

Transcranial Magnetic Stimulation in the Treatment of Depression

A Double-blind, Placebo-Controlled Trial

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Background: High-frequency left-sided repetitive transcranial magnetic stimulation (HFL-TMS) has been shown to have antidepressant effects in double-blind trials. Low-frequency stimulation to the right prefrontal cortex (LFR-TMS) has also shown promise, although it has not been assessed in treatment-resistant depression and its effects have not been compared with those of HFL-TMS.

Objective: To prospectively evaluate the efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group.

Design: A double-blind, randomized, sham-controlled trial.

Setting: Two general psychiatric services.

Participants: Sixty patients with treatment-resistant depression who had failed to respond to therapy with multiple antidepressant medications were divided into 3 groups of 20 that did not differ in age, sex, or any clinical variables. All patients completed the double-blind phase of the study.

Interventions: Twenty 5-second HFL-TMS trains at 10 Hz and five 60-second LFR-TMS trains at 1 Hz were applied daily. Sham stimulation was applied with the coil angled at 45° from the scalp, resting on the side of one wing of the coil.

Main Outcome Measure: Score on the Montgomery-Åsberg Depression Rating Scale.

Results: There was a significant difference in response among the 3 groups ($F_{56,2}=6.2$), with a significant difference between the HFL-TMS and sham groups and between the LFR-TMS and sham groups ($P<.005$ for all) but not between the 2 treatment groups. Baseline psychomotor agitation predicted successful response to treatment.

Conclusions: Both HFL-TMS and LFR-TMS have treatment efficacy in patients with medication-resistant major depression. Treatment for at least 4 weeks is necessary for clinically meaningful benefits to be achieved. Treatment with LFR-TMS may prove to be an appropriate initial repetitive TMS strategy in depression taking into account safety, tolerability, and efficacy considerations.

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SEVERAL STUDIES during recent years have evaluated the use of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depression. Most studies of depression have used high-frequency stimulation (5-20 Hz) and have targeted the left dorsolateral prefrontal cortex (eg, see George et al¹ and Pascual-Leone et al²). A variety of sham-controlled double-blind studies of this sort have found significant differences between active treatment and placebo,³ although in some studies^{4,5} the differences between the groups have been of marginal clinical significance. An alternative paradigm has also shown promise: low-frequency stimulation (1 Hz) applied to the right dorsolateral prefrontal cortex. In the only double-blind evaluation of this

type of stimulation, Klein et al⁶ randomized patients with major depression to either 1-Hz rTMS applied to the right dorsolateral prefrontal cortex or a sham condition. During 2 weeks, 17 of 35 patients in the active treatment group experienced a greater than 50% reduction in depression rating scores compared with 2 of 32 patients in the sham group. However, compared with studies of left-sided rTMS, the patients in this study were not "treatment resistant." No published research, to our knowledge, has directly compared high-frequency left-sided TMS (HFL-TMS) and low-frequency right-sided TMS (LFR-TMS).

The aim of this study was to prospectively evaluate the efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression (TRD) under double-blind con-

Table 1. Demographic and Baseline Clinical Characteristics of 60 Patients With Major Depression*

Characteristic	HFL-TMS Group (n = 20)	LFR-TMS Group (n = 20)	Sham Group (n = 20)
Age, y	42.20 (9.80)	45.55 (11.49)	49.15 (14.243)
Sex, M/F, No.	12/8	13/7	9/11
Age at onset, y	29.3 (11.1)	31.2 (14.9)	33.7 (11.4)
Episodes, No.	2.35 (1.46)	3.83 (6.03)	2.71 (2.91)
MADRS score	36.05 (7.55)	37.70 (8.36)	35.75 (8.14)
BDI score	33.15 (12.12)	35.05 (9.25)	32.30 (9.10)
GAF scale score	43.00 (6.76)	43.55 (9.94)	42.75 (7.15)
CORE score	8.60 (3.56)	8.75 (3.27)	8.80 (5.46)

Abbreviations: BDI, Beck Depression Inventory; GAF, Global Assessment of Functioning; HFL-TMS, high-frequency left-sided transcranial magnetic stimulation; LFR-TMS, low-frequency right-sided TMS; MADRS, Montgomery-Åsberg Depression Rating Scale.

