A Controlled Study of Repetitive Transcranial Magnetic Stimulation in Medication-Resistant Major Depression

David H. Avery, Paul E. Holtzheimer III, Walid Fawaz, Joan Russo, John Neumaier, David L. Dunner, David R. Haynor, Keith H. Claypoole, Chandra Wajdik, and Peter Roy-Byrne

Background: *Repetitive transcranial magnetic stimulation (TMS) as a treatment for depression has shown statistically significant effects, but the clinical significance of these effects has been questioned.*

Methods: *Patients with medication-resistant depression were randomized to receive 15 sessions of active or sham repetitive TMS delivered to the left dorsolateral prefrontal cortex at 110% the estimated prefrontal cortex threshold. Each session consisted of 32 trains of 10 Hz repetitive TMS delivered in 5-second trains. The primary end point was treatment response defined as a ≥50% decrease in Hamilton Depression Rating Scale (HDRS) score at both 1 and 2 weeks following the final repetitive TMS treatment. Remission was defined as a HDRS score <8.*

Results: *The response rate for the TMS group was 30.6% (11/35), significantly ($p = .008$) greater than the 6.1% (2/33) rate in the sham group. The remission rate for the TMS group was 20% (7/35), significantly ($p = .033$) greater than the 3% (1/33) rate in the sham group. The HDRS scores showed a significantly ($p < .002$) greater decrease over time in the TMS group compared with the sham group.*

Conclusions: *Transcranial magnetic stimulation can produce statistically and clinically significant antidepressant effects in patients with medication-resistant major depression.*

Key Words: Repetitive transcranial magnetic stimulation, major depression, medication resistance, prefrontal cortex

Repetitive transcranial magnetic stimulation (TMS) is a noninvasive technique for stimulating the cerebral cortex and altering cortical and subcortical function (Avery 2001; Chouinard et al 2003; George and Belmaker 2000; Wassermann and Lisanby 2001). Meta-analyses of numerous sham-controlled studies have shown TMS to produce statistically significant antidepressant effects with few, generally mild side effects (Burt et al 2002; Holtzheimer et al 2001, 2003, 2004b; Kozel and George 2002; Martin et al 2003). However, these studies have also shown inconsistent and relatively modest clinical improvements in depressed patients, such that the clinical relevance of TMS has been questioned (Martin et al 2003; Sackeim 2000; Schlaepfer et al 2003).

Studies using more intensive TMS treatment parameters have been associated with better response rates (Gershon et al 2003); however, studies using more intensive parameters have typically had no sham control. In addition, sample size in most TMS studies has been small, and the degree of medication resistance has not been well defined. Higher levels of medication resistance are associated with poorer response to treatment, even with electroconvulsive therapy (ECT) (Prudic et al 1996). In a prospective study of usual standard of care treatment in a treatment-resistant population, only 13% responded during the 1-year follow-up period (Dunner and Russell 2003). To better define the clinical efficacy of TMS, we carried out a large, double-blind, sham-controlled investigation of TMS, using a more aggressive treatment protocol than that used in nearly all previous sham-controlled studies: greater intensity of stimulation, greater number of sessions, greater number of pulses per session, and greater number of total pulses. We applied 10 Hz TMS to the left dorsolateral prefrontal cortex (DLPFC) in patients with major depression who had failed to respond to at least two antidepressant medications and whose level of medication resistance was well characterized. Treatment response was rigorously defined, and treatment responders were placed on maintenance pharmacotherapy and followed for 6 months. We hypothesized that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation.

Methods and Materials

Patients

The study procedures were approved by the Human Subjects Review Committee of the University of Washington. In addition, an Investigational Device Exemption was received from the U.S. Food and Drug Administration. All subjects gave written informed consent to participate in the study. The subjects were judged to have capacity to give informed consent by a board-certified psychiatrist. We carefully assessed the subjects for suicide risk and excluded subjects with active suicidal ideation or a recent suicide attempt. Because some patients discontinued antidepressant medication to participate in the study, patients were carefully followed to make sure that their depression was not significantly worsening or that active suicidal thoughts were not emerging during the study. Because of concerns about relapse into depression following response to the treatment, responders who were not taking antidepressants were offered antidepressant medication as a continuation therapy 2 weeks after the last transcranial magnetic treatment session.

Subjects were recruited from January 2001 to February 2004 via physician referrals and local advertisements and enrolled during a screening visit by a board-certified psychiatrist (D.H.A). Subjects had to be 21 to 65 years old and meet DSM-IV criteria for current major depressive disorder (MDD); diagnoses were confirmed with the Structured Clinical Interview for DSM-IV, Research Version (SCID-I) (First et al 1996). The subjects must have

From the Department of Psychiatry and Behavioral Sciences (DHA, PEH, WF, JR, JN, CW, PR-B); Department of Psychiatry (DLD); Center for Anxiety and Depression, and Department of Radiology (DRH), University of Washington School of Medicine, Harborview Medical Center, Seattle, Washington; Department of Psychiatry and Behavioral Sciences (PEH), Wesley Woods Health Center, Emory University, Atlanta, Georgia; Tanta University (WF), Tanta, Egypt; and Department of Psychology (KHC), University of Hawaii, Honolulu, Hawaii.

Address reprint requests to David H. Avery, M.D., Harborview Medical Center, Box 359896, 325 Ninth Ave, Seattle, WA 98104-2499; E-mail: averydh@u.washington.edu.

