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Low Frequency rTMS Stimulation of the Right Frontal Cortex Is as Effective as High Frequency rTMS Stimulation of the Left Frontal Cortex for Antidepressant-Free, Treatment-Resistant Depressed Patients

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Background. *Repetitive transcranial magnetic stimulation (rTMS) is a promising relatively non-invasive alternative for the treatment of depression. The purpose of this study was to compare the apparent effectiveness of high frequency (20 Hertz) rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) with that of low frequency (1 Hz) rTMS applied over the right DLPFC.*
Methods. *Twenty-eight antidepressant-free adults with major depressive (n = 25) or bipolar (n = 3) disorder (not on mood stabilizers) in a current major depression (Hamilton Rating Scale for Depression [HAM-D-21] ≥ 18; Mean = 24.5, SD = 5.51) were treated (14 right, 14 left) for 4 weeks.*
Results. *Overall paired t-tests revealed a significant reduction in mean HAM-D-21, Beck Depression Inventory (BDI-II), and Clinical Global Impression of Change (CGIC) scores at the end of treatment for both groups (high frequency left DLPFC and low frequency right DLPFC). The treatment response rate found (32%) was typical of other response rates reported in the literature (6,30). One-month follow-up data was obtained from 50% of participants. At 1-month follow-up no significant differences were noted as compared to patients' performance at last treatment visit, indicating moderate robustness of rTMS treatment over time. Furthermore, magnetic stimulation did not substantially alter patient memory over the course of treatment.*
Conclusion. *rTMS given at low frequency over the right frontal cortex appears to be as effective treatment of refractory depression as high frequency treatment over the left frontal cortex.*

Keywords rTMS, Treatment-resistant depression, Memory

INTRODUCTION

Conventional antidepressant treatment results in an adequate response (greater than 50% improvement in the baseline Hamilton Rating Scale for Depression score) in about 50% of patients participating in randomized, clinical trials. Although subsequent treatment with an alternative agent may be effective, substantial portions of depressed patients do not achieve the desired result (1,2,3). Electroconvulsive therapy is an efficacious alternative but patients who have failed less invasive treatment desire another helpful option. Treatment of depression by magnetic field application to the frontal cortex is one

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promising possibility. Repetitive transcranial magnetic stimulation (rTMS) involves the application of repeated magnetic field applications to induce electrical activity in the underlying cortical areas of the brain. The initial efforts involved the application of high frequency (10–20 Hertz) stimulation of left dorsolateral prefrontal cortex (DLPFC), selected in the belief that stimulation would increase neuronal activity in this hypofunctioning area. Many small trials suggest that this approach has a modest antidepressant effect that might be enhanced by increasing field intensity, increasing the number of stimuli per session, or increasing the number of treatments (4).

An alternative rTMS stimulation paradigm involves low frequency (1 Hz) stimulation of the right DLPFC. Recent trials indicate that this approach has antidepressant effects (5,6,7). This study compared the apparent effectiveness of high frequency (20 Hz) rTMS applied over the left DLPFC with the apparent effectiveness of low frequency (1 Hz) rTMS applied over the right DLPFC for antidepressant-free patients with refractory depression.

METHODS

Prior to conducting this study, approval was obtained from the Washington University Medical School's Human Studies Committee. The treatment procedures were explained and potential risks, benefits and alternatives reviewed prior to obtaining written consent.

Patients

Thirty patients with a DSM-IV (8) diagnosis of major depression were recruited into the study (Table 1). Physicians in the community were informed about the study through direct contact and mailings to refer patients for treatment. Two patients were dropped from the final analyses due to failure to complete any evaluation beyond baseline measures (n = 1) and an intercurrent illness (i.e., fall with scapular fracture, n = 1). There were no differences between the 2 groups (low frequency, right dorsolateral prefrontal cortex (DLPFC) or high frequency, left dorsolateral prefrontal cortex (DLPFC); n = 14 each) in gender, level of education, or clinical variables. There was a significant age difference between the 2 groups, with individuals receiving rTMS treatment on the right side being notably older. The treating psychiatrist and a nurse-clinician assigned a DSM-IV diagnosis, confirmed in a standardized interview (SCID) completed by the nurse clinician.