*Data are given as mean (SD).

ditions and compared with a sham-treated control group. We hypothesized that both forms of treatment would show greater efficacy than a sham control but, based on studies in patients with TRD, that HFL-TMS would be more effective than LFR-TMS. We also aimed to establish whether differences could be found in tolerability and adverse effect profiles associated with the differing types of stimulation.

METHODS

PATIENTS

Sixty patients with a *DSM-IV* diagnosis of major depression participated in the study (**Table 1**). There were no differences among the 3 groups in age, sex, or clinical variables. Patients were recruited from the outpatient departments of 2 public mental health services (Alfred Psychiatry, Melbourne, and Dandenong Area Mental Health Service, Dandenong, Australia) and by referral from a variety of private psychiatrists. Seventy-four patients were screened. Eight patients did not meet the diagnostic criteria, and in 6 patients, the depression was not of sufficient severity. All patients were outpatients during the trial. Recruitment for the trial occurred between October 1, 2000, and September 30, 2002.

The treating psychiatrist and a study psychiatrist (P.B.F.) assigned a *DSM-IV* diagnosis. Fifty-four patients had a diagnosis of major depressive episode and 6 had a diagnosis of bipolar I disorder, depressive episode (1 in each active treatment group and 4 in the sham group; $\chi^2=3.3$; $P=.19$). All patients scored greater than 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (mean±SD score, 36.5±7.9) and had failed a minimum of 2 courses of antidepressant medications for at least 6 weeks (mean±SD number of courses, 5.68±3.40). Patients were not deliberately withdrawn from medication before the trial, but their doses were not allowed to have changed in the 4 weeks before commencement of or during the trial. Forty-six patients were taking medication during the trial: 13 were taking a selective serotonin reuptake inhibitor, 1 a tricyclic antidepressant, 8 a monoamine oxidase inhibitor, and 21 a serotonin-noradrenaline reuptake inhibitor or another class of medication (venlafaxine hydrochloride, mirtazapine, or reboxetine), and 3 patients were taking a combination of antidepressants. Eight patients were receiving lithium carbonate, 3 valproate sodium, 2 carbamazepine, 2 lamotrigine, and 1 combined lithium-carbamazepine. Fourteen

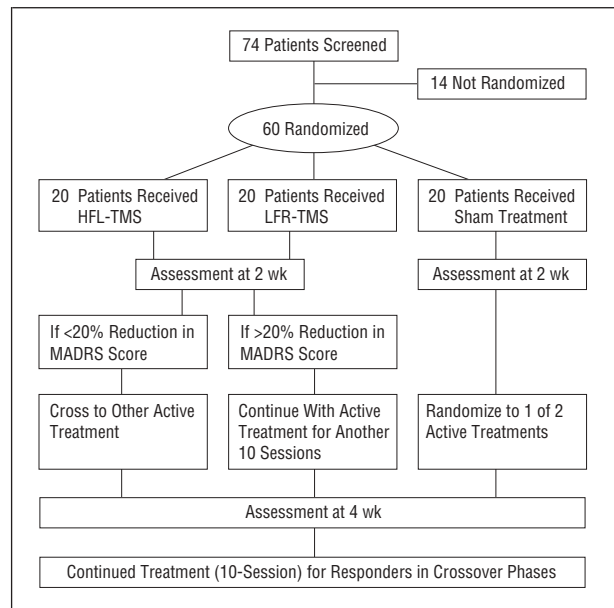


Figure 1. Study design. HFL-TMS indicates high-frequency left-sided transcranial magnetic stimulation; LFR-TMS, low-frequency right-sided TMS; and MADRS, Montgomery-Åsberg Depression Rating Scale.

patients were receiving antipsychotic medications (7 were taking olanzapine, 3 quetiapine, and 4 risperidone), although only 3 had symptoms rated mild or above (all mild) on the Brief Psychiatric Rating Scale⁷ psychosis symptom items (2 had hallucinations and 1 had suspiciousness). There were no differences in the proportions of patients taking any of the medication types among the 3 groups. Sixteen patients had previously received treatment with electroconvulsive therapy, 3 during the current episode. Patients with significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders were excluded. Five patients were left-handed (2 in the HFL-TMS group and 3 in the sham group; $\chi^2=2.2$; $P>.05$).

