Brain Stimulation (2011) 4, 266–74

ELSEVIER

BRAIN
STIMULATION

www.brainstimjrnl.com

Differential effects of deep TMS of the prefrontal cortex on apathy and depression

Yechiel Levkovitz,[a] Aharon Sheer,[b] Eiran V. Harel,[a] Leor N. Katz,[b] Dana Most,[b] Abraham Zangen,[b] Moshe Isserles[c]

[a]*Cognitive and Emotional Laboratory, Shalvata Mental Health Care Center, Hod-Hasharon, Israel*
[b]*Weizmann Institute of Science, Neurobiology Department, Rehovot 76100, Israel*
[c]*Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel*

Background
Apathy is one hallmark of major depression (MDD). It is distinguished by lack of emotion, whereas other aspects of depression involve considerable emotional distress. Investigating both apathy and depression may increase the degree of treatment efficacy for both ailments together and apart.

Objective
Evaluate the differential effects of deep transcranial magnetic stimulation (DTMS) over the prefrontal cortex (PFC) on apathy and other aspects of depression in patients suffering from a depressive episode.

Methods
Fifty-four treatment-resistant MDD patients were evaluated with the Hamilton Rating Scale for Depression (HRSD), and then treated with DTMS. Apathy-related items from HRSD (ApHRSD) were compared with the remaining items from HRSD (DepHRSD). Antidepressant medications were withdrawn and active DTMS treatment was administered at 20 Hz, 5 days a week for 4 weeks. Changes in HRSD were recorded. Primary efficacy time point was 1 week after the end of active treatment.

Results
At screening, ApHRSD distribution was unimodal (moderate apathy), with low correlation ($r = 0.17$) between ApHRSD and DepHRSD. After treatment, a third had remitted apathy, and the correlation between ApHRSD and DepHRSD had dramatically increased ($r = 0.83$). Severe ApHRSD (≥ 7) at screening correlated with nonremission for both ApHRSD ($R^2 = 0.1993$, $P = .0012$) and DepHRSD ($R^2 = 0.0860$, $P = .0334$).

This study was supported by the Rosenzweig-Coopersmith Fund and Brainsway Inc.

Drs. Levkovitz and Zangen are consultants for and have financial interests in Brainsway Inc., which has commercial interests in the development of deep TMS coils. Dr. Isserles receives financial support from Brainsway Inc.

Yechiel Levkovitz and Aharon Sheer contributed equally to this work.

Correspondence: Dr. Moshe Isserles, Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
E-mail address: moshayi@yahoo.com

Submitted May 31, 2010; revised December 21, 2010. Accepted for publication December 21, 2010.

1935-861X/$ - see front matter
doi:10.1016/j.brs.2010.12.004

Conclusions
DTMS over the PFC improved both apathy and depression similarly. However, DTMS did not lead to MDD remission if ApHRSD at screening was $\geq$ 7 of 12. Further investigation using a larger sample will determine whether screening apathy at baseline could be used to predict efficacy of DTMS in MDD patients.

Keywords MDD; treatment-resistant; DTMS; H-coil; ApHRSD; DSM-V

Apathy is not depression

DSM-IV and the Hamilton rating scale for depression (HRSD) treat apathy as one aspect of a depressive episode.[1] However, apathy has unique characteristics that can partly overlap with those of depression, but should be analyzed as a separate condition. Apathy involves lack of emotion: loss of interest, lack of motivation, reduced spontaneity, less affection, reduced enthusiasm, and not caring about doing new things.[2] In contrast, depression can involve considerable emotional distress: tearfulness, sadness, anxiety, agitation, insomnia, anorexia, feelings of worthlessness and hopelessness, recurrent thoughts of death.[2]

To compare apathy with depression, Marin et al.[3] evaluated patients with Alzheimer's disease (AD), stroke, and major depression, and developed an Apathy Evaluation Scale (AES). AES uses 18 questions, with a total score ranging from 18 to 72 points. Marin compared depression with apathy by using HRSD for depression compared with AES for apathy alone.[4] Despite some correlation between the scores, Marin found apathy and depression to be independent concepts. For example, apathy was typical of AD patients, either without (43%) or with (37%) depression. Depression was found in 56% of Parkinsonian (PD) patients, but only half of these depressed PD patients showed apathy.