Received March 11, 2005; revised June 9, 2005; accepted June 21, 2005.

0006-3223/05/$32.00
doi:10.1016/j.biopsych.2005.07.003

failed to respond to, or been unable to tolerate, at least two previous adequate antidepressant trials. Failed treatment trials could be for the current or any prior depressive episode; medication resistance for the current episode was not required. Subjects had to have a 17-item Hamilton Depression Rating Scale (HDRS) score of 17 or more at both screening and treatment day 1 and a decrease of no more than 20% between these two visits (an interval of at least 2 weeks).

Exclusion criteria included previous TMS exposure, bipolar disorder, previous failure of nine or more bitemporal ECT treatments, a current major depressive episode longer than 5 years, a history of substance abuse or dependence within the past 2 years, antisocial or borderline personality disorder, active suicidal ideation with plan and/or intent, current symptoms of psychosis, a history of seizure disorder, a history of closed head injury with loss of consciousness, prior brain surgery, or any other major psychiatric or medical comorbidity.

Subjects were encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; subjects who had significant worsening of depression in the past when they discontinued their medication were allowed to continue these at stable doses. Those stopping medications had to be medication-free for at least 2 weeks before the first TMS session (6 weeks for those taking fluoxetine). Proconvulsant medications (e.g., bupropion, tricyclic antidepressants, neuroleptics) had to be tapered and discontinued at least 2 weeks before entering the study. Benzodiazepines had to be reduced to a dose equivalent to 1 mg clonazepam per day. If a subject continued antidepressant medications and/or benzodiazepines, the subject must have been on the medication for at least 2 months and on a stable dose for at least 4 weeks. Doses were to be kept constant during the 2-week baseline period, the 3-week treatment period, and the 2-week posttreatment assessment period. Subjects in psychotherapy for at least 12 weeks were allowed to continue during the study but the type and frequency of therapy could not change during the study period. Patients were categorized according to the Thase-Rush Stages of Antidepressant Resistance (Thase and Rush 1997) based on the Antidepressant Treatment History Form (ATHF) (Sackeim 2001) with a score of at least 3, defining adequacy for a given medication. A physical examination, screening laboratory tests, and magnetic resonance imaging (MRI) were performed to rule out comorbid medical illness. The flow of subjects is summarized in Figure 1. Among the sham subjects, three did not complete the protocol: one stopped because of lack of response, one stopped for unknown reasons, and one changed her medication and had a protocol violation. Data subsequent to the violation were not included in the efficacy analyses. Among the TMS patients, two did not complete the protocol, both because of the inconvenience of the study.

Sample size was determined by power analysis using previously published effect size estimates (Klein et al 1999; Pascual-Leone et al 1996) (differences in rates of response between the sham and TMS groups), 90% power, and a one-tailed test of significance at $p < .05$. The baseline characteristics of the 68 evaluable subjects are summarized in Table 1. There were no significant differences between subjects randomized to receive TMS ($n = 35$) and those randomized to receive sham ($n = 33$).

Study Design

At the baseline/first treatment session, subjects were randomized to receive active or sham TMS to the left DLPFC. Randomization was performed with a computer program using urn randomization (Stout et al 1994; Wei 1978). Nine urns were used: 1) Thase-Rush stage of medication resistance; 2) baseline HDRS score; 3) current depressive episode duration; 4) melancholic features; 5) gender; 6) age; 7) presence of treated hypothyroidism; 8) currently taking a benzodiazepine; and 9) currently taking an antidepressant.

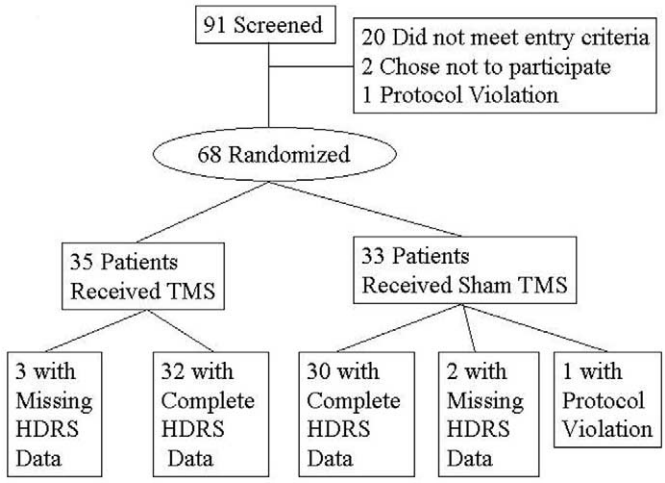

Figure 1. Study design. TMS, transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale-17 item.

The 15 TMS treatment sessions (visits 1–15) were given only on weekdays and had to be completed within a 4-week period. Subjects were evaluated 1 week after the last TMS session (visit 16). If the HDRS had decreased by at least 50% at visit 16, the subject was reevaluated 2 weeks after the last TMS session (visit 17). Subjects who met response criteria were followed with continuation pharmacotherapy every month for 6 months after the last TMS session. The antidepressant chosen was based on a preferential list of antidepressants: 1) venlafaxine XR; 2) bupropion SR; 3) nefazodone; 4) mirtazapine; and 5) phenelzine. Each medication was increased to the maximum allowable dose as tolerated. Relapse was defined as a HDRS of equal or greater than 15 (Frank et al 1991) for at least 2 weeks.