Twenty-five patients had a diagnosis of major depressive episode and 3 had a diagnosis of bipolar I disorder, depressive episode. Patients with psychosis were excluded. In addition, patients with significant medical illnesses, neurologic disorders, implanted metal devices, or other major Axis I psychiatric disorders were excluded from the study. All patients scored greater than (or equal to) 18 on the Hamilton Depression Rating Scale (9,10) (HAM-D-21) (Mean = 24.5, SD = 5.51).

Table 1 Demographic and Baseline Clinical Characteristics of 28 rTMS Patients

Characteristic	Right-Side Tx. Group	Left-Side Tx. Group
Age, y	55.57 (9.71)*	43.36 (9.72)
Gender, M/F, No.	6/8	6/8
Level of education	15.57 (1.95)	14.29 (2.02)
BDI-II score	27.79 (8.81)	35.07 (10.37)
Primary Rater-HAM-D-21	23.93 (6.18)	25.07 (4.92)
State Anxiety Scale	47.58 (12.97)	57.92 (8.54)
Trait Anxiety Scale	59.50 (7.43)	63.85 (9.20)

*$t_{26} = -3.33$, $p \leq .01$.

BDI, Beck Depression Inventory; HAM-D-21, Hamilton Depression Rating Scale – 21 point scale. Data are given as mean (SD).

Detailed treatment histories were obtained and all enrolled patients were judged to suffer from treatment resistant depression (failed to respond to at least two treatment trials of different antidepressant medication types, each used for an adequate period of time at an adequate dose) (11). Of the three patients with bipolar disorder, depressed phase, one had failed to respond to adequate trials of lithium and divalproex in combination with antidepressants, another had failed to respond to an adequate trial of lithium in combination with an antidepressant and one patient had not received a concurrent antidepressant/mood stabilizing medication trial although had failed independent trials of both. Fourteen patients had received electroconvulsive therapy (ECT) prior to enrollment, none administered in the 6 months preceding rTMS; five patients reported a good response to ECT.

A potential confound of many previous investigations of rTMS effectiveness is concomitant treatment with psychotropic medications. For this study, all participants were tapered off psychotropic medications prior to initiating rTMS treatment. The tapering began as early as was possible to insure that psychotropic drugs (save as listed below) had been discontinued for at least 3 half-lives of the prescribed compound prior to initiation of treatment. Rescue treatment of insomnia with zolpidem was allowed and six patients took this medication on an intermittent basis. Two patients continued taking gabapentin (cervical neck pain s/p fusion; chronic musculoskeletal pain) and 1 patient continued receiving oxycodone/acetaminophen (cervical neck pain from spinal stenosis) for management of chronic pain.

Study Design

The design for the study is illustrated in Figure 1. Patients were randomized to 1 of 2 treatment arms (low frequency,

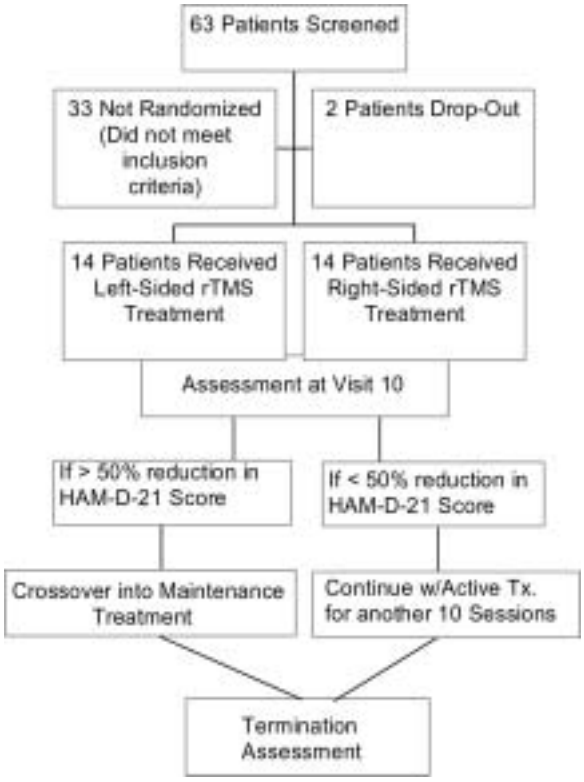

Figure 1 Study design.