Written informed consent was obtained from all patients on a form approved by the human research ethics committees of Southern Health, Dandenong Hospital, and The Alfred Hospital.

STUDY DESIGN

The design for the study is illustrated in **Figure 1**. Patients were randomized to 1 of 3 treatment arms (n=20 each) via sealed envelopes opened immediately before commencement of the first treatment session by the clinician administering the rTMS. Patients and raters were blind to treatment, but the clinician administering rTMS was aware of the treatment group. All patients initially received 10 treatment sessions daily, 5 d/wk (phase 1). After the 10th session, a blinded assessment was made and the patients, but not the raters, were informed of their treatment group. Patients who had a reduction in MADRS score of greater than 20% in the active treatment arms could continue with the same TMS condition for another 10 sessions. Patients who did not achieve this improvement were offered the option of crossing over to the other active treatment. Patients initially randomized to the sham condition were randomized to 1 of the 2 active treatments after the initial review. During this second phase of study, the raters remained blind to treatment type. Patients were carefully and repeatedly instructed not to provide the raters with any information that would allow unblinding of group.

TMS TREATMENT

Repetitive TMS was administered using a Magstim Super Rapid magnetic stimulator (Magstim, Sheffield, England) and hand-held 70-mm figure 8 coils, which were interchanged to allow cooling at times during treatment sessions. Patients sat in a reclining chair with a headrest for stabilization of the head, and there was limited interaction between the patient and the physician during the rTMS sessions. Prior to the commencement of the first rTMS treatment session, single-pulse TMS was used to measure the resting motor threshold (RMT) for the abductor pollicis brevis muscle in both hands using electromyographic recordings using the standard method of limits.^{2,8} At all times, the coil was held tangential to the scalp, with the handle pointing back and away from the midline at 45°. The induced current flow was posterior to anterior in the cortex perpendicular to the central sulcus. The site of stimulation during the TMS sessions was defined by a point 5 cm anterior to that required for maximum stimulation of the abductor pollicis brevis.

In LFR-TMS, five 60-second trains were applied at 1 Hz and at 100% of RMT. There was a 1-minute intertrain interval (total of 300 stimuli per session). In HFL-TMS, twenty 5-second trains were applied at 10 Hz and at 100% of RMT. There was a 25-second intertrain interval (total of 1000 stimuli per session). Patients allocated to the sham condition were further randomized to receive sham stimulation on the left or right side. Sham stimulation was applied with stimulation parameters identical to those for active treatment on the side allocated but with the coil angled at 45° off the head. The medial wing of the coil was resting on the scalp. This produced some degree of scalp sensation in most participants but has been shown to produce a limited degree of intracortical activity.^{9,10} At the completion of each phase of treatment, patients were questioned about whether they thought they had received active or sham stimulation. As previous studies have shown minimal fluctuation of the RMT across treatment sessions,¹¹ this was not adjusted on a daily basis.

CLINICAL RATINGS

The primary outcome measure for the study was the MADRS score.¹² All patients were assessed at baseline and at each 10-session review via the MADRS, the Beck Depression Inventory,¹³ the Brief Psychiatric Rating Scale,⁷ and the CORE rating of psychomotor disturbance (CORE).¹⁴ Ratings at follow-up were also made using the Clinical Global Impressions scale.¹⁵ Handedness was recorded using the Edinburgh Handedness Inventory.¹⁶ In addition, a group of cognitive tasks were administered at baseline and at the end of the study. The cognitive measures were not administered at each review to minimize practice effects and because the primary reason for their inclusion was to assess the cognitive implication of the treatment sessions, including the accumulation of stimulation across study phases. The battery was designed to focus on memory effects and frontally mediated executive functions. The tasks included the Personal Semantic Memory Schedule, the Autobiographical Memory Schedule,¹⁷ the Wechsler Adult Intelligence Scale-Revised (Block Design test, verbal paired associates recall and recognition subscale, and digit span subscale),¹⁸ Tower of London,¹⁹ and the Controlled Oral Word Association Test.²⁰

