary NC, USA)). The model which aims to compare the rating scale change from baseline between the treatment groups included the following effect: emotional reactivation (treatment group) and the baseline rating scale values as a covariate.

Missing rating scale data, at sessions 15 and 20, were imputed by carrying forward the last available value (LOCF).

Cognitive assessment, as assessed by the Mindstreams cognitive battery was compared between baseline and week 4 with a paired T-test (or the signed rank test, when the normality of the variable was questionable).

All statistical tests were two sided and tested at a 5% level of significance.

5. Results

57 adult patients suffering from Major Depression (HDRS-24 of 22 or more) and fulfilling inclusion and exclusion criteria were enrolled in the study (34 at Hadassah-Hebrew University Medical Center and 23 at Beer Ya'acov Mental Health Center). Baseline demographic and clinical characteristics are summarized in Table 1. There were no significant differences between treatment groups. Analysis of outcome measures took place on 46 patients who completed at least two weeks of treatment (i.e. baseline plus two weekly assessments). Reasons for dropout and time points are specified in Fig. 1. 25 patients were treated without any specific cognitive–emotional directive. 17 patients were treated with written directives to concentrate on their positive thoughts and emotions during each stimulation session and 15 patients were treated with directives to concentrate on their negative thoughts and emotions during each stimulation session, as detailed in the Methods section.

5.1. Safety and tolerability

Overall, the treatment proved easy to tolerate and most patients suffered no side-effects, nor complained of any significant discomfort. Few patients complained of mild headaches, typically during the first week and mostly transient without any treatment or with common analgesics. Fifteen patients withdrew consent during the daily treatment phase: one after one treatment due to treatment intolerance and another after 7 treatment sessions, due to headaches and significant discomfort during – and for a few hours following – the stimulation. The other 13 patients withdrew consent of their own accord, mainly due to lack of satisfactory effect or due to personal reasons. Five patients were withdrawn from the study due to suicidal ideation (but no suicidal attempts occurred). These patients had a history of suicidal ideation or gestures and were withdrawn to ensure their safety.

One patient suffered from a short tonic–clonic generalized seizure during his second treatment session and was removed from the study. The seizure was self-limited and the patient did not require any treatment. Importantly, this patient was on high doses of three different antidepressants (venlafaxine, mianserine and mirtazepine) that apparently increased his vulnerability.

None of the patients fulfilled exacerbation criteria defined as more than 30% increase in their baseline HDRS-24 or BDI score by the end of their participation.

5.2. Treatment outcomes

The primary outcome measure was the HDRS-24 score at the end of four weeks of the daily treatment phase. Overall, 21 out of 46 patients (46%) achieved the response criterion (defined as an improvement of 50% or more in the HDRS-24 score) and 13 (28%) achieved the remission criterion (defined as HDRS-24 of 10 or less (Frank et al., 1991)) by the end of the daily treatment phase.

In the treatment group that was directed to concentrate on the positive themes during stimulation, 6/14 (43%) patients achieved both response and remission criteria. On the other hand, in the treatment group that was directed to concentrate on the negative themes during stimulation, only 3/12 (25%) achieved response, one of them (8%) achieving remission. In the group that received stimulation with no cognitive–emotional directives 12/20 patients (60%) achieved response and six of them (30%) achieved remission. These differences were however not significant (Fisher's Exact Test p-values of 0.1604 and 0.1529 for the difference between the three treatment groups in response rate and remission rate respectively).

During the four weeks of daily treatment the HDRS-24 mean score significantly improved, reaching a mean im-

Table 1
Baseline demographic and clinical characteristics for the treatment groups. No significant difference was found.