Subjects were blind to treatment allocation throughout the entire treatment protocol. Transcranial magnetic stimulation treaters (D.H.A., P.E.H., W.F., J.N.) interacted minimally with the subjects to guard against revealing treatment allocation. Subjects were asked to guess which treatment had been received ("active TMS," "sham TMS," "can't guess") at the beginning of visit 2 and after visit 15.

TMS Treatment

A Dantec Magpro Magnetic Stimulator (Medtronic, Inc, Minneapolis, Minnesota) with a 70-mm figure-eight coil was used. Transcranial magnetic stimulation was performed at Harborview Medical Center. At screening, investigators identified and marked the vertex, the scalp location for optimal stimulation of the right first dorsal interosseous (FDI) muscle and the point 5 cm anterior in a parasagittal line (treatment stimulation site) on a Lycra swim cap (Speedo USA, Los Angeles, California). This facilitated location of the motor cortex and the site of stimulation in subsequent sessions. Following this initial visit, subjects had magnetic resonance imaging with vitamin E capsules placed over the motor cortex and treatment stimulation sites.

In previous TMS studies, scalp-cortical distances (SCDs) were assumed to be identical at the prefrontal cortex and the motor

Table 1. Demographic and Baseline Clinical Characteristics of 68 Patients with Major Depression Treated with Either Transcranial Magnetic Stimulation (TMS) or Sham Stimulation

Characteristic	TMS Group (n=35)	Sham Group (n=33)
Age, Years	44.3 (10.3)	44.2 (9.7)
Sex: M/F (% Female)	14/21 (60%)	17/16 (52%)
Age of Onset	26.2 (12.3)	25.4 (11.7)
Baseline HDRS	23.5 (3.9)	23.5 (2.9)
Baseline BDI	28.1 (8.7)	28.4 (8.0)
Duration of Current Episode, Months	28.1 (16.4)	26.3 (16.9)
Chronic Depression: Yes/No (% Yes)	20/15 (57%)	20/13 (61%)
Melancholic: Yes/No (% Yes)	22/13 (63%)	20/13 (61%)
Concomitant Antidepressant: Yes/No (% Yes)	11/24 (31%)	9/24 (27%)
Concomitant Benzodiazepine: Yes/No (% Yes)	9/26 (26%)	8/25 (24%)
Stage of Antidepressant Resistance - Lifetime (Thase-Rush Criteria)[a]		
Stage 1	7 (20%)	5 (15%)
Stage 2	26 (74%)	26 (79%)
Stage 3	1 (3%)	2 (6%)
Stage 4	1 (3%)	0 (0%)
Adequate Antidepressant Trials - Current Episode (% Yes)	32 (92%)	31 (94%)
Adequate Antidepressant Trials - Lifetime (% Yes)	35/35 (100%)	33/33 (100%)
Number of Adequate Antidepressant Trials - Current Episode	1.46 (.78)	1.48 (.67)
Number of Adequate Antidepressant Trials - Lifetime	3.20 (2.44)	3.30 (1.72)
Intolerant To At Least One Antidepressant - Current Episode (% Yes)	19 (58%)	18 (52%)
Total number of medication trials - Lifetime	8.23 (4.09)	8.91 (3.64)
History of Positive ECT response	3 (9%)	4 (12%)
History of Nonresponse to <9 Bilateral ECTs	0 (0%)	1 (3%)

Data concerning age, age of onset, duration of current illness, baseline depression ratings, and number of medication trials are presented as means (SD). TMS, transcranial magentic stimulation, HDRS, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; ECT, electroconvulsive therapy.
[a]Thase and Rush (1997).

cortex. However, these distances often differ, leading to differences in amount of cortical stimulation at the same TMS intensity (Fabre et al 2004; Kozel et al 2000). To correct for these differences, the neuroradiologist (D.R.H.) measured SCD at the site of prefrontal stimulation and the motor cortex using visualization of vitamin E capsules on the MRI. The estimated prefrontal threshold (PT) was estimated based on the motor threshold (MT) and on the physics of magnetic stimulation (George and Belmaker 2000) and the known decrease in the magnetic field as the distance from the coil increases as expressed by the equation, $B(d) = 1.05\ e^{(-0.36d)}$, where d = the distance from the coil and B = magnetic field in tesla. From this equation, we derived and used the equation, $PT = MT \times e^{(+0.36d)}$, where d = frontal SCD - motor SCD in cm. Treatment stimulation intensity was 110% of the estimated PT.

At the beginning of each treatment session, resting motor threshold was determined by delivering single TMS pulses to the motor cortex for the right first dorsal interosseous muscle, with continuous electromyographic monitoring. Motor threshold was defined as the percent output of the stimulator that induced at least a 50-μV motor evoked potential in 5 of 10 single stimulations.

Repetitive TMS was delivered at a frequency of 10 Hz in 5-second trains at 110% of the estimated PT. Thirty-two trains were given in each session (1600 pulses per session) with a 25- to 30-second intertrain interval. Fifteen sessions (24,000 total pulses) were given within a 4-week period. For active TMS, the coil was placed flat against the scalp with the handle and short axis of the coil oriented in a parasagittal plane and the intersection of the figure-eight windings centered over the left DLPFC. Sham TMS was delivered in the same anatomical location with identical stimulation parameters but with the lateral edge of the coil rotated 90° away from the scalp. The sham subjects went through the same procedures as the TMS subjects up to the point of the coil rotation.

