A Randomized Controlled Comparison of Electroconvulsive Therapy and Repetitive Transcranial Magnetic Stimulation in Severe and Resistant Nonpsychotic Major Depression

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Background: *Studies published over the past few years suggest that transcranial magnetic stimulation (TMS) may have significant antidepressant actions. In a previous report, we compared electroconvulsive therapy (ECT) and repetitive TMS (rTMS) and found ECT to be superior for psychotic major depression (MD); however, ECT and rTMS had similar results in nonpsychotic MD. We now report on a controlled randomized comparison of ECT and rTMS in patients with nonpsychotic MD.*

Methods: *Forty patients with nonpsychotic MD referred for ECT were included. Electroconvulsive therapy was performed according to established protocols. Repetitive TMS was performed over the left dorsolateral prefrontal cortex at 90% motor threshold. Patients were treated with 20 sessions (five times per week for 4 weeks) of 10-Hz treatments (1200 pulses per treatment-day) at 90% motor threshold. Response to treatment was defined as a decrease of at least 50% in the Hamilton Rating Scale for Depression (HRSD) score, with a final HRSD equal or less than 10 points and a final Global Assessment of Function Scale rating of 60 or more points.*

Results: *The overall response rate was 58% (23 out of 40 patients responded to treatment). In the ECT group, 12 responded and eight did not; in the rTMS group, 11 responded and nine did not ($\chi^2 = .10$, ns). Thus, patients responded as well to either ECT or rTMS.*

Conclusions: *This study adds to the growing literature supporting an antidepressant effect for rTMS. This study is particularly relevant because it suggests that rTMS and ECT reach similar results in nonpsychotic major depressive disorder.* Biol Psychiatry 2003;53:324–331 © *2003 Society of Biological Psychiatry*

Key Words: Major depressive disorder, repetitive transcranial magnetic stimulation, transcranial magnetic stimulation, electroconvulsive therapy, treatment

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Introduction

Transcranial magnetic stimulation (TMS) was introduced by Barker et al (1985) as a technique for noninvasively and almost painlessly stimulating the central nervous system. Soon after its introduction, and especially after the development of repetitive TMS (rTMS), studies concerning the potential antidepressant effects of TMS and rTMS began to appear in the literature (George et al 1999). Seminal studies by Pascual Leone and colleagues and George and colleagues describing the antidepressant effects of rTMS in controlled studies of patients with major depression (MD) created significant enthusiasm among clinicians managing these difficult-to-treat patients (George et al 1995, 1997; Pascual-Leone et al 1996).

Over the following years, a number of important studies were published, some of them supporting the antidepressant effects of TMS and rTMS (Epstein et al 1998; Figiel et al 1998; Garcia-Toro et al 2001; George et al 2000; Grunhaus et al 2000; Janicak et al 2002; Menkes et al 1999; Pascual-Leone et al 1996; Pridmore et al 2000) and others not finding it different from placebo, or as having at best mild antidepressant effects (Berman et al 2000; George et al 1997; Loo et al 1999; Padberg 1999). Several recent comprehensive reviews have discussed the issue of the antidepressant effects of TMS and rTMS extensively (Burt et al 2002; Pridmore et al 2001). Sackeim (2000), in a recently published editorial, concluded that "rTMS (to the left DLPFC) exerts antidepressant effects over and beyond those of placebo contributions." Nonetheless, Sackeim questioned whether enough evidence has accumulated to suggest clinical utility for rTMS. He proposed two directions for research to clarify this question: one, to attempt to identify individual differences in patients that are predictive of response, and two, to optimize the parameters for TMS delivery.

In a study from our group (Grunhaus et al 2000), we compared the effects of electroconvulsive therapy (ECT)

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and rTMS on a population of severely depressed patients referred for ECT. Patients were treated for up to 20 days with rTMS. We found that ECT was significantly more effective for patients with psychotic MD; however, in patients with nonpsychotic MD, ECT and rTMS were equally effective. We believe this to be a significant finding because no other antidepressant treatment has similar efficacy to ECT in severe depression. Our conclusions were limited by the facts that raters were not blind to treatment modality and patients in the ECT group were permitted to continue psychotropic medications during the ECT course, whereas patients in the rTMS group were allowed lorazepam only.

To attempt to replicate our findings, we recruited treatment-resistant, severely depressed patients with nonpsychotic MD who had been referred to us for ECT. These patients were randomly assigned to either ECT or rTMS groups. We now report the results of this study.

Methods and Materials

Patients

This study was performed at the Psychiatry Division at the Sheba Medical Center, Tel Hashomer, Israel. All protocols were approved by the local Committee for Research on Human Subjects and by the Ministry of Health. All patients had been referred for ECT by their treating clinician after having failed at least one course of antidepressant medications (at adequate levels and for at least 4 weeks of treatment). We included both inpatients and outpatients in the study. Patients signed informed consent forms for participation in research. The consent form for rTMS describes the study and its potential main side effects; it emphasizes the experimental nature of the procedure and that it is being compared with ECT because of the potential for clinical efficacy with fewer side effects. Patients in the ECT group had to sign an additional consent form for ECT.