right dorsolateral prefrontal cortex (DLPFC) or high frequency, left dorsolateral prefrontal cortex (DLPFC); n = 14 each) via alternate assignment based upon date of entry into the study. All patients initially received 10 treatment sessions (1 per day, 5 d/wk). After the 10th treatment, patients were assessed and if their performances on clinical variables (primarily a 50% decrease in their HAM-D-21 score) warranted, they were placed into maintenance therapy (4 once weekly treatments) (n = 6). Otherwise, patients who did not achieve a 50% decrease in their HAM-D-21 score were entered into a 2-week continuation of rTMS treatment with the original treatment parameters. One-month follow-up assessments were completed on 15 of the 28 patients involved in the study (9 left-sided treatment, 6 right-sided treatment). All clinician ratings were blind to treatment status.

rTMS Treatment

rTMS was provided with a Neotonus Neopulse^{TM} utilizing a magnetic head of the manufacturer's proprietary design. Patients were placed in a recliner and ear plugs were inserted; study personnel also utilized earplugs, in both cases to minimize possible hearing impairment. Resting motor threshold was estimated by stimulating the cortex at low frequency (1 Hz) and device output (45%), advancing the power and repositioning the coil to elicit a reliable (5 out of 10 trials) muscle twitch of the abductor pollicis brevis in the appropriate contralateral hand. The stimulating coil was advanced forward 5 cm to initiate antidepressant treatment — patients treated with high frequency left DLPFC received 20 Hz stimulation at 80% of the estimated motor threshold as 50 trains of 40 stimuli each given over 2 seconds with an intertrain interval of 30 seconds and patients treated with low frequency right DLPFC stimulation received 1 Hz stimulation at 110% of the estimated motor threshold as two 1-minute trains separated by 3 minutes. Patients were treated five days a week for up to four weeks.

Clinical Ratings

The primary outcome measure for the study was the HAM-D-21 (9,10); in addition to rating patients blind to treatment condition, videotapes were made of the interviews to demonstrate rater reliability. No statistically significant differences were noted in scores between the blind rating of HAM-D videotapes and the blind in-person ratings, attesting to the reliability of the measure. Thus, the independent videotape ratings are dropped from further consideration. All patients were assessed at baseline and at 5-session intervals via the HAM-D-21 (9,10), the Beck Depression Inventory-II (12,13), Clinical Global Impression of Change (CGIC) (14), Speilberger's State and Trait Anxiety Inventories (15), and the Folstein Mini-Mental Status Exam (16). A semantic memory task (17) was also administered at each 5-session interval to assess the impact of rTMS on semantic memory. Finally, at each 10-session interval, Cloninger's Temperament and Character Inventory (18) was completed to examine any correlated changes in anxiety and/or behavioral patterns of those whose depressive symptoms may have been altered by the treatment.

Data Analysis

Student's t-tests and chi-square tests were used to investigate differences among the two treatment groups on demographic and baseline clinical variables. The primary outcome analysis was conducted on baseline to 4-week clinical measures' mean scores. Data was analyzed using paired *t* tests comparing baseline and end study scores. In cases where a patient's session 20 data were missing, the last observation made (other than the baseline score) was carried forward and used in the final analyses. All procedures were 2-tailed and significance was set at alpha = .05. All statistical analyses were conducted using statistical software (SPSS for Windows 12.0; SPSS Inc., Chicago, IL).

RESULTS

Patients

Baseline clinical characteristics are summarized in Table 1. There were no statistically significant baseline differences between the two groups with the exception of age. Individuals receiving rTMS treatment on the right side were significantly older (right side: Mean = 55.57, SD = 9.71; left side: Mean = 43.36, SD = 9.72; $t_{26} = -3.33$, p = 0.003). The mean motor threshold (MT) was 68% of the device output (SD 12%) with a range from 50 to 91%; there was no significant difference in mean motor threshold for the right versus left condition (left side MT = 65% and right side MT = 71%, $t_{26} = -1.37$, $p = .182$).