Clinical Ratings

Prior to the first TMS session (visit 1), raters administered the 17-item HDRS and subjects completed the Beck Depression Inventory (BDI). These measures were repeated after visits 5, 10, and 15, and 1 week after the last TMS session (visit 16). Subjects with a ≥50% decrease in HDRS score from baseline to visit 16 were reassessed 1 week later (visit 17). Response was defined as a ≥50% decrease in HDRS score from baseline to visit 16 that persisted at visit 17. Remission was defined as a HDRS < 8 at visit 16 that persisted at visit 17. Nonresponders to sham stimulation were offered 15 sessions of active TMS in an open fashion.

Raters were trained in the use of the HDRS by an experienced investigator (D.L.D.) and certified using the rater's assessments of videotapes of HDRS interviews and videotapes of the raters themselves conducting HDRS assessments. The raters achieved an agreement of ±5% with the score of the experienced investigator on several interviews. The raters, who were never the treaters, were blind to treatment allocation and did not ask the subjects about side effects. The subjects were told that if they had a guess concerning the treatment allocation, they should neither share that with the rater nor discuss the reason for the guess.

A neuropsychological battery using equivalent alternate test forms was administered at screening, at baseline, and after the last TMS session. Two test administrations before the first TMS session were used to minimize practice effects at the third administration after treatment. The second baseline test administration was compared with the posttreatment administration in the statistical analysis. The battery included the Rey Auditory

Verbal Learning Test (RAVLT), Digit Symbol Test and Digit Span (from the Wechsler Adult Intelligence Scale - Revised [WAIS-R]), Trail Making Test Parts A and B, Mini-Mental State Examination (MMSE), the Controlled Word Association Test (COWAT), and the color Stroop Test (Spreen and Strauss 1991). In addition, the Galveston Orientation and Amnesia Test (GOAT) (Levin et al 1979) was administered within 5 minutes after each TMS session.

The Systematic Assessment for Treatment Emergent Effects (SAFTEE) (Levine and Schooler 1983), a self-rating instrument, was given before the first session and after sessions 5, 10, and 15 and at visit 16. A symptom was considered treatment emergent if there was at least a one-point increase compared with the pretreatment level. In addition, scalp pain was assessed by the treaters for each TMS session using a four-point discomfort-pain scale: 0 = no discomfort, 1 = discomfort, 2 = slight pain, 3 = moderate pain, 4 = severe pain. At visit 2 and after visit 15, subjects were asked by the treaters to guess whether they had received real TMS or sham treatment; raters were not asked to guess the treatment assignment.

Statistical Analyses

All analyses were performed using SPSS for Windows 11.0.1 (SPSS Inc., Chicago, Illinois), except for random regression modeling, which was performed using the MIXREG computer program (Gibbons et al 1993). The level of statistical significance was set at $p \leq .05$. Two-tailed Fisher's exact tests and independent sample *t* tests were used to compare baseline characteristics between the active and sham TMS groups.

The primary outcome variable was response as defined above. Fisher's one-tailed exact tests were used to examine the unadjusted rates of response and remission in the treatment groups. For response/remission analyses, a last observation carried forward (LOCF) method was employed. To determine if group differences were significant after controlling for the stratification variables, logistic regressions were performed. Response and remission were the outcomes with covariates of gender, age, stage, current antidepressant use, melancholia, treated hypothyroidism, current benzodiazepine use, and duration of current episode entered into the model followed by group status. Transcranial magnetic stimulation was hypothesized to have higher response rates compared with the sham condition, and one-tailed tests were used throughout.

Random effects repeated-measures models were used with the intent-to-treat sample to determine whether patients in the active versus sham TMS groups manifested a different pattern of change in depression over time. These models were selected because they allow the use of correlated longitudinal data with missing observations. Missing data were assumed to be missing at random. This procedure uses maximum likelihood estimates to evaluate treatment group, time, and group by time effects. In addition, these models allow for the use of covariates. A significant group by time interaction indicates a difference in the patterns of change over time.

Models were developed separately for HDRS and BDI scores. The assessments used were visit 1 (baseline), visit 5, visit 10, visit 15, and visit 16. Due to the curvilinear form of depression scores over time, time-squared (quadratic term) was included in the models. We used the intercept as a random effect, while time and treatment group were fixed effects. A time-squared by group interaction term was tested but was not statistically significant, so it was not included in subsequent analyses. However, time-squared, due to its statistical significance, was retained in all models. Three models were tested for each dependent variable. The first model included eight covariates mentioned above and main effects of time, time-squared, treatment group, and the treatment group by time interaction. The second model was the same as the first but included only statistically significant covariates. The final model included the main effects of time, time-squared, treatment group, and the treatment group by time interaction only. Because the *p* values for the interaction were identical in all three models, we will present the model without any covariates. In the event of a significant group or group by time interaction, one-tailed *t* tests were performed at each visit to examine group differences.

Random effects repeated-measures analyses were also used to examine changes between pretreatment and posttreatment neuropsychological test results between the two groups. The intercept was assumed to be random, while time and group and their interaction were fixed effects. A significant time by group interaction would indicate that the groups had different patterns of change over time.

Chi-square analyses were used to compare the TMS and sham groups for the percentages who experienced at least slight pain during the sessions, the percentages of those who scored less than 100 in the GOAT assessment, the percentages of those who had at least a one-point increase in the SAFTEE items, and the percentages that guessed their treatment allocation. Bonferroni corrections were applied.