DATA ANALYSIS

One-way analysis of variance models and χ^2 tests were used to investigate differences among the 3 groups on demographic and baseline clinical variables. The primary outcome analysis was conducted on baseline to 2-week psychopathologic change scores, calculated by subtraction of the 2-week scores from the

baseline scores. Differences between the groups were calculated using analysis of variance models for each psychopathologic variable. Post hoc tests (least squares difference) were only calculated where a significant effect was found in the analysis of variance model. Secondary analyses included calculation of differences in dichotomous outcome measures (percentage response criteria) using χ^2 tests. Repeated-measures general linear models were calculated to study the effects of rTMS over multiple times (baseline to 4 weeks). The primary analysis of change in MADRS score was also recalculated using medication treatments (use of antidepressants, mood stabilizers, and antipsychotics) as covariates.

Linear regression models were calculated to test for predictors of clinical response in the 40 patients receiving active treatment. The change in MADRS score in the double-blind phase was entered as the dependent variable. The following were entered into the models as independent variables: baseline depression severity (MADRS score), psychotic symptoms (Brief Psychiatric Rating Scale thought disturbance and hostile-suspiciousness subscale scores), measures of melancholia (CORE total score and noninteractiveness, retardation, and agitation subscale scores), demographic variables (age, sex, age at illness onset, and number of previous episodes), and medication treatment status (antidepressants, mood stabilizers, and antipsychotics).

The cognitive data were analyzed using paired *t* tests comparing the baseline and end study scores. Separate analyses were conducted for the group as a whole and for patients who received HFL-TMS only, LFR-TMS only, or both active treatment conditions. Pearson correlation coefficients were calculated between change in MADRS and Beck Depression Inventory scores and change in cognitive variables for the equivalent times.

All procedures were 2-tailed, and significance was set at $\alpha = .05$, except during the correlations in which the Bonferroni procedure was used to correct for multiple comparisons. All statistical analyses were conducted using statistical software (SPSS for Windows 10.0; SPSS Inc, Chicago, Ill).

RESULTS

PATIENTS

Baseline clinical characteristics are summarized in Table 1. There were no statistically significant baseline differences among the groups. All patients who entered the study completed the double-blind randomized phase.

TREATMENT EFFICACY

Double-blind Phase: Baseline to Week 2

There was a reduction in mean \pm SD MADRS scores in the 2 active treatment groups (HFL-TMS: 13.5% \pm 16.7%; LFR-TMS: 15.0% \pm 14.1%) and minimal change in the sham group (0.76% \pm 16.2%) (**Table 2** and **Figure 2**). There was an overall effect of group ($F_{56,2} = 6.2$; $P = .004$), with significant differences between the HFL-TMS and sham groups and between the LFR-TMS and sham groups ($P < .005$ for both). There was no significant difference between the 2 treatment groups ($P = .91$). There was also a significant difference among the groups for change in Beck Depression Inventory scores ($F_{56,2} = 5.1$; $P = .03$). On post hoc tests there was a trend toward a significant difference between the LFR-TMS and sham groups ($P = .08$) but not between the HFL-TMS and sham groups ($P = .16$). There was no significant difference between the 2 treat-

Table 2. Baseline and Week 2 Scores for Each Outcome Measure in 60 Patients With Major Depression*