Treatment Effectiveness

Overall paired *t*-tests revealed a significant reduction in mean HAM-D-21 scores, BDI-II scores, and CGIC at week 4 of treatment. (see Table 2 and Figures 2 & 3). As seen in sham-controlled studies, both stimulus approaches had weak antidepressant effects. There was no significant difference between the right and left-sided rTMS treatment groups ($t_{26} = .162$, $p = .87$). Nine patients (32%) were judged to be responders (at least a 50% reduction in HAM-D-21), 5 who received left-sided treatment and 4 who were stimulated on the right side. Five patients were remitters (HAM-D-21 ≤ 7; 3 from the left DLPFC group and 2 from the right DLPFC group). Prior response to ECT or lack thereof did not predict rTMS response ($\chi^2 = 0.207$, $p = 0.604$). One of the three participants with bipolar disorder, depressed phase, responded to rTMS ($\chi^2 = 0.039$; Fisher's exact $p = 0.658$).

At 1-month follow-up, no significant differences were noted between patients' performance at Visit 20 and 1-month follow-up ($t_{13} = .761$, $p = .46$), indicating moderate robustness of the rTMS treatment over time. Additionally, comparison of patients' scores at baseline and 1-month follow-up indicated sustained improvement (BDI-II: $t_{14} = 3.58$, $p = .003$; HAM-D-21: $t_{11} = 2.72$, p = .020; CGIC: $t_{13} = 3.83$, $p = .002$). At 1-month follow-up, patients who had received right-sided treatment demonstrated improvement on the HAM-D-21 that approached a significant difference from left-sided treatment receivers ($t_{12} = 2.08$, $p = .059$).

Anxiety measures changed significantly with rTMS treatment but were highly correlated with Hamilton scores (Speilberger's State and Trait Anxiety Inventory, State $t_{24} = 2.03$, $p = .053$; $r = 0.758$, p < 0.001; Trait $t_{24} = 3.18$, $p = .004$; $r = 0.804$, $p = 0.001$). Temperament and Character Inventory scores did not predict response to treatment or show a significant change during treatment unlike the changes observed in an open–label study considering the antidepressant impact of maprotiline (19).

Adverse Events

Ten (36%) of the 28 patients reported site discomfort or pain during rTMS and 7 (25%) reported a headache after rTMS. Two patients reported increased ringing in their ears, 2 reported eye twitching, 2 reported feeling light-headed, 2 reported increased body sensitivity or "tingly skin," 1 reported an itchy nose, 1 reported blood pressure problems (patient was mildly hypertensive throughout treatment course and blood pressure at the time of complaint was not remarkably different from blood pressure at other treatments when no complaint was made), 1 reported temporomandibular joint problems, 1 reported balance problems and 1 reported increased fatigue following rTMS treatment. No seizures were noted. The tolerability of the treatment for participants did not differ by group.

Impact of rTMS on Cognitive Function and Memory

MMSE scores were uninfluenced by rTMS (pretreatment, 29.5 ± 0.7; 29.4 ± 1.4 at visit 20, $t_{27} = .406$, $p = .688$; one month follow-up, 29.9 ± 0.34, $t_{15} = -1.576$, $p = .136$. No significant site differences (right vs. left) were observed (pretreatment, $t_{26} = -.268$, $p = .791$; visit 20, $t_{26} = .790$, $p = .437$; one month follow-up, $t_{14} = 1.775$, $p = .098$). Measurement of semantic

Table 2 Baseline and Week 4 Scores for Each Primary Clinical Outcome Measure

Characteristic	Baseline Score	4-Week Score	*t*	Significance Level
Primary Rater-HAM-D-21	24.50 (5.51)	16.39 (8.02)	5.46	p ≤ .001
BDI-II score	31.43 (10.15)	22.57 (12.16)	4.56	p ≤ .001
CGIC	4.00 (0.00)	2.93 (1.25)	3.78	p ≤ .001
State Anxiety Scale	52.96 (11.89)	46.24 (13.76)	2.03	p = .053
Trait Anxiety Scale	61.76 (8.52)	54.44 (10.81)	3.18	p ≤ .01

BDI, Beck Depression Inventory; HAM-D-21, Hamilton Depression Rating Scale – 21 point scale; CGIC, Clinical Global Impression of Change. Data are given as mean (SD).