Results

Treatment Efficacy

The TMS group had a significantly greater response rate, 30.6% (11/35), compared with 6.1% (2/33) in the sham group (Fisher's $p = .008$, effect size = .69). The TMS group had a significantly greater remission rate, 20.0% (7/35), compared with 3.0% (1/33) in the sham group (Fisher's $p = .033$, effect size = .58) (see Figure 2).

Logistic regression analyses, adjusting for the stratification variables, resulted in similar findings: the TMS group had significantly greater odds of response (adjusted odds ratio = 21.08, 95% confidence interval [CI] = 2.07–214.16) and remission (adjusted odds ratio = 25.49, 95% CI = 1.09–595.75) than the sham group.

Random regression analyses for HDRS scores revealed a significant time by treatment group interaction ($z = 3.06$, $p = .002$, effect size = .64). The statistical significance of this interaction was not altered either in the presence of all potential covariates or with only the statistically significant covariates. This result was due to the differential decrease in depressive symptom severity over time: the active TMS group had a mean decrease of 7.8 (SD = 7.8) in comparison with the sham TMS group who averaged a 3.7 point decrease (SD = 6.3) from visit 1 to visit 16 (see Figure 3).

Random regression analyses for BDI scores revealed a significant time by treatment group interaction ($z = 2.94$, $p = .003$, effect size = .67). The statistical significance of this interaction was not altered either in the presence of all potential covariates or with only the statistically significant covariates. This result was due to the statistically significant differential decrease in symptom severity over time: the active TMS group had a mean decrease of 11.3 points (SD = 12.8) in comparison with the sham TMS group who averaged a 4.8 point decrease (SD = 8.5) from visit 1 to visit 16.

Among sham nonresponders who received open active TMS,

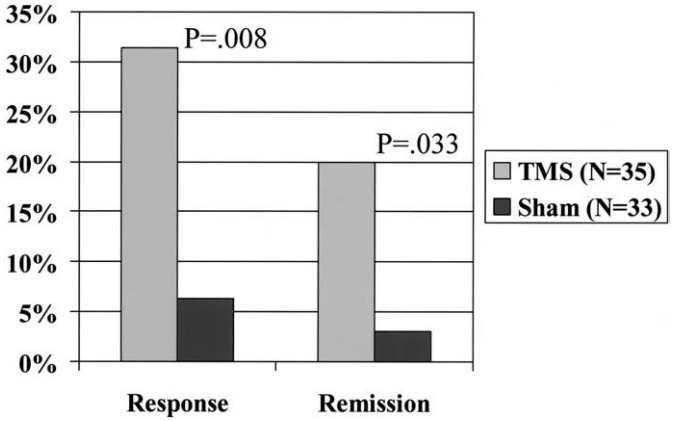

Figure 2. Response (50% or more decrease in the Hamilton Depression Rating Scale-17 item) and remission (Hamilton Depression Rating Scale-17 item less than 8) in TMS group and sham group. TMS, transcranial magnetic stimulation.

29% (8/28) had a 50% reduction in the HDRS at visit 15 and 14% (2/28) had a HDRS score of 7 or less at visit 15.

Follow-Up Data

The 11 responders to active TMS were treated with antidepressant medication (venlafaxine XR [5 patients], nefazodone [3 patients], bupropion [1 patient], phenelzine [1 patient], mirtazapine [1 patient]). One patient discontinued venlafaxine after 1 month because of side effects. Of the 11 responders to TMS, 5 (44%) did not relapse during the 6-month follow-up period; mean HDRS of these subjects at 6 months was 4.6 ± 2.7. One subject did not relapse during the first 3 months of follow-up but was lost to follow-up. Of the five other active TMS responders, one each relapsed at 1, 2, 3, 4, and 5 months. Of the two responders to sham treatment, one was started on fluoxetine and relapsed after 2 weeks; the other started on venlafaxine, was intolerant to it, and did not relapse after 3 months but was then lost to follow-up.

Cognitive Functioning

There were no statistically significant ($p > .05$) time by treatment group interactions for any of the neuropsychological test measures. This indicates that the pattern of change in cognitive functioning was similar for both the TMS and sham treatment groups. When the models were refit without the interaction term, there was no significant treatment group main effect ($p > .05$) evident for any of the neuropsychological tests, indicating the groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test performances for both groups.

No confusion was associated with the TMS treatments. The GOAT assessments were well within the normal range and ranged from 98 to 100. There were no significant ($p > .05$) differences between groups for any session.

Adverse Effects

The TMS treatments were well tolerated. No seizures were associated with active or sham TMS. No subject dropped out because of pain or discomfort of the TMS treatment. However, the TMS sessions were significantly more associated with pain at the site of stimulation compared with the sham sessions at each session (chi-square with Bonferroni correction, $p < .05$). At the first session in the sham group, none (0/33) experienced pain; in the TMS group, 41% (14/35) experienced at least slight pain. At the 15th session, 33% (11/33) of the TMS group experienced pain compared with 3% (1/30) in the sham group. The discomfort-pain scale ratings decreased in the TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (±1.02) at session 1 to 1.11 (±1.03) at session 15 ($t = 4.24$, $p < .001$).

The changes from baseline in the 128 individual SAFTEE scores were assessed. When the emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of the emerging symptoms.

One patient with a history of benign positional vertigo experienced vertigo and nausea both after the initial motor threshold determination and after each TMS session.