MDD patients have elevated levels of apathy compared with healthy adults.[3] For caregivers of patients, apathy may be a more distressing symptom than depression, because the patient does not give feedback to the caregiver; often, apathy was the most commonly complained of behavior.[5]

Apathy appears to be associated with poor outcome in antidepressant treatment. In one MDD study, apathy at baseline correlated inversely with depression outcome with an $r = -0.46$ ($P = .001$). In that study, apathy was measured using the Scale for Assessment of Negative Symptoms in 34 patients with endogenous depression who were treated according to clinical practice, mainly with antidepressants for 1 year.[6] Similarly, in a study of late life MDD, 16 elderly nonpsychotic outpatients without dementia were evaluated for 6 years; all were treated according to clinical practice, mainly with antidepressants. Unfortunately, apathy was only measured at the end of the 6 years, but not at baseline. Nevertheless, high apathy at study end (measured using AES) was associated with poor antidepressant treatment outcome.[7]

Apathy subset of HRSD

By looking at the HRSD items having the strongest correlations with the AES total score, Marin et al.[4] chose an apathy subset of HRSD, here denoted ApHRSD. ApHRSD uses four HRSD questions: "loss of interest" [Work and Activities], "psychomotor retardation" [Retardation: Psychomotor], "loss of energy" [Somatic Symptoms General], and "loss of insight" [Insight]. Potential ApHRSD scores range from 0 to 12 and have content validity as a measure of apathy.[8] The convergent validity of ApHRSD was indicated by a moderately high correlation between AES and the ApHRSD ($r = 0.70$, $P < .001$, n = 107).[4] Convergence between AES and ApHRSD was also demonstrated by Lee et al.[9] The correlation coefficients were 0.77 ($P < .001$) and 0.67 ($P < .001$) for the two clinicians who separately assessed the subjects (n = 92). When the analysis was examined with the HRSD excluding the apathy related items, no significant correlation between AES and HRSD scores was found in any of the groups assessed (normal controls, currently depressed, and remitters).[9]

Because the protocol of the current study did not measure apathy directly, ApHRSD was used as a proxy measure.

Some studies have used ApHRSD to study apathy in MDD in older adults. For example, Feil et al.[10] used ApHRSD to examine older adults with MDD, but without dementia, age 50-85 (mean 62). Mean ApHRSD was 4.5, and apathy was not associated with age, sex, IQ, education, or medical illness burden.[10]

The neurobiology of apathy

One common measure of apathy is the Neuropsychiatric Inventory (NPI), which assesses neuropsychiatric symptoms using 12 independent domains, two of which are dysphoria/depression, and apathy/indifference.[11] The NPI score for apathy can range from 0 (no apathy present) to 12 (severe apathy). In three studies using NPI, (1) apathy was assessed in both nondemented and AD patients and was associated with anterior cingulate cortex (ACC) hypofunction (n = 41)[12]; (2) high apathy in AD was associated with gray matter density loss in the ACC, orbitofrontal cortex, and regions of the dorsolateral prefrontal cortex

(PFC) bilaterally, in the head of the left caudate nucleus and in the putamen bilaterally (n = 31)[13]; and (3) apathy in AD (n = 23) was associated with hypoperfusion of regional blood flow in the left ACC and right orbitofrontal cortex, compared with both nonapathetic AD patients (n = 28), and matched healthy controls (n = 23).[14]

Using AES, the severity of apathy in both geriatric depressives and nondepressed controls was associated with decreased gray matter volume in the right ACC (n = 43).[15] Using the Scale for the Assessment of Negative Symptoms in AD, apathy was associated with reduced metabolic activity in the bilateral ACC and medial orbitofrontal cortex (n = 41).[11]

The five studies cited previously all found hypofunction of the ACC in apathy. Similarly, in studies of depression, dysfunction of the ACC is reported as well.[16-18]

Deep transcranial magnetic stimulation

Deep transcranial magnetic stimulation (DTMS) is a unique form of TMS using special coils to allow direct stimulation of deeper cortical layers. In the current study, the H-coil was used to induce an effective field at a depth of about 3 cm below the skull.[19] This coil is designed to stimulate deep regions of the PFC and their connections to subcortical areas such as the nucleus accumbens and the ventral tegmentum, which are associated with reward and motivational functions.[19,20] The treatment was well tolerated and there were no neuropsychologic or physical adverse events, aside from minor, transient headaches in some patients.[21]

The current study is a secondary study of data from Levkovitz et al.[22] where the antidepressant effects of three different DTMS H-coils were evaluated. All coils were activated at 20 Hz over the PFC, but differed in their field distribution. Each coil stimulated deep prefrontal brain regions, the H1-coil preferentially in the left hemisphere, the H2-coil bilaterally (without preference for either hemisphere), the H1L-coil in the left hemisphere only. Common to all three coils was stimulation of the left dorsolateral PFC (DLPFC) in an excitatory fashion (high frequency), the same area that was stimulated in other successful standard TMS treatments of major depression.[23,24] (The coils and their induced fields are described in the Supplementary Material). In the current study, changes in ApHRSD and DepHRSD were analyzed.

Materials and methods

Subjects

Subjects were 62 nonpsychotic treatment-resistant unipolar depressed patients, age 18-65,[22] who met strict inclusion and exclusion criteria (detailed in the Supplementary Material), who completed medication washout and started treatment. Demographic and disorder-related measures were similar in all treatment groups, as was the degree of treatment resistance in the current episode of depression. Initial screening used a medical interview and a safety screening questionnaire for DTMS. Candidates fulfilling both inclusion and exclusion criteria were given a description of the study. They signed informed consents according to the local and national Institutional Review Board (IRB) committee guidelines.