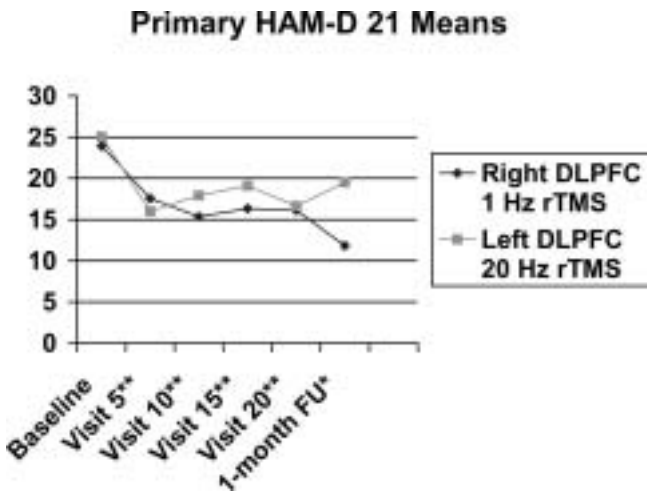

Figure 2 Primary HAM-D-21 means right vs. left across study duration.

*p ≤ .01; **p ≤ .001 (Note: Statistical significance compared to baseline is indicated at each follow-up interval) .
The difference between low frequency right frontal cortex stimulation and high frequency left frontal cortex stimulation approached, but was not statistically different (t_{12} = 2.08, p = .059), at one-month follow-up.

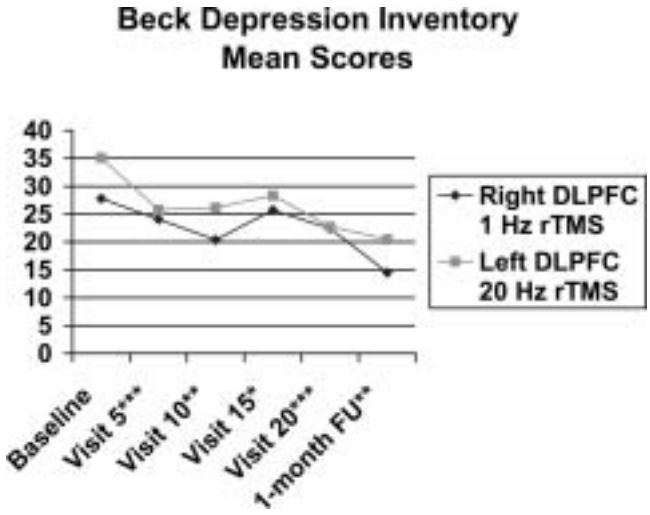

Figure 3 Beck Depression Inventory-II right vs. left across study duration.

*p ≤ .05; **p ≤ .01; ***p ≤ .001 (Note: Statistical significance compared to baseline is indicated at each follow-up interval) .
The difference between low frequency right frontal cortex stimulation and high frequency left frontal cortex stimulation was not statistically significant (t_{13} = .945, p = .362) at one-month follow-up.

memory function using the tools developed by Roediger and his associates (17) was performed to tap true memory functions and willingness to make false attributions, a type of false memory. The stimulated region of the brain in rTMS (prefrontal cortex) has been proposed to play an executive function role in working memory (19), suggesting that memory deficits, more subtle than detected by the MMSE, could result from rTMS stimulation. Magnetic stimulation did not change immediate and delayed recall over the course of treatment (see Table 3) nor rate of endorsement of correct items after a ~5 hour delay (Table 4). Performance was no different from normal samples (20). Subjects who received rTMS endorsed the false associates at very high rates, as has been observed in normal populations (20). This type of performance appeared to decrease over the course of rTMS. These changes were modest and only statistically significant for endorsement of the false associate for lists learned before rTMS at the 6th visit time point, with a return to prior rates at subsequent testing points. Thus, any effect of rTMS on false memory was very modest, at most.

DISCUSSION

In this small sample, low frequency right DLPFC stimulation and high frequency left DLPFC stimulation were equally effective, weak, antidepressant interventions. The rTMS experience was well tolerated by most patients although one person did not complete the first treatment. Patients experienced mild discomfort, largely pain at the site of stimulation and headaches, as the result of receiving rTMS. There is no evidence that any patient suffered a seizure.

Most rTMS treatment trials (21,22,23,24,25) have stimulated the left DLPFC at relatively high frequencies (10 to 20 Hz) with modest antidepressant effects in treatment resistant patient populations. Three trials have considered the antidepressant effectiveness of relatively low (1 Hz) frequency stimulation of the right DLPFC (26,27,28). Examination of the data suggests that either stimulation paradigm is likely to be effective, an observation supported by the three trials that compared low frequency R DLPFC stimulation, high frequency L DLPFC and sham treatment (29,30,31). Two of these trials allowed the concomitant administration of psychotropic medications as is the case with most rTMS trials (32,33).