Maintenance of the Blind

The TMS group and the sham group did not differ significantly in their guesses about which treatment they received after either the first ($p > .05$) or last TMS session ($p > .05$). After the first session, 15% (5/34) of the TMS group guessed that they were receiving TMS compared with 15% (5/33) of the sham group. After the 15th session, among those who received TMS, 58% (19/33) of the TMS group guessed that they had received TMS compared with 43% (13/30) of the sham group.

After the first session, those who ultimately met response criteria at visits 16 and 17 made similar ($p > .05$) guesses as those who ultimately did not respond, but after the 15th session, the responders were significantly more likely than the nonresponders to guess that they had received TMS ($p > .05$). After the first session, 23% (3/13) of the responders thought that they had received TMS compared with 13% (7/54) of the nonresponders. After the 15th session, 85% (11/13) of the responders thought they had received TMS compared with 42% (21/50) of the nonresponders.

Discussion

In the largest sham-controlled study to date of high-frequency repetitive TMS as a treatment for medication-resistant depression, the response rates and remission rates were higher in the TMS group compared with the sham group. In addition, the HDRS and

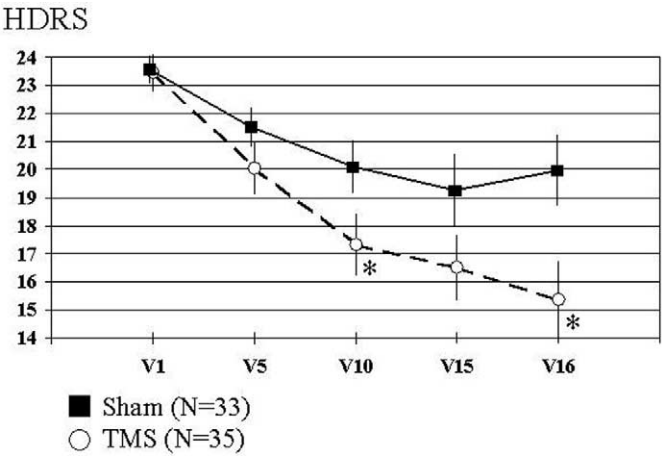

Figure 3. Hamilton Depression Rating Scores-17 item (HDRS) with standard errors for TMS and sham groups. *indicates a significant ($p < .05$) difference between TMS and sham groups. TMS, transcranial magnetic stimulation.

BDI score changes over time in the two groups indicated superiority of TMS over sham. There was no evidence of any cognitive compromise or adverse effects on neuropsychological functioning with TMS compared with sham, consistent with other studies (Hausmann et al 2004). Both treatment groups exhibited significant improvements in cognitive functioning at follow-up, likely reflecting continued influence of procedural practice effects despite our methodological efforts to minimize this. The TMS treatments were generally well tolerated without any major adverse events.

Meta-analyses of sham-controlled studies of TMS in depression have shown statistically significant differences from sham, but reviewers have questioned the clinical significance of the results given low response rates. However, because response rates to antidepressant treatments and placebo may vary depending on sample selection, it is more meaningful to examine treatment-placebo differences rather than absolute response rates; this is especially true when evaluating clinical significance for a treatment-resistant population (a population less likely to respond to *any* treatment). In meta-analyses of antidepressant medication studies, the antidepressant-placebo response and remission rate differences are usually between 14% and 20% (Bech 2001; Thase et al 2001; Walsh et al 2002). In the current study, the TMS group and sham group differed by 25% (31% - 6%) in response rate and by 17% (20% - 3%) in remission rate. In addition, the effect sizes for antidepressant studies average .40 to .43(Walsh et al 2002), while the effect sizes in the current study were .58 to .69. Therefore, the response and remission rates of 31% and 20%, respectively, seen in this study were statistically, as well as *clinically,* significant.

The data from the present study show higher response and remission rates compared with other sham-controlled studies using lower intensities, fewer sessions, and fewer pulses; this study is consistent with the hypothesis that more intensive treatment with TMS may lead to greater response rates.

The sample selection may account for the low absolute response rates seen in both the TMS group and the sham group. Both medication resistance (Nierenberg et al 1994; Prudic et al 1996; Stimpson et al 2002; Thase and Rush 1997) and chronicity (Khan et al 1991) of major depression are associated with poor treatment response. All the patients in this study had medication resistance and over half the sample met DSM-IV criteria for chronic depression.

The TMS treatment given to some of the patients in the earlier studies may not have even reached the prefrontal cortex because of differences in scalp-cortical distances in the prefrontal cortex and the motor cortex (Fabre et al 2004; Kozel et al 2000). Nearly all previous TMS studies have assumed that the SCD in the prefrontal cortex was similar to the SCD in the motor cortex; in the current study, we corrected for differences based on the MRI measurements of SCD, assuring stimulation of the prefrontal cortex.

This study has several limitations. Although this is the largest sham-controlled study of medication-resistant major depression, the sample size is still relatively small compared with antidepressant medication trials. The generalizability of these results is limited. We excluded patients who had a history of ECT nonresponse. At this point in the exploration of a new treatment such as TMS, we felt that it was premature to test TMS in this group. One patient has been reported to respond to TMS even though he had failed to respond to ECT (Levy et al 2000). Nonetheless, TMS has not been shown in controlled trials to be effective in those who have failed to respond to ECT. We also excluded patients who were very chronically depressed, those with the duration of their current episode of greater than 5 years based on our pilot data (Holtzheimer et al 2004a). Therefore, our results are not relevant to ECT nonresponders or the very chronically ill population. In addition, because of ethical concerns, subjects with strong suicidal ideation were excluded from the study. However, more severely ill patients have been successfully treated with TMS in trials that have compared TMS and ECT. In the TMS-ECT trials, TMS efficacy has been shown to be similar to ECT in nonpsychotic depressed patients (Grunhaus et al 2000, 2003; Janicak et al 2002; Pridmore et al 2000).