Patients were randomly assigned to the following DTMS treatment groups: H1-coil at 120% motor threshold (MT) (n = 23), H2-coil at 120% MT (n = 21), H1L-coil at 120% MT (n = 10), and HIL-coil at 110% MT (n = 8). Stimulation frequency was 20 Hz and each session consisted of 42 trains of 2 seconds each. Treatment with the H1L-coil at 110% MT had no significant effect on either apathy or depression and none of the patients in this group reached remission or response. This was in sharp contrast to the three coils at 120% MT, which were all similarly effective.[22] The four treatment groups did not differ with regard to demographic variables. Because H1L at 110% MT was found to be an ineffective treatment, and in this study the main purpose was to evaluate differential DTMS effects on apathy compared with depression, we decided to remove this treatment group from the analysis.

Physical and psychiatric assessments were conducted weekly and a comprehensive computerized cognitive battery was administered before and after the treatment phase to assure safety. The main outcome measure was the 24-question version of HRSD ($HRSD_{24}$). Scores were recorded at screening, and each week during treatment. Follow-up testing was done after 1 week, and after 3 months.

A final score ≤ 10 on $HRSD_{24}$ was considered remission of depression. We chose remission as the primary outcome, rather than a 50% reduction in HRSD scores, because remission significantly improves long-term outcome of patients, including lower risk of relapse, and improved functioning.[25,26]

For the purpose of looking at ApHRSD and DepHRSD, the current study defined remission of these two variables as follows: Remission of ApHRSD required ApHRSD ≤ 2. Remission of DepHRSD required DepHRSD ≤ 8. Logic: At screening, mean $HRSD_{24}$ was 32.4 ($\pm$ 5.6). The required remission value for $HRSD_{24}$ of 10 is about a third of that (32/10 = 3.2). At screening, mean DepHRSD was 26.3 $\pm$ 5.24; a remission value of 8 is about a third of that (26/8 = 3.25). At screening, mean ApHRSD was 6.1 $\pm$ 1.23; a remission of value 2 is about a third of that.

Materials

DTMS coils and procedure

All three H-coils are extracorporeal devices positioned on the patient's scalp. The frame of the inner rim of each coil is flexible to fit the variability in human skull shape. At each treatment, the optimal spot on the scalp for stimulation of

the right abductor pollicis brevis muscle was located, and the resting MT (rMT) was established. In many previous studies evaluating the antidepressant effects of rTMS, coils were placed 5 cm anterior to the hand motor cortex. However, in this study, the coil was placed 5.5 cm anteriorly, because the 5 cm method was shown to often result in placement over the premotor cortex rather than over the prefrontal cortex.[27] All three coils were localized in the same way.

Study overview

The study was a randomized, prospective, open feasibility study conducted at the Shalvata Mental-Health Care Center (affiliated with Tel-Aviv University, Israel). Active enrollment extended from April 2006 through May 2008 with candidates recruited through newspaper advertisements. The study was registered (clinicaltrials.gov, NCT00445237), approved by the Institutional and National Review Boards (IRB) committees, and consisted of three phases: the Lead-in Phase, Acute Treatment, and Follow-up Assessments.

Screening procedure

Patients were tested with HRSD to determine suitability for this study. Consenting candidates signed an informed consent and were randomly assigned to DTMS treatment with one of the H-coil designs, as described previously.

Lead-in phase (2-weeks): Antidepressants or other psychotropic medications (eg, mood stabilizers), if used, were tapered down (medication washout). During the treatment phase patients were allowed only limited use of either hypnotics or anxiolytics for treatment-emergent insomnia or anxiety, respectively. Up to 14 daily doses (lorazepam 2 mg/d equivalent) were permitted.

Acute DTMS treatment phase (4 weeks): Daily DTMS sessions were scheduled in a 5-day sequence each week. A total of 20 sessions were conducted: visit 1 (baseline) through visit 20. Fifty-four MDD patients were actively treated with DTMS, using 20 Hz at 120% MT. All DTMS treatments and psychiatric evaluations were conducted by a physician blinded to the patients' DTMS coil treatment group. HRSD was administered at visit 1 (before first DTMS treatment), and after treatments at visit 4, visit 10, visit 15, and visit 20 (the last DTMS treatment).

Follow-up assessments: The primary efficacy time point was visit 21, 1 week after the last DTMS treatment session. The primary outcome measure for MDD was $HRSD_{24}$. This efficacy time point was chosen to reduce the acute and transient effects of the treatment. This meeting also assessed which patients were to be titrated onto antidepressant medication. An additional follow-up meeting was held 3 months after treatment termination for further clinical evaluations (visit 22).

Data analysis

Screening evaluations were performed on all patients. In this study, efficacy analyzes were performed on those patients with a screening measurement and at least 5 weeks of assessment (ie, participated in visits 1 through 21) according to the study protocol (n = 43). No imputations were made as to measurements missing if patients dropped out before visit 21. However, a very few missing individual HRSD question scores in a longitudinal series were estimated by taking the mean of the score for the previous and following visit, and rounding up.