Measure	HFL-TMS Group (n = 20)		LFR-TMS Group (n = 20)		Sham Group (n = 20)		F	P Value	η^2
	Baseline	Week 2	Baseline	Week 2	Baseline	Weeks 2			
MADRS score	36.1 ± 7.5	30.8 ± 7.5	37.7 ± 8.4	32.2 ± 9.0	35.7 ± 8.1	35.4 ± 7.5	6.2	.004	0.18
BDI score	33.1 ± 12.1	26.7 ± 11.9	35.0 ± 9.2	27.2 ± 10.8	32.3 ± 9.1	29.0 ± 8.7	5.1	.03	0.08
BPRS score	20.8 ± 6.3	18.8 ± 6.3	22.1 ± 6.8	19.2 ± 5.9	21.4 ± 6.0	20.1 ± 5.2	1.0	.38	0.03
CORE score	8.6 ± 3.6	6.6 ± 3.1	8.7 ± 3.3	6.6 ± 3.5	8.8 ± 5.5	7.6 ± 4.2	1.7	.499	0.02
GAF scale score	43.0 ± 6.8	45.2 ± 7.1	43.5 ± 9.9	46.3 ± 8.5	42.7 ± 7.1	42.5 ± 6.8	2.6	.08	0.08

Abbreviations: BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; HFL-TMS, high-frequency left-sided transcranial magnetic stimulation; LFR-TMS, low-frequency right-sided TMS; MADRS, Montgomery-Åsberg Depression Rating Scale.

*Data are given as mean ± SD. F scores, P values, and effect sizes (η^2) are presented for analysis of variance models for each variable.

ment groups ($P=.61$). There was an increase in Global Assessment of Functioning scale scores for the 2 active treatment groups but not for the sham group (overall: $F_{56,2}=2.6$; $P=.08$; LFR-TMS vs sham: $P=.03$; and HFL-TMS vs sham: $P=.09$). There was no significant difference among the groups for changes in Brief Psychiatric Rating Scale and CORE rating measures. There was a significant overall difference among the 3 groups on the Clinical Global Impressions scale score at 2 weeks ($F_{57,2}=4.9$; $P=.01$). Scores on the Clinical Global Impressions scale were significantly lower in the LFR-TMS group than in the sham group ($P=.005$) and in the HFL-TMS group than in the sham group ($P=.01$).

The primary efficacy analysis was repeated using models controlling for age, sex, diagnosis, baseline MADRS score, and treatment with any antidepressant, mood stabilizing, or antipsychotic medication as covariates. The effect of group remained significant ($F_{2,56}=4.8$; $P=.01$), as did the post hoc differences between the HFL-TMS and sham groups ($P=.02$) and between the LFR-TMS and sham groups ($P=.006$). There were no other statistically significant effects. Concurrent use of antidepressant medication had a positive effect on outcome, but this was not significant ($F=1.49$; $P=.23$). There was an effect of diagnosis (greater improvement for patients with a diagnosis of unipolar depression), but this did not reach significance ($F=2.8$; $P=.01$).

A separate analysis was conducted of the number of patients who met the initial response criteria of a greater than 20% reduction in MADRS score by 2 weeks. Eight patients in the HFL-TMS group, 7 in the LFR-TMS group, and 2 in the sham group met these criteria. This difference approached significance ($\chi^2=5.1$; $P=.07$). Of the 17 patients who met the response criteria, 7 were concurrently receiving a mood stabilizer. This proportion was not significantly different from the proportion not receiving a mood stabilizer ($\chi^2=2.5$; $P=.11$). Of the 3 patients reporting psychotic symptoms at baseline, 2 were randomized to LFR-TMS, and 1 met the response criteria. The third patient responded to LFR-TMS in the single-blind phase after initially receiving sham stimulation. Only 1 patient (LFR-TMS) achieved a 50% improvement in MADRS score during the initial 2 weeks.

Baseline to Week 4

All of the patients who met the initial response criteria continued to receive single-blind treatment for another 2 weeks. For the group as a whole, after 4 weeks of treatment, the mean ± SD percentage change in the MADRS score from baseline was 48.0% ± 17.9% (range, 15.1%–87.5%) (Figure 2). There was a greater improvement in the LFR-TMS group compared with the HFL-TMS group from week 2 to week 4 (mean ± SD change in MADRS score: HFL-TMS, 14.1% ± 21.5%; LFR-TMS, 38.8% ± 19.7%; $t_{13}=-2.12$; $P=.05$). A repeated-measures general linear model was calculated using time (baseline, week 2, and week 4) as the repeated measure and group (HFL-TMS and LFR-TMS) as the between-patients factor. There was a significant overall effect of time ($F_{12,2}=68.9$; $P<.001$; $\eta^2=0.92$) but no time × group interaction ($F_{12,2}=0.29$; $P=.75$). Seven of these patients had a reduction in the MADRS score of greater than 50% by the end of the 4 weeks (4 in the LFR-TMS group and 3 in the HFL-TMS group).