Another limitation of this and previously published TMS studies is that treaters were not blind to treatment allocation, potentially jeopardizing the blinding of subjects. In addition, subjects receiving real TMS were more likely to experience pain during the TMS sessions compared with the subjects receiving sham. However, TMS and sham guesses were not statistically different in the two groups at either visit 2 or after visit 15. After visit 15, 58% of the TMS group guessed that they were receiving TMS compared with 43% of the sham group; with a larger sample, it is possible that this difference could have reached significance. In addition, a theoretical limitation is that the raters were not asked to guess the treatment allocation.

Loo et al (2000) raised concern that using a sham that involves tilting the coil might produce some neuronal depolarization and a therapeutic effect. However, in the Loo et al (2000) study, the coil was tilted at a 45° angle; in the current study, the coil was tilted at a 90° angle, a sham condition that others have found to produce only 29% of the peak integrated voltage of the actual TMS stimulation (Lisanby et al 2001).

Another limitation of this study is that we used a "fixed-dose" design in that we gave all subjects that same TMS parameters and the same number of sessions. In the antidepressant medication research, flexible-dose design studies are significantly more likely to show statistical superiority to placebo compared with fixed-dose designs (Khan et al 2003). Transcranial magnetic stimulation treatment might have been even more effective had the protocol been more flexible, allowing higher TMS intensities, more pulses, or more sessions.

The follow-up period following the TMS responses was not optimal scientifically. Because of ethical concerns about leaving responders untreated, continuation medication was started 2 weeks after the last TMS session. Therefore, this study cannot comment on the duration of effects from the TMS treatment alone beyond 2 weeks.

From the meta-analyses of TMS in depression, there is a clear antidepressant signal compared with sham stimulation. The current study and the study of Fitzgerald et al (2003). indicate that clinically relevant antidepressant responses can be obtained in sham-controlled TMS studies if higher intensities and more sessions are used. Future research with TMS in depression should use larger sample sizes and higher intensities and allow for the possibility of more sessions to determine whether TMS treatment can be optimized further.

We thank the patients who generously gave of their time participating in the study. We thank Suzanne Craft, Ph.D., Christopher Wilson, M.D., Cara Fuchs, Priscilla Schwantes, and Linda Floyd for their expert assistance.

This study was supported by grants from the National Institute of Mental Health, RO1 MH 62154 and R25 MH60486.

These data were presented in part at the Society of Biological Psychiatry Meeting, May 1, 2004, New York, New York.

Disclosures: DHA has been a speaker for Cephalon, Eli Lilly, Janssen, Pfizer, and Wyeth-Ayerst and a consultant or on an advisory board for Abbott Laboratories, Bristol-Myers-Squibb, Cyberonics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Pfizer, Janssen, Neuronetics, Mindcare Centres, Veterans Administration Cooperative Study Group, and UBC Pharma. DHA has had research grants from the National Institute of Mental Health, Philips, and Neuronetics. PEH has had grant support from Neuronetics, Inc. and the National Institute of Mental Health. WF had grant support from the government of Egypt. JN has been a speaker for Eli Lilly, GlaxoSmithKline, and Wyeth-Ayerst and has been on an advisory board for Shire. JN has had grant support from the National Institute of Mental Health, the National Institute of Drug Abuse, and the National Alliance for Research on Schizophrenia and Depression. DLD has been a speaker for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers-Squibb, Organon, and Forrest. DLD has been a consultant or on an advisory board for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers-Squibb, Cypress, Corcept, Janssen, Novartis, Shire, Somerset, and Otsuka. DLD has had recent grant support form Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Cyberonics, Merck, Janssen, and the National Institute of Mental Health. PRB has been a speaker for GlaxoSmithKline, Forrest, Novartis, Pfizer, Pharmacia, and Wyeth-Ayerst. PRB has been a consultant or on an advisory board for Alza, Cephalon, GlaxoSmithKline, Forrest, Eli Lilly, Janssen, Pfizer, Pharmacia, Roche, and Wyeth-Ayerst. PRB has had research support from GlaxoSmithKline, Pfizer, Forrest, and the National Institute of Mental Health.

Avery D (2001): Transcranial magnetic stimulation in the treatment of depression. *Essent Psychopharmacol* 4:37–48.

Bech P (2001): Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *Int J Neuropsychopharmacol* 4:337–345.

Burt T, Lisanby SH, Sackeim HA (2002): Neuropsychiatric applications of transcranial magnetic stimulation: A meta-analysis. *Int J Neuropsychopharmacol* 5:73–103.

Chouinard PA, Van Der Werf YD, Leonard G, Paus T (2003): Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *J Neurophysiol* 90:1071–1083.

Dunner DL, Russell JM (2003): A long-term, naturalistic study of usual standard-of-care treatment in patients with treatment resistant depression. *Proceedings of the ACNP Annual Meeting, San Juan, Puerto Rico, December 2003.* Nashville, TN: American College of Neuropsychopharmacology, 2003: 150.

Fabre I, Galinowski A, Oppenheim C, Gallarda T, Meder JF, De Montigny C, et al (2004): Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: An open trial. *Int J Geriatr Psychiatry* 19:833–842.