Inclusion criteria for the study were 1) a diagnosis of MD (unipolar) according to DSM-IV criteria. Diagnosis was reached following detailed and semi-structured clinical interviews by senior clinicians (LG, SS, PND); 2) a score of 18 or more in the 17-item Hamilton Rating Scale for Depression (HRSD); 3) not meeting any of the exclusion criteria stipulated in the safety guidelines for TMS and rTMS (Wasserman 1998); 4) being over 18 years of age; and 5) that the MD was not secondary to a general medical condition or substance abuse. Patients with additional Axis I diagnoses, including MD with psychosis, were excluded from the study.

Patients were evaluated at baseline, 2 weeks into the treatment, and at the end of treatment with a variety of clinical ratings that included the 17-item HRSD, the Brief Psychiatric Rating Scale (BPRS), the Global Assessment of Function Scale (GAF), the Global Depression Scale (GDR), the Pittsburgh Sleep Quality Index (PSQI) and the Mini-Mental State Examination (MMSE). Adequacy of antidepressant treatment was evaluated with the Michigan Adequacy of Treatment Scale (MATS; Grunhaus and Remen 1993). The MATS reviews all treatments received by the patient during the current episode (doses and length of time on the medication). A numerical score is then derived for each treatment, higher scores indicating more complete trials. The final rating for the rTMS group was obtained after 20 treatments, whereas for the ECT the final rating was obtained when the clinician in charge of the patient judged that remission was achieved or that no further improvement was expected. Patients were assigned to the rTMS or ECT groups based on a previously defined random list. Ratings were performed by trained research assistants, blind to treatment modality. This was achieved by hiring staff that did not regularly work with the program. All patients had to undergo a thorough medical, psychiatric, and laboratory evaluation before being included in the study. Patients in both groups were progressively withdrawn from psychotropic medications. The tapering process was finalized in all cases within 3 days of starting the study. During the study the only medication allowed, to both groups of patients, was lorazepam up to 3 mg/day. Occasionally a patient was allowed to take brotizolam, a short-acting benzodiazepine, for sleep induction. Patients in the both groups were required to delay the intake of the first daily dose of lorazepam until after the rTMS or ECT treatment for that day.

Demographic and baseline clinical data are presented in Table 1. Ratings for most demographic and clinical variables were similar in both groups; however, ratings for the BPRS and the GAF were significantly worse in the ECT-treated group. This difference probably arises from the higher proportion of older patients and inpatients in the ECT group.

rTMS Methods

A trained psychiatrist (LG, PND) delivered rTMS using a Magstim Rapid instrument (Magstim Corporation, Sheffield, England) using a 70-mm wing span figure-eight coil cooled in ice. Patients were seated in a comfortable chair and wore a swim cap and ear plugs. Medications taken during the previous day were carefully noted. Each patient was instructed before the rTMS course was initiated that interactions between the treatment team and the patients would be limited during this period to simple behavioral recommendations. Motor threshold (MT) was determined in all individuals following the methods described by Rossini and Rossi (1998). Briefly, mildly suprathreshold stimulations were administered over the left motor cortex to determine the optimal area for stimulation of the abductor pollicis brevis (APB) muscle (seen as the most potent muscular twitch or the most intense motor evoked potential response). The output of the machine was decreased by 2% each time until the least amount of machine power that induced a 50-μV deflection or a visible twitch in 5 out of 10 trials over the cortical area controlling the contralateral APB was identified. Surface electrodes were attached over the APB and first dorsal interossi areas. Electromyographic responses were measured with MacLab and bioamplifier system equipment (AD Instruments, Pty, Ltd, Oxfordshire, UK). Motor evoked potentials were recorded and stored for later analysis in a MacIntosh computer (Apple Computer, Cupertino, CA) using the SCOPE MacLab software. Treatments were administered five times per week for 4 weeks (a total of 20 rTMS

Table 1. Demographics and Baseline Assessments for ECT and rTMS Groups

	ECT Group (n = 20)	rTMS Group (n = 20)	t	Confidence Interval	χ^2	p
Age (y)	61.4 ± 16.6	57.6 ± 13.7	0.8	(−5.9, 13.6)		ns
Age Group (<65/≥65)	8/12	13/7			2.5	ns
Duration of Episodes (mo)	10.35 ± 11.5	16.6 ± 17.5	−1.34	(−15.83, 3.18)		ns
HRSD	25.5 ± 5.9	24.4 ± 3.9	.72	(−2.0, 4.3)		ns
BPRS	37.0 ± 5.9	33.4 ± 4.6	2.1	(.24, 7.0)		.036
GAS	39.8 ± 9.3	48.9 ± 10.8	−2.8	(−15.6, −2.6)		.007
GDR	2.5 ± .6	2.4 ± .5	.85	(−.2, .5)		ns
MMSE	25.8 ± 3.4[