Because no significant differential effect on depression was found between the three coils, and because all coils stimulated the left DLPFC, all results were combined into one database.

Continuous variables are summarized by a mean and standard deviation and compared with a *t* test or an analysis of variance model (ANOVA). For categorical subgroups a Pearson χ^2 test was used. Statistical tests were two sided and tested at a 5% level of significance. All statistics were performed with the package JMP 8.0.1 (SAS product).

Results

The objective was to evaluate the differential effects of DTMS over the PFC of MDD patients, comparing apathy with depression. ApHRSD was used as a measure of apathy and DepHRSD as a measure of depression.

ApHRSD = the total score on the Apathy Subscale of HRSD (ApHRSD terminology borrowed from reference 8).

DepHRSD = the total score on $HRSD_{24}$ minus the score for ApHRSD (our terminology).

Figure 1 and Figure 2 show striking changes in ApHRSD and DepHRSD, respectively, over time. Both sets of histograms exhibit a reduction of scores, from screening, through visit 10 (after 2 weeks of treatment), to visit 21 (1 week after termination of DTMS treatment). At screening, scores were unimodal. By visit 10 scores were bimodal.

Screening characteristics: n = 54

Screening ApHRSD did not correlate with screening DepHRSD ($r = 0.17$, not significant). The lack of correlation shows that, at screening, ApHRSD (apathy) and DepHRSD (depression) were independent.

ApHRSD at screening was 6.1 ± 1.23 (mean ± standard deviation [SD]). All patients had apathy, between moderate (ApHRSD of 4-6) to severe (7 or 8) (Figure 1). ApHRSD at screening was not correlated with any demographic measures (age, education in years, gender, length of current depressive episode in months). This was similar to results of Feil et al.[10]

DepHRSD at screening was 26.1 ± 5.45; 49 of 54 patients had severe DepHRSD (≥ 20) (Figure 2). DepHRSD at

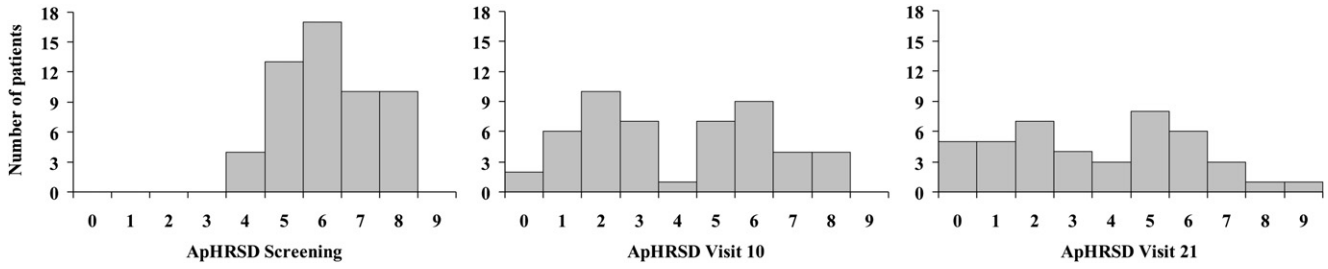

Figure 1 Longitudinal histograms of ApHRSD, for screening, visit 10 (after 2 weeks of treatment) and visit 21 (1 week after last DTMS treatment). HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD.

screening was correlated with one demographic measure: length of current depressive episode (months) ($r = -0.41$, $P = .0050$*).

Baseline characteristics

Visit 1 was considered baseline. Cessation of medication did not seem to have affected either apathy or depression. Mean ApHRSD (± SD) at visit 1 was 6.1 ± 1.14. Mean DepHRSD at visit 1 was 26.2 ± 5.5. Baseline ApHRSD did not correlate with baseline DepHRSD ($r = 0.17$, not significant).

Visit 21, 1 week after last DTMS treatment

This was the primary efficacy time point (ApHRSD [Figure 1] and DepHRSD scores [Figure 2]). ApHRSD: 3.7 ± 2.45; DepHRSD: 13.1 ± 8.3; n = 43 (after dropouts). Only five patients still had severe ApHRSD (≥ 7); those five had a mean DepHRSD of 25 ± 5.43. The remaining 38 patients had moderate ApHRSD (< 7); their mean DepHRSD (± SD) was 11.5 ± 7.33. DTMS treatment produced a strong correlation between ApHRSD and DepHRSD at visit 21 ($r = 0.83$, $P < .0001$*, $R^2 = 0.69$). This is in contrast to the screening visit, where there was no correlation (Figure 3).

Differential effects of coils on Apathy

In the main study, it was found that the three coils at 120% MT were all similarly effective in improving depression by the primary efficacy time point.[22] The current study found a similar result with respect to apathy, as follows: At screening, the differences between the ApHRSD means for the three coils were not significant (F ratio = 0.53, $P = .5928$). For those treated with the H1 coil, ApHRSD dropped from 6.3 ± 1.2 at screening to 3.2 ± 2.3 at visit 21; for the H1L coil, from 5.9 ± 1.1 to 3.3 ± 3.1; for the H2 coil, from 6.1 ± 1.3 to 4.4 ± 2.2. Although this seems to show that the H2 coil was less effective, the differences were not significant (F ratio = 1.86, $P = .1693$).