First MB, Gibbon M, Spitzer RL, Williams JBW (1996): *Structured Clinical Interview for DSM-IV Disorders-Research Version (SCID-I, Version 2.0).* New York: Biometrics Research Department, New York State Psychiatric Institute.

Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J (2003): Transcranial magnetic stimulation in the treatment of depression: A double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 60: 1002–1008.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al (1991): Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Remission, recovery, relapse, and recurrence.* Arch Gen Psychiatry 48:851–855.

George M, Belmaker R (2000): Transcranial Magnetic Stimulation in Neuropsychiatry. Washington, DC: American Psychiatric Association Press, Inc.

Gershon AA, Dannon PN, Grunhaus L (2003): Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry* 160:835–845.

Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, et al (1993): Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Application to the NIMH treatment of Depression Collaborative Research Program dataset.* Arch Gen Psychiatry 50:739–750.

Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, et al (2000): Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: An open study. *Biol Psychiatry* 47:314–324.

Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN (2003): A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 53:324–331.

Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, et al (2004): No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *J Clin Psychiatry* 65:772–782.

Holtzheimer P, Russo J, Avery D (2001): A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull* 35:149–169.

Holtzheimer P, Russo J, Avery D (2003): Erratum for "A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression." Psychopharmacol Bull 37:5.

Holtzheimer PE, Avery D, Schlaepfer TE (2004b): Antidepressant effects of repetitive transcranial magnetic stimulation. *Br J Psychiatry* 184:541–542.

Holtzheimer PE 3rd, Russo J, Claypoole KH, Roy-Byrne P, Avery DH (2004a): Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety* 19:24–30.

Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al (2002): Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: Preliminary results of a randomized trial. *Biol Psychiatry* 51:659–667.

Khan A, Dager SR, Cohen S, Avery DH, Scherzo B, Dunner DL (1991): Chronicity of depressive episode in relation to antidepressant-placebo response. *Neuropsychopharmacology* 4:125–130.

Khan A, Khan SR, Walens G, Kolts R, Giller EL (2003): Frequency of positive studies among fixed and flexible dose antidepressant clinical trials: An analysis of the food and drug administration summary basis of approval reports. *Neuropsychopharmacology* 28:552–557.

Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, et al (1999): Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: A double-blind controlled study. *Arch Gen Psychiatry* 56:315–320.

Kozel FA, George MS (2002): Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract* 8:270–275.

Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al (2000): How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *J Neuropsychiatry Clin Neurosci* 12:376–384.

Levin HS, O'Donnell VM, Grossman RG (1979): The Galveston Orientation and Amnesia Test. *A practical scale to assess cognition after head injury.* J Nerv Ment Dis 167:675–684.

Levine J, Schooler N (1983): *Assessment for Emergent Event (SAFTEE) Symptoms*. Rockville, MD: Pharmacologic and Somatic Treatment Branch, National Institute of Mental Health.

Levy NA, Janicak P, Maritis B, Beedle D, Krasuski J, Peterson J, et al (2000): Repetitive transcranial magnetic stimulation (rTMS) after electroconvulsive therapy (ECT): A case report. *Psychline* 3:31–37.

Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA (2001): Sham TMS: Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry* 49:460–463.

Loo CK, Taylor JL, Gandevia SC, McDarmont BN, Mitchell PB, Sachdev PS (2000): Transcranial magnetic stimulation (TMS) in controlled treatment studies: Are some "sham" forms active? *Biol Psychiatry* 47:325–331.

Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J (2003): Repetitive transcranial magnetic stimulation for the treatment of depression: Systematic review and meta-analysis. *Br J Psychiatry* 182: 480–491.

Nierenberg AA, Feighner JP, Rudolph R, Cole JO, Sullivan J (1994): Venlafaxine for treatment-resistant unipolar depression. *J Clin Psychopharmacol* 14:419–423.

Pascual-Leone A, Catala MD, Pascual-Leone Pascual A (1996): Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood. *Neurology* 46:499–502.

Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M (2000): Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol* 3:129–134.

Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, et al (1996): Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry* 153:985–992.

Sackeim HA (2000): Repetitive transcranial magnetic stimulation: What are the next steps? *Biol Psychiatry* 48:959–961.

Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62:10–17.

Schlaepfer TE, Kosel M, Nemeroff CB (2003): Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of affective disorders. *Neuropsychopharmacology* 28:201–205.

Spreen O, Strauss E (1991): *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York: Oxford University Press.

Stimpson N, Agrawal N, Lewis G (2002): Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. *Systematic review*. Br J Psychiatry 181:284–294.

Stout RL, Wirtz PW, Carbonari JP, Del Boca FK (1994): Ensuring balanced distribution of prognostic factors in treatment outcome research. *J Stud Alcohol Suppl* 12:70–75.

Thase M, Rush A (1997): When at first you don't succeed: Sequential strategies for antidepressant non-responders. *J Clin Psychiatry* 58(suppl 13): 23–29.

Thase ME, Entsuah AR, Rudolph RL (2001): Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 178:234–241.

Walsh BT, Seidman SN, Sysko R, Gould M (2002): Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA* 287:1840–1847.

Wassermann EM, Lisanby SH (2001): Therapeutic application of repetitive transcranial magnetic stimulation: A review. *Clin Neurophysiol* 112:1367–1377.

Wei LJ (1978): The application of an urn model in controlled clinical trials. *J Am Stat Assoc* 73:559–563.