Sham Group

Eleven patients who received sham treatment initially were subsequently randomized to active treatment and received at least 10 sessions of TMS (7 received HFL-TMS and 4 received LFR-TMS) (Figure 2). Change scores from the commencement of active treatment until the end of treatment were calculated and compared among the groups. There was a mean ± SD improvement of 15.0 ± 10.4 points (45.3%) in MADRS scores in the LFR-TMS group and a change of 0.3 ± 4.1 points (1.3%) in the HFL-TMS group ($t_9=-3.4$; $P<.005$). Two patients in the LFR-TMS group achieved a greater than 50% reduction in the MADRS score.

Crossover After Failed Active Treatment

After the initial 2 weeks, 17 patients who initially received active treatment and were classified as nonresponders progressed to receive the other active treatment condition (10 right-sided nonresponders and 7 left-sided nonresponders). For the second phase of treat-

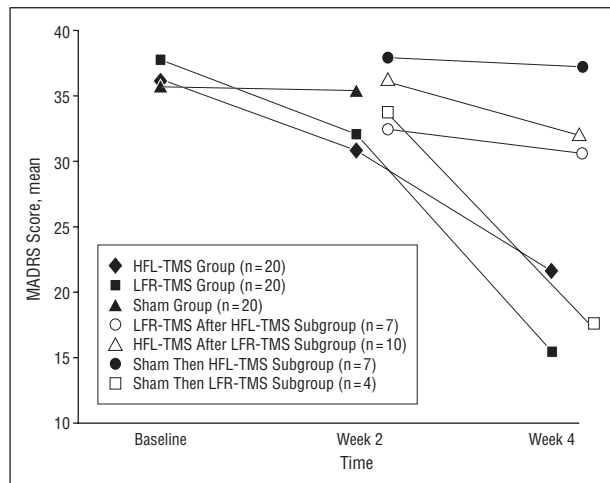


Figure 2. Mean Montgomery-Åsberg Depression Rating Scale (MADRS) scores across all phases of the study. A significant difference in response is present between the 2 active treatment groups and the sham group in the double-blind phase. Patients in both active groups who continued with treatment continued to achieve significant therapeutic responses. There was limited improvement in most patients in the crossover phases. HFL-TMS indicates high-frequency left-sided transcranial magnetic stimulation; LFR-TMS, low-frequency right-sided TMS.

ment, analyzed using a repeated-measures general linear model, there was a significant effect of time ($F_{1,15}=4.4$; $P=.05$) but no effect of group \times time ($F_{1,15}=0.89$; $P=.36$), with both groups showing a small but significant effect. However, significant improvement in this phase was limited to a few patients. Three patients in the HFL-TMS after LFR-TMS group and no patients in the LFR-TMS after HFL-TMS group achieved a greater than 50% reduction in the MADRS score.

PREDICTION OF RESPONSE

Several linear regression models were calculated using improvement in MADRS score in the double-blind phase as the dependent variable. The CORE agitation score was the only significant predictor (mean \pm SE parameter estimate, 1.426 ± 0.46 ; $P=.004$), predicting 20% of the variance. A greater degree of baseline agitation was associated with better response. When these models were calculated separately for response to the 2 active treatments, the CORE agitation score predicted response for the LFR-TMS group (mean \pm SE parameter estimate, 1.426 ± 0.53 ; $P=.01$; $r^2=0.29$) but not for the HFL-TMS group.

ADVERSE EFFECTS

After phase 1, 7 (11%) of the 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. Although there was no difference in the incidence of these adverse effects ($P=.08$), patients in the HFL-TMS group seemed to report more discomfort during the procedure itself. Only 1 patient (in the HFL-TMS group) reported persistence of the headache for longer than 1 hour. Two patients (1 in each group) reported transient dizziness for a short time after treatment.