Severe ApHRSD at screening was correlated with both ApHRSD and DepHRSD nonremission at visit 21

We attempted to identify the factors that contributed to treatment success. Of those who did not drop out: 17 of 43 (40%) had remitted apathy (ApHRSD ≤ 2); 15 of 43 (35%) had depression remission (DepHRSD ≤ 8) (Table 1). Severe ApHRSD (≥ 7) at screening correlated with ApHRSD nonremission at visit 21 ($R^2 = 0.1993$, $P = .0012$*) (Pearson χ^2 test); only 2 of 18 (11%) achieved ApHRSD remission in this group. In sharp contrast, 15 of 25 (60%) of patients with moderate ApHRSD (< 7) at screening achieved ApHRSD remission at visit 21.

ApHRSD at screening was also correlated with DepHRSD remission after DTMS treatment, although less significantly ($R^2 = 0.0860$, $P = .0334$*). Of subjects with ApHRSD ≥ 7 at screening, only 3 of 18 (16.7%) achieved

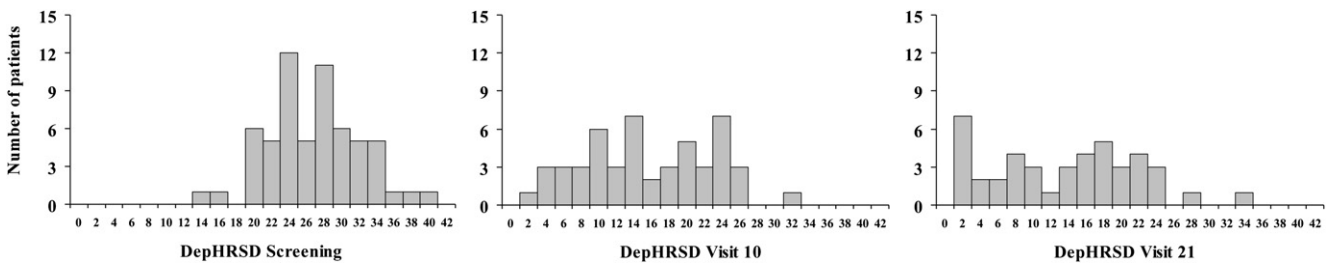

Figure 2 Longitudinal histograms of DepHRSD, for screening, visit 10 (after 2 weeks of treatment) and visit 21 (1 week after last DTMS treatment). HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD; DepHRSD, depression subscale of HRSD (total HRSD − ApHRSD).

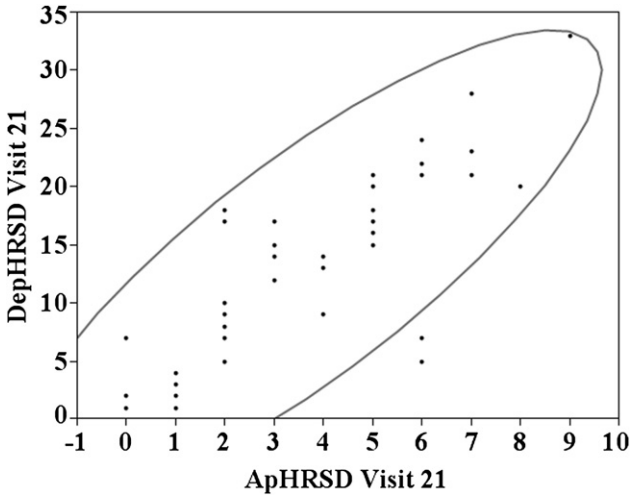

Figure 3 Correlation between ApHRSD visit 21 and DepHRSD visit 21: 1 week after LAST DTMS treatment: DTMS treatment produced a strong correlation between ApHRSD and DepHRSD at the 1-week follow-up, which was not present at screening. This was the primary efficacy time point. Bivariate Fit of DepHRSD visit 21 by ApHRSD visit 21: correlation: $r = 0.83$, $P < .0001$*, $R^2 = 0.69$. n = 43. HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD; DepHRSD, depression subscale of HRSD (total HRSD − ApHRSD).