CONCLUSION

This trial indicates that 1 Hz R DLPFC stimulation and 20 Hz L DLPFC stimulation produced weak antidepressant effects in the absence of antidepressant pharmacotherapy. This design feature, the blinded nature of therapeutic assessment and the apparent sustained nature of the response one month after completion of treatment suggest the robustness of the antidepressant response observed in this trial. Furthermore, patient rating of response (BDI-II) matched the evaluation of blinded observers (HAM-D-21). A recent meta-analysis of the sham-controlled rTMS literature expressed concern about a disparity between observers report of a response that was not noted by patients (33). In the trial reported here, patients expected to receive potentially effective treatment, which may have influenced the patient's impression of clinical response as well as

Table 3 Longitudinal Impact of rTMS on Immediate and Delayed Recall

Task	Pre rTMS Mean (%) (n = 22)	1st rTMS Mean (%) (n = 22)	6th rTMS Mean (%) (n = 22)	Last rTMS Mean (%) (n = 18)	1-month FU Mean (%) (n = 15)
Pre immediate recall (uncued)	14.82 (49%)	14.00 (47%)	14.55 (49%)	15.94 (53%)	14.73 (49%)
Post immediate recall (uncued)	15.41 (51%)	15.05 (50%)	15.09 (50%)	15.06 (50%)	15.13 (50%)
1 hour delayed recall (uncued)	7.86 (26%)	7.95 (27%)	6.95 (23%)	8.53 (28%)	8.20 (27%)

Table 4 Longitudinal Impact of rTMS on True and False Items in Cued Recognition

Task	Pre rTMS Mean (%) (n = 20)	1st rTMS Mean (%) (n = 20)	6th rTMS Mean (%) (n = 18)	Last rTMS Mean (%) (n = 13)	1-month FU Mean (%) (n = 11)
True items (anterograde)	5.05 (63%)	4.80 (60%)	5.39 (67%)	4.77 (60%)	5.55 (69%)
True items (retrograde)	4.90 (61%)	5.45 (68%)	4.78 (60%)	4.69 (59%)	5.82 (73%)
Critical false items (anterograde)	1.90 (95%)	1.90 (95%)	1.61 (81%)	1.69 (85%)	1.82 (91%)
Critical false items (retrograde)	1.85 (93%)	1.90 (95%)	1.61*(23%)	1.54 (77%)	1.73 (87%)

*$p \leq .05$.

evaluations performed by blinded assessors. Nevertheless, this study adds to the growing body of experience that suggests the effectiveness of rTMS. Demonstration of rTMS efficacy will presumably require improvement of methodology to blind patients and practitioners (32,33).

The size of this trial was comparable to others comparing the effectiveness of high (left DLPFC) versus low (right DLPFC) frequency rTMS treatment for depression (N = 28) (30,31). The power, or the probability that a study will successfully detect a difference, of this study was very weak (0.247). It is encouraging that despite samples being of small size, they have been able to detect some degree of effectiveness of rTMS, although this may be a publication bias for positive studies. Power calculations indicate that a sample size that exceeds all previously published reports on the administration of rTMS by a factor of roughly 2 (or a total of 128 participants, 64 persons per cell, based on two cell design) would be required to effectively achieve adequate power (effect size d = 0.5, alpha = .0498, power = 0.801). This size of sample suggests the implementation of a multi-site study using a similar design would be necessary to efficiently gain access to an adequate number of participants.

ECT and rTMS have been compared (34,35,36,37), perhaps because both are procedures that involve neuronal stimulation or perhaps because both are frequently administered to patients with treatment refractory depression. ECT has significant adverse effects on memory, particularly semantic memory (38). Although the effects of rTMS on semantic memory have not been completely explored, this study did not detect gross changes in cognitive function as would be detected by the MMSE or more subtle problems with accurate recall of word lists devised by Roediger and his associates (17). rTMS appears to be an alternative to ECT with much less adverse impact on cognitive function. However, rTMS may have limitations with regard to its usefulness in the elderly population (22) and for those with a diagnosis of psychotic depression (4). Overall, rTMS is a well-tolerated procedure that may be a useful treatment for refractory depression.

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