No patients withdrew because of adverse effects during the double-blind phase. One patient, originally ran-

domized to the sham condition, withdrew after 1 session of HFL-TMS treatment in the single-blind phase of the study owing to site pain. One patient with bipolar disorder, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of the trial after ceasing treatment with valproate sodium at the end of the TMS trial independent of his treating clinicians. The episode resolved with reinstatement of the medication.

COGNITIVE ASSESSMENTS

No deterioration in performance was found in any cognitive measures in the group as a whole or in the analyses of patients who received HFL-TMS only, LFR-TMS only, or both active treatment conditions. Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on the verbal paired associates ($t_{50}=-7.3$; $P<.001$), verbal fluency ($t_{48}=-3.8$; $P<.001$), and digit span forwards ($t_{48}=-1.8$; $P=.003$) subscales; the Personal Semantic Memory Schedule ($t_{50}=-2.4$; $P=.02$); and the Autobiographical Memory Schedule ($t_{50}=-1.9$; $P=.05$). A similar pattern of improvements was seen for each of the treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). Changes in performance on the cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across the same times.

MAINTENANCE OF BLIND

Twenty-nine patients (48%) correctly guessed their type of treatment before disclosure, 17 (42%) of 40 in the active treatment group ($\chi^2=0.90$; $P=.34$) and 12 (60%) of 20 in the sham group ($\chi^2=0.80$; $P=.37$). The degree of response was the predominant reason given for the guess.

COMMENT

The results of this study indicate that HFL-TMS and LFR-TMS have clinical efficacy in patients with TRD. There did not seem to be a significant difference in efficacy between the 2 active TMS treatments. The clinical improvements achieved with 2 weeks of rTMS are clinically modest and occur only in a subset of patients, although further improvement occurs in most patients with additional treatment. A higher score on the CORE agitation scale was the only variable associated with greater clinical improvement, specifically with response to LFR-TMS. Concurrent anticonvulsant therapy was not associated with clinical response. Repetitive TMS was generally well tolerated and was not associated with any major adverse events.

These results add to the evidence supporting the antidepressant efficacy of HFL-TMS in TRD. This efficacy has been established in a variety of sham-controlled clinical studies^{2,5,11} and has been supported by findings from several meta-analyses.²¹⁻²⁴ Our analysis indicates that greater response accumulates with a longer period of stimulation than the frequently applied 2 weeks of treatment. It seems likely that this relates to the accumulated dose of TMS achieved over time. There is a trend

in published studies for improved response rates when rTMS has been applied at a higher intensity or with a higher number of pulses per day.²⁵ The number of stimuli applied in the HFL-TMS condition in this study (10 000 stimuli during 10 sessions) was significantly higher than that applied in several previous studies with results of limited clinical significance (1250 stimuli in the study by Padberg et al⁵ and 4000 stimuli in the study by Berman et al⁴) but less than that in the study by George et al¹¹ (16 000 stimuli), in which the clinically relevant response rate was higher than we found. It is also possible, although it seems less likely, that improved responses during the 4-week period do not relate to accumulated “dose” but just to a longer duration of intervention. However, the differing time course of response in depression to medication and electroconvulsive therapy would suggest that the rapidity of clinical response is unlikely to be a property of the illness process itself.

To our knowledge, this study is the first to demonstrate the antidepressant efficacy of LFR-TMS in patients with TRD, although the overall response rate was lower than that seen where this treatment condition has been applied in medication-responsive patients despite the application of a greater number of pulses than in previous studies (300 vs 100–120 pulses).^{6,26,27} As rTMS is most likely to be of clinical utility in medication-nonresponsive patients, demonstration of its clinical efficacy is crucial in this patient group. In addition to the clinical differences between the patients, it is possible that the smaller effect size compared with that in the study by Klein et al⁶ relates to differences in methods of administration. In that study, TMS was applied with a 9-cm-diameter round TMS coil, which produces a less focused area of stimulation compared with the coil used in the present study. This may be of benefit given recognized limitations in stimulation site localization,²⁸ although the results of our study give more assurance that the antidepressant effects have been produced via right prefrontal cortex stimulation.