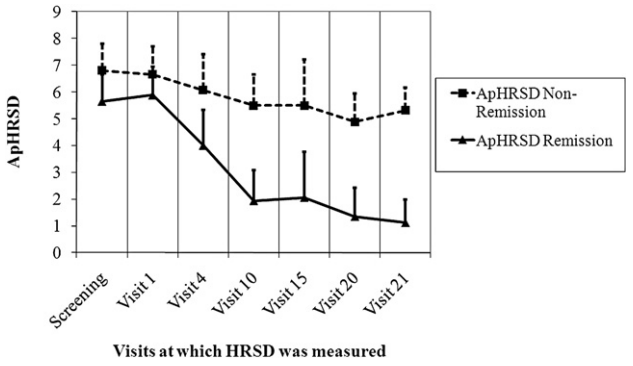

Figure 4 Changes in ApHRSD over time depending on remission of ApHRSD at visit 21. Data are presented as means ± SD. The ApHRSD remission group (ApHRSD ≤ 2) improved steadily until reaching remission; the nonremission group responded only slightly to DTMS treatment. Using a *t* test at each time point, the difference between ApHRSD in the remission group and ApHRSD in the nonremission group was significant, at screening (where $P = .0011$*) and at every time point from visit 4 through visit 21 ($P < .0001$*). Note the bimodal distribution. Visit 21 was the primary efficacy time point, 1 week after the last DTMS treatment session. ApHRSD ≤ 2 at visit 21 is considered remission of apathy (n = 17/43); nonremission at visit 21 is ApHRSD ≥ 3 (n = 26/43). HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD.

DepHRSD remission at visit 21. In contrast, of subjects with ApHRSD < 7 at screening, 12 of 25 (48%) achieved DepHRSD remission at visit 21.

Changes in ApHRSD and DepHRSD over time depending on remission of ApHRSD at visit 21

The ApHRSD remission group improved steadily until reaching remission; the ApHRSD nonremission group responded only slightly to DTMS treatment (Figure 4). Using a *t* test at each time point, the difference between ApHRSD in the remission group and ApHRSD in the nonremission group was significant, starting from screening ($P = .0011$*). At every time point starting from visit 4 and through visit 21, the difference was highly significant ($P < .0001$*).

The ApHRSD remission group improved steadily in their DepHRSD scores until reaching a low level of DepHRSD. The ApHRSD nonremission group responded much less to DTMS treatment as evident by little change in DepHRSD scores (Figure 5). Using a *t* test at each time point, the difference between DepHRSD in the remission group and DepHRSD in the nonremission group was significant at every time point except for visit 1. From visit 4 on through visit 21, the difference was highly significant ($P < .0001$*).

The remission relationship between ApHRSD and DepHRSD was reciprocal. Subjects who achieved remission of DepHRSD (≤ 8) at visit 21, had a mean ApHRSD of 1.53 (± 1.96), whereas those who did not achieve DepHRSD remission had a mean ApHRSD of 4.79 (± 1.87) (*t* ratio = 5.34, $P < .0001$*).

Table 1 Remission results (visit 21) (1-week follow-up)

Number of subjects at visit 21 (1-week follow-up)	Depression remission (DepHRSD ≤ 8)	No depression remission (DepHRSD > 8)	Totals apathy/ no apathy
Apathy (ApHRSD > 2)	2	24	26
Remitted apathy (ApHRSD ≤ 2)	13	4	17
Totals	15	28	43
Depression remission/no depression remission			

HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD; DepHRSD, depression subscale of HRSD (total HRSD − ApHRSD).
Of the patients that achieved DepHRSD remission, 13 of 15 were not apathetic (ApHRSD ≤ 2). Four patients had ApHRSD Remission but did NOT achieve DepHRSD remission (DepHRSD ≤ 8).

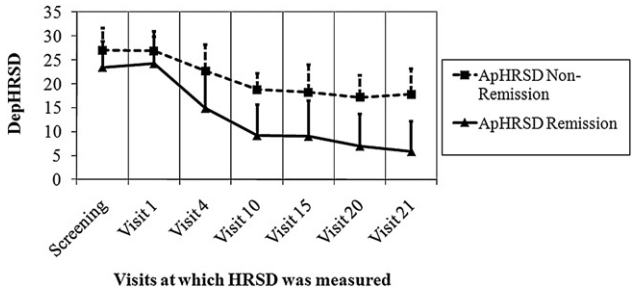

Figure 5 Changes in DepHRSD over time depending on remission of ApHRSD at visit 21. Data are presented as means ± SD. The ApHRSD remission group (ApHRSD ≤ 2) DepHRSD improved steadily; the ApHRSD nonremission group DepHRSD responded much less to DTMS treatment. Using a *t* test at each time point, the difference between DepHRSD in the remission group and DepHRSD in the nonremission group was significant, at screening (where $P = .0318$*) and at every time point from visit 4 on through visit 21 ($P < .0001$*). Visit 21 was the primary efficacy time point, 1 week after the last DTMS treatment session. DepHRSD ≤ 8 at visit 21 is considered remission of DepHRSD (n = 15/43); nonremission is DepHRSD ≥ 9 (n = 28/43). HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD; DepHRSD, depression subscale of HRSD (total HRSD − ApHRSD).

Visit 22, 3-month follow-up, 3 months after last DTMS treatment

The 30 of 43 subjects who came for this follow-up had ApHRSD of 1.8 ± 1.95 and DepHRSD of 8.8 ± 8.1. None had severe apathy. DepHRSD at visit 22 correlated almost as strongly with the ApHRSD at visit 22 ($r = 0.77$, $P < .0001$*) as the correlation at the 1-week follow-up (visit 21) ($r = 0.83$, $P < .0001$*), suggesting that subjects who came for this follow-up retained improvements shown at visit 21.