	Negative	No cognitive	Positive	P-value
	(N = 11)	(N = 20)	(N = 14)	
Age (in years)[a]	41.75 (12.70)	45.40 (13.18)	45.93 (12.98)	0.40
Gender — male[b]	6 (50%)	11 (55.0%)	7 (50.0%)	0.95
Education (in years)[a]	14.17 (2.12)	14.50 (3.55)	14.36 (2.87)	0.96
Age at onset (in years)[a]	22.17 (9.31)	28.60 (14.59)	24.71 (10.13)	0.33
Current episode (months)[a]	24.58 (19.37)	25.00 (24.46)	54.25 (99.42)	0.29
Number of episodes[a]	3.82 (2.96)	3.70 (3.15)	6.14 (8.37)	0.38
Treatment trial current episode[a]	3.33 (1.21)	3.36 (2.11)	3.33 (1.83)	0.99
Baseline HDRS[a]	31.73 (7.38)	29.10 (5.82)	29.29 (5.95)	0.51
Affective family history[b] (positive)	3 (25%)	8 (40.00%)	9 (64.29%)	0.12
Typical stimulation intensity[a]	65.08 (7.33)	60.00 (7.15)	63.21 (7.2)	0.15

[a] ANOVA, mean (SD).
[b] χ^2 test N (%).

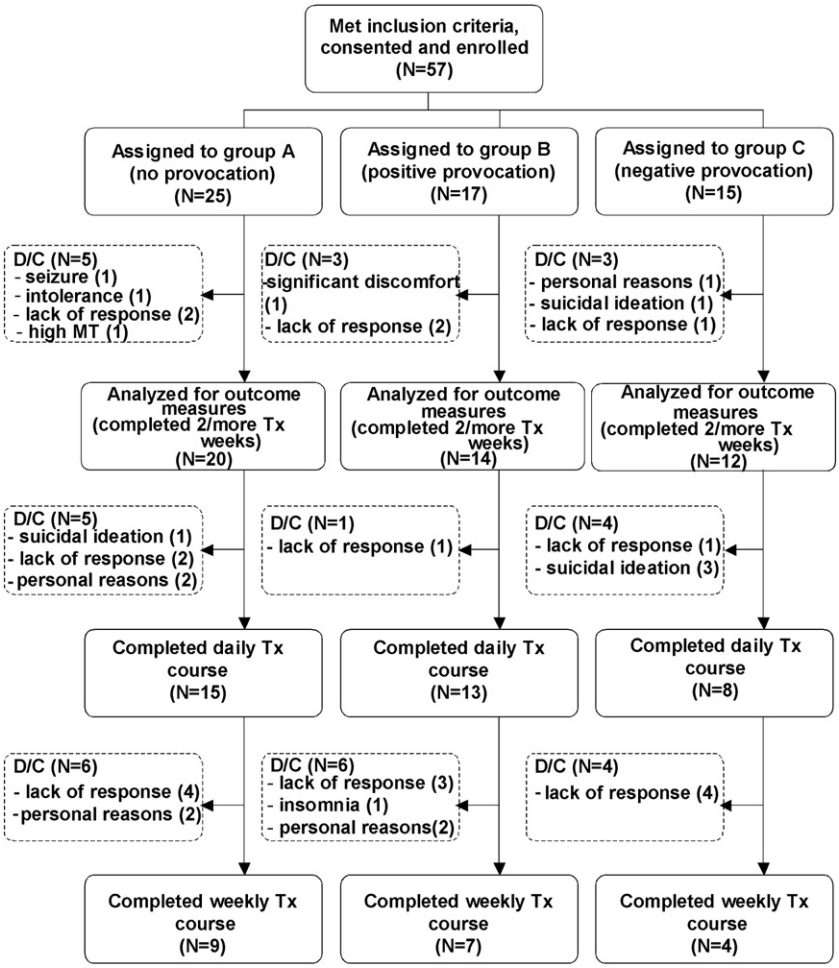

Fig. 1. Overview of study progression. Reasons for dropout and discontinuation of patients are specified by group and stage (D/C — discontinued from the study; MT — motor threshold; Tx — treatment).

provement (adjusted for baseline value) ± SE, [95% CI] of: 9.7 ± 2.1 [5.5–13.9], 15.8 ± 1.6 [12.5–19.0] and 13.1 ± 1.9 [9.1–17.0] points for the negative, no cognitive and positive groups, respectively (p-values for each group <0.0001) (Fig. 2A). HDRS-24 showed a near significant treatment effect ($p = 0.0816$) and in post-hoc analysis improvement was found to be significantly lower in the negative group than in the no cognitive group ($p = 0.026$). The change in self reported BDI-II scores from baseline to week 4 corroborated these results (Fig. 2B), mean improvement (adjusted for baseline value) ± SE, [95% CI] of: 4.2 ± 2.3 [0.35–8.7]; 10.0 ± 1.7 [6.5–13.5]; 12.1 ± 2.0 [8–16.2] for the negative, no cognitive and positive groups, respectively and significantly correlated with the change in HDRS-24. In the BDI-II there was a significant treatment effect ($p = 0.038$). The improvement in the negative group was significantly lower than in the positive group and near significantly lower than in the no cognitive group (P-values of 0.0131 and 0.0508 respectively). Analysis of BDI scores for each group separately revealed that while the positive and no cognitive groups showed a significant improvement along the 4 weeks of treatment, the improvement of the negative group did not reach significance (P-values of 0.0696, <0.0001 and <0.0001 for the negative, no cognitive and positive groups, respectively). HAM-A mean ± SE, [95% CI] scores improved significantly by 7.5 ± 1.4 [4.7–10.2], 7.7 ± 1.0 [5.6–9.7] and 7.3 ± 1.2 [4.9–9.8] points for the negative, no cognitive and positive groups, respectively.

Following the daily phase, 11 out of 13 remitters continued to a four week maintenance phase. One of these patients left the study after 2 weeks of maintenance due to insomnia while still fulfilling remission criteria. All other 10 remitters concluded this phase, preserving remission criteria.

5.3. Cognitive assessments

The results of the Mindstreams cognitive tests are presented in Fig. 3. 26 patients (8 remitters and 18 non-remitters) performed the tests before and after the daily treatment phase and were included in the analysis. Patients that achieved remission showed marked improvement in information processing speed (T-test, $p = 0.002$) and near significant improvement in attention (T-test, $p = 0.057$). Analysis of the cognitive tests in all patients (remitters and non-remitters) showed significant improvements in information processing speed (T-test, $p = 0.023$) and memory (Signed Rank Test,

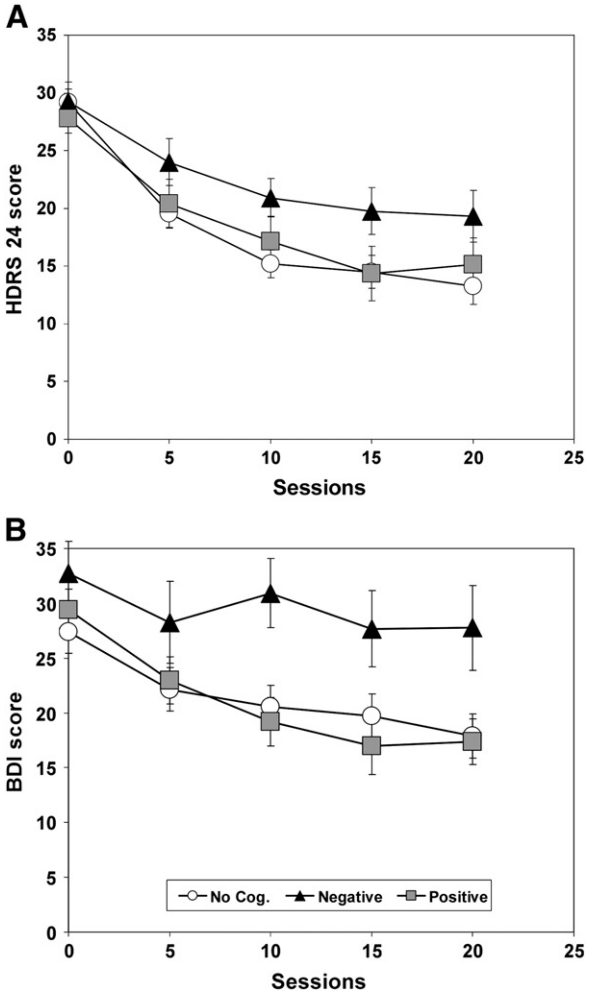

Fig. 2. Time course of DTMS effect on depressive symptoms. Panel A depicts the 24 item Hamilton Depression Rating Scale (HDRS-24) change over the four weeks of acute treatment course for the negative, positive and non-provocated groups. Panel B depicts the corresponding Beck Depression Inventory II (BDI-II) scores (data are presented as means ± standard error).

p = 0.038). Noteworthy, the positive effect of DTMS on memory was significant (Signed Rank Test, p = 0.026) only in patients who did not reach remission.