The antidepressant effects of LFR-TMS were of similar magnitude as those seen with HFL-TMS despite the LFR-TMS condition consisting of considerably fewer pulses per session (300 vs 1000 pulses). The number of 1-Hz pulses was chosen to equalize the treatment times and because there was limited information regarding the safety of a greater number of 1-Hz pulses at the time of inception of the study. It is possible that an equal number of pulses between conditions may have produced results in favor of the 1-Hz condition. Although the mechanism of action of rTMS is not clear, it has been suggested that it relates to synaptic changes such as long-term potentiation and long-term depression.²⁹ Results of animal studies of electrically induced long-term potentiation/long-term depression and of human studies of motor cortical responses to rTMS indicate that these effects depend on the total number of pulses delivered in any conditioning regimen (eg, see Trepel and Racine³⁰ and Maeda et al³¹).

The potential advantage of low-frequency stimulation has implications for the development of clinical rTMS protocols, as low-frequency stimulation has several advantages. First, as the potential for seizure induction is

directly related to increasing frequency, LFR-TMS is associated with a significantly lower risk of seizure induction. In fact, 1-Hz stimulation may have some antiseizure properties.^{32,33} Therefore, low-frequency stimulation would be preferred in patients with any risk factors for seizure induction or with substantial medical comorbidity. Second, although not clearly illustrated by study data, our definite clinical impression was that patients better tolerate LFR-TMS than HFL-TMS, which produces a greater degree of local scalp discomfort during stimulation. Low-frequency stimulation may prove to be the best “universal” first choice if predictors of response to one or another therapy cannot be established. High-frequency left-sided TMS would be an option for patients who do not respond to LFR-TMS. Because there is some suggestion that slow left-sided stimulation may have antidepressant effects,⁵ a direct comparison of low-frequency left- and right-sided stimulation seems timely. The relationship of clinical variables, such as agitation, as seen in this study, to response to differing stimulation types also requires further assessment.

Several limitations of this study require consideration. First, although the sample size was large enough to distinguish between active and sham stimulation, it is possible that the lack of a difference between the 2 active conditions is a type II error. Although there was some variation in responses in the crossover phases, the equivalence of the effects in the double-blind phase of the study suggests that a very large sample size will be required to detect real differences between these 2 treatments if they exist. Second, although the clinical changes that occurred during the extension phase of the study in patients who continued active treatment were statistically significant and clinically meaningful, interpretation of this phase of the study is limited, as the patients were aware of their treatment type. Considerable efforts were made to ensure that the raters remained blind to the treatment condition during this period, but this does not exclude placebo effects. We also have limited capacity to draw conclusions about the value of swapping between treatments in patients who did not respond to one stimulation type. However, these data suggest that there is potential value in a trial of HFL-TMS after failed LFR-TMS, but perhaps less value in the opposite. This supports the idea of offering LFR-TMS as a first-line stimulation type with crossover to HFL-TMS in nonresponders.

Several medication issues are worthy of comment. First, most patients were receiving some form of antidepressant medication during the trial. However, we were careful to ensure that patients had been taking their current medication for several months and were taking a stable dose for at least 1 month before commencement of rTMS. We also excluded patients who seemed to be improving in clinical state in response to the medication, as judged by the patient or the treating clinician. Presumably, because of this careful screening, there was no effect of medication treatment on outcome. Second, the patient group as a whole had tried many antidepressant medications before the trial. This would indicate a high degree of treatment resistance and may explain the low sham response rate in the double-blind phase of the trial. Given the low rate of successful guessing, it is un-

likely that the low sham response rate, and the overall results of this phase, were biased by unblinding of the patients.

In conclusion, our results support the efficacy of HFL-TMS and LFR-TMS in the treatment of TRD and suggest the equivalence of these treatments. Treatment for at least 4 weeks seems to be necessary for clinically meaningful benefits to be achieved with the parameters applied in this study. Further evaluation of whether alterations in stimulation parameters can increase the response rate or the rapidity of response to rTMS is required. Treatment with LFR-TMS may prove to be an appropriate initial rTMS strategy in depression taking into account safety, tolerability, and efficacy considerations.

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