Remission results (visit 22) (3-month follow-up): Table 2

Half of the 30 subjects who came (15/30) had remitted DepHRSD (≤ 8). The ten of 15 DepHRSD remitted patients had ApHRSD = 0; the one apathetic patient had ApHRSD = 5. The six of 30 patients had ApHRSD ≤ 2 but did NOT achieve DepHRSD remission. There was no bimodal distribution of DepHRSD; only 5 of 30 had severe DepHRSD (≥ 20).

Discussion

Medication-free nonpsychotic treatment-resistant unipolar depressed patients were treated with DTMS over the PFC. The differential effects of DTMS on apathy and depression were examined in this study.

Apathy involves lack of emotion; depression involves considerable emotional distress. Both DSM-IV and the HRSD treat apathy as an aspect of depression. In this retrospective analysis, apathy was measured using a 4-question subset of HRSD (ApHRSD), whereas depression was measured using the balance of questions from $HRSD_{24}$ (DepHRSD). At the screening visit, there was no correlation between ApHRSD and DepHRSD, suggesting that apathy and depression were independent.

One week after the last DTMS treatment (the primary efficacy time point), ApHRSD and DepHRSD were highly correlated ($r = 0.83$). ApHRSD distribution was unimodal at screening (most patients having moderate apathy), but bimodal after treatment (a third had remitted apathy, two-thirds remaining with at least moderate apathy). DepHRSD was also bimodal after treatment (a third having remitted depression, two-thirds having at least moderate depression). Our study suggests that for those patients for whom apathy reached remission, depression also dropped dramatically, mostly reaching remission. For those patients for whom apathy did not reach remission, depression mostly also stayed high. The reverse was also true: patients who reached depression remission also reached low apathy, and patients who did not reach depression remission did not reach apathy remission. This suggests that DTMS of the PFC affected both apathy and depression similarly.

Of those who came to the 3-month follow-up, none had severe ApHRSD. Subjects who came for this follow-up retained improvements shown at the 1-week follow-up, in both ApHRSD and DepHRSD.

Two studies compared apathy and antidepressive effects after a course of antidepressant treatment (medications, and/or ECT). One found that high apathy at baseline predicted poor depression outcome after treatment, as in

Table 2 Remission results (visit 22) (3-month follow-up)

Number of subjects at visit 22 (3-month follow-up)	Depression remission (DepHRSD ≤ 8)	No depression remission (DepHRSD > 8)	Totals Apathy/ no apathy
Apathy (ApHRSD > 2)	1	9	10
No apathy (ApHRSD ≤ 2)	14	6	20
Totals	15	15	30
Depression remission/no depression remission			

HRSD, Hamilton Rating Scale for Depression; ApHRSD, apathy subscale of HRSD; DepHRSD, depression subscale of HRSD (total HRSD − ApHRSD).
At 3-month follow-up, patients with high ApHRSD or DepHRSD mostly did not come. All patients but one who achieved DepHRSD remission were not apathetic. The ten of 15 DepHRSD remitted patients had ApHRSD = 0 (no apathy).

the current study.[6] In the other, high apathy at study end was correlated with poor antidepressant treatment outcome.[7] Our results for DTMS are similar.

Several apathy studies of older populations found hypofunction of the ACC as typical of apathy. Dysfunction of the ACC has been found in depression, with some imaging studies showing the dorsal ACC as hypometabolic, but the rostral ACC as hypermetabolic.[16] Because most measures of depression (such as HRSD) include symptoms of apathy, perhaps the dorsal ACC is the hypometabolic part of ACC involved in apathy. Because, in this study, apathy and depression were not correlated at screening, it may suggest that different areas of the ACC are involved in each.

We found that ApHRSD $\geq$ 7 (severe apathy) at screening was significantly correlated with ApHRSD nonremission at visit 21, and to a lesser extent also significantly correlated with DepHRSD nonremission at visit 21. Perhaps stimulation is less likely to benefit patients with severe apathy at screening. This test needs replication, because, if true, it could be used to save time and expense by referring patients with severe apathy, who are not likely to achieve remission, to alternative treatments.

An important limitation of the original study was the lack of a sham control group. Although a sham treatment was not incorporated, the lower intensity group (H1L-110%) showed an important contrast despite its small sample size (n = 7). The choice of 110% MT was not meant to form a pseudo control group, but rather to obtain insight regarding the efficacy of direct effective stimulation depth of 1 cm (induced by H1L at 110% MT) as opposed to 3 cm (at 120%). Patients treated by the H1L-coil at 110% MT improved only mildly, none reaching remission or response.[22] This fact strongly suggests that improvements observed in the other three groups were not merely because of placebo effects. Still we cannot exclude the possibility that those that were less apathetic were more motivated to get well.