5.4. Response related parameters

We searched for parameters that can predict response and remission, based on the baseline cognitive assessments, stimulation parameters and demographic data. The only parameter found to be correlated with response and remission was the stimulation intensity. Patients who achieved remission or response were treated with significantly higher stimulation intensities than patients who did not respond to the treatment (mean stimulator power output [95% CI] of: 64.6 [62.2–67.0] for responders vs. 61.9 [60.9–63.0] for non-responders (p-value = 0.0411) and 67.4 [64.4–70.4] for remitters vs. 62.0 [61.0–63.0] for non-remitters (p-value = 0.0009)).

6. Discussion

The present study shows that deep TMS utilizing the H1-coil is generally safe and effective as an augmentation treatment in patients who did not sufficiently respond to at least two antidepressant medications in the current episode. Using DTMS as an add-on instead of monotherapy might be preferred when medications achieve a partial effect or when the clinical judgment is that taking the patient off medication might be unsafe. On the other hand, magnetic stimulation of medicated patients can increase the risk of inducing a seizure, especially when high doses of antidepressants that increase neural excitability are used. Indeed in this study, one patient suffered from a brief transient seizure. Since this patient had received markedly high dosages of various antidepressants, it is

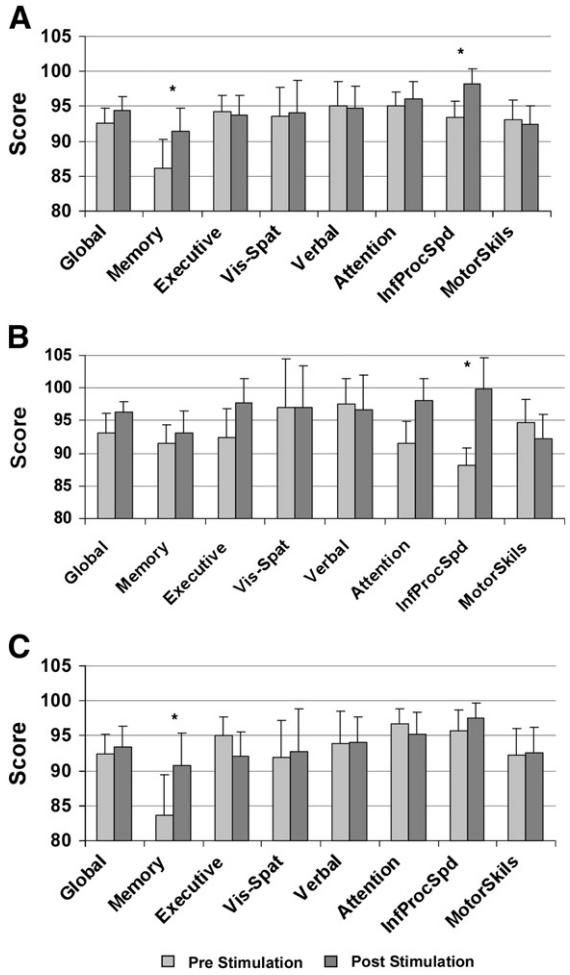

Fig. 3. Effects of DTMS treatment on cognitive outcome. Cognitive assessments before and after 4 weeks of daily stimulation using the Mindstreams computerized battery are presented as mean ± SE of the normalized (according to age- and education-specific normative data) scores for: memory (verbal and non-verbal), executive function, visual–spatial function (Vis–Spat), verbal function, attention, information processing speed (InfProcSpd), motor function and a global score that composites all of the above (15 points denote one SD). Results presented for all assessed patients (panel A, n = 26), remitters only (panel B, n = 8) and non-remitters only (panel C, n = 18).

recommended that in cases where patients are on high dosages of psycho-active medications that are known to increase convulsive vulnerability, extra caution should be exercised. In such cases, the medication dosages should be lowered or DTMS should be avoided.

The response and remission rates obtained in this study are promising, taking into account the treatment resistance of the study population. These positive results warrant a wider study that will include a sham control arm and would confirm DTMS efficacy as a novel treatment for resistant depression.

The present study also aimed to explore the possibility that the antidepressant effect of DTMS over the PFC might be affected by the ongoing neural activity during the stimulation. We therefore explored the effects of guided cognitive–emotional manipulation on the antidepressant outcome of the DTMS treatment. We aimed to assess two alternative hypotheses, one presuming that DTMS can act in concert with "physiological" top-down control of depressive emotions, a process that was implicated to be impaired in depression (Johnstone et al., 2007). The alternative hypothesis is that DTMS can induce disruption of circuitries mediating negative emotions that might contribute to depression. Repeated brain stimulation can induce long-lasting neuroadaptations in these circuitries (Levy et al., 2007; Zangen 2009; Gersner et al., 2010) and thereby affect behavioral outcomes. According to these hypotheses, we produced individual scripts of either positive or negative emotions based on a comprehensive interview with the patient during the screening session and instructed one group of patients to concentrate in scripts describing the positive emotions during the PFC stimulation sessions, while the other group was instructed to concentrate in scripts describing the negative emotions during the PFC stimulation sessions. It is important to note that while high frequency magnetic stimulation used in this study is considered excitatory, due to brain feedback mechanisms and the disruptive nature of brain stimulation, even high frequency stimulation can eventually result in 'inhibitory' effects. The results show that while neither the positive, nor the negative directives induced a significant beneficial effect on the clinical outcome (relative to the no cognitive group), the negative directives caused a significant reduction in the antidepressant outcome. In this group, the improvement in depression rating scales was significantly smaller. To the best of our knowledge, this is the first study that looked at the possible interactions between cognitive processes and magnetic brain stimulation in depression treatment.

Our computerized cognitive assessments show that unlike electroconvulsive therapy, repeated DTMS does not induce cognitive impairments. Moreover, in several cognitive tasks we even found significant improvements. Interestingly, memory significantly improved in patients who did not achieved remission. This finding indicates on a beneficial effect of DTMS over the PFC that is unrelated to an antidepressant effect.

Noteworthy is the fact that responders and remitters were stimulated with higher absolute intensities. Since in a former study (Levkovitz et al., 2009) stimulation at 110% of motor threshold was virtually ineffective, one can assume that the brain region that would form the optimal substrate for antidepressive effect resides in deeper cortical layers. This finding also raises some questions regarding the use of the motor threshold to determine the PFC stimulation intensity for antidepressant treatments with TMS.

A major drawback in this study, despite ethical debates, is the absence of a sham control group. However, placebo effect in treatment resistant depressive patients was found to be low and transient. In a large multicenter TMS study on a similar population, placebo effect was found to be as low as 8.2% (O'Reardon et al., 2007).

In conclusion, this study shows DTMS to be an effective therapeutic augmentation modality in resistant depressive patients. Furthermore, while cognitive–emotional directives failed to further enhance the antidepressant effect, the present study provides evidence for a critical effect of such directives, as negative cognitive–emotional directives disrupted the antidepressant effect of DTMS applied over the PFC.

Role of funding source

Funding for this study was provided by Brainsway, Inc, a company that is interested in the development of deep TMS coils.

Conflict of interest

Dr. Isserles receives financial support from Brainsway, Inc. which develops the H-coils.

Prof. Lerer has no conflicts to report in relation to this project.

Prof. Dannon and Dr. Rosenberg received an unrestricted educational grant for deep TMS research from Brainsway, Inc.

Prof. Kotler has no conflicts to report in relation to this project.

Frederic Deutsch is a consultant to Brainsway, Inc. but has no financial interest in the company.

Prof. Levkovitz and Dr. Zangen are consultants for and have financial interests in Brainsway, Inc.

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