Another limitation of our study is that we could not use a separate apathy evaluation rating scale. Because we looked at apathy only after the treatment stage had been completed, the only way to measure longitudinal apathy was by using ApHRSD, which took advantage of the existing measurement of HRSD at each stage of the treatment. ApHRSD is limited to a range of values from 0 to 12, and only two studies have estimated its validity thus far.[4,9] A more specific test might have a larger variance, giving better psychometric characteristics. A recent study of apathy measures[28] recommends using either the AES, or the NPI apathy subscale, for general diseased populations. We think that ApHRSD has the important advantage that it is derived from the very commonly used HRSD, but future studies that wish to assess apathy should use the specific scales mentioned previously.

Future studies should select for subtypes of depression, as well as specific questions characterizing apathy. There may be a relation between ApHRSD and melancholic depression, because ApHRSD includes a question on psychomotor retardation, and melancholic depression always involves psychomotor dysfunction.[29] This subtype of depression may respond differently to treatment. Another subtype to consider is typical versus atypical depression, especially because hypersomnia, an atypical feature, is also characteristic of apathy.[30] By refining the diagnosis of patients' affective states and placing particular emphasis on apathy, tailored treatments may be used thus yielding significantly more favorable results, especially in the case of refractory patients. Moreover, dimensional assessments are currently being proposed for inclusion in DSM-V. In light of the above, we think that apathy is a distinct, important and functional dimension which is relevant to various psychiatric diagnoses. Its assessment should be considered as part of this proposed DSM-V novel approach.

Supplemental Data

Supplemental data associated with this article can be found, in the online version, at doi:10.1016/j.brs.2010.12.004

References

1. Hamilton M. Hamilton rating scale for depression (HAM-D). In: Handbook of psychiatric measures. Washington, DC: American Psychiatric Association; 2000. p. 526-529.
2. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998;10(3):314-319.
3. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 1991;38(2):143-162.
4. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. J Affect Disord 1993;28(2):117-124.
5. van Reekum R, Stuss DT, Ostrander L. Apathy: why care? J Neuropsychiatry Clin Neurosci 2005;17(1):7-19.
6. Chaturvedi SK, Sarmukaddam SB. Prediction of outcome in depression by negative symptoms. Acta Psychiatr Scand 1986;74(2):183-186.
7. Lavretsky H, Lesser IM, Wohl M, Miller BL, Mehringer CM. Clinical and neuroradiologic features associated with chronicity in late-life depression. Am J Geriatr Psychiatry 1999;7(4):309-316.
8. Marin RS, Butters MA, Mulsant BH, Pollock BG, Reynolds CF 3rd. Apathy and executive function in depressed elderly. J Geriatr Psychiatry Neurol 2003;16(2):112-116.
9. Lee SH, Wen MC, Chao CC, Chen YJ, Yen CF. Apathy in late-life depression among Taiwanese patients. Int Psychogeriatr/IPA 2008; 20(2):328-337.
10. Feil D, Razani J, Boone K, Lesser I. Apathy and cognitive performance in older adults with depression. Int J Geriatr Psychiatry 2003;18(6):479-485.
11. Marshall GA, Monserratt L, Harwood D, et al. Positron emission tomography metabolic correlates of apathy in Alzheimer disease. Arch Neurol 2007;64(7):1015-1020.
12. Migneco O, Benoit M, Koulibaly PM, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and nondemented patients. Neuroimage 2001;13(5):896-902.
13. Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain 2008;131(Pt 9):2455-2463.

14. Lanctot KL, Moosa S, Herrmann N, et al. A SPECT study of apathy in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24(1):65-72.
15. Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. Am J Geriatr Psychiatry 2007;15(5):386-394.
16. Alexopoulos GS, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Murphy CF. Anterior cingulate dysfunction in geriatric depression. Int J Geriatr Psychiatry 2008;23(4):347-355.
17. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex 2008;18(6): 1374-1383.
18. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 1997;8(4):1057-1061.
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(1):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(4):775-779.
21. Levkovitz Y, Roth Y, Harel EV, et al. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin Neurophysiol 2007;118(12):2730-2744.
22. Levkovitz Y, Harel EV, Roth Y, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. Brain Stimulation 2009;2: 188-200.
23. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010; 67(5):507-516.
24. 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(11):1208-1216.
25. Thase ME, Ninan PT. New goals in the treatment of depression: moving toward recovery. Psychopharmacol Bull 2002;36(Suppl. 2):24-35.
26. Taylor M, Fink M. Melancholia the diagnosis, pathophysiology, and treatment of depressive illness. Cambridge, UK: Cambridge University Press; 2006.
27. 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(1):58-61.
28. Clarke D, Ko J, Kuhl EA, et al. Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res 2010;70(1):73-97.
29. Parker G. Defining melancholia: the primacy of psychomotor disturbance. Acta Psychiatr Scand Suppl 2007;433:21-30.
30. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. Mol Psychiatry 2002;7(3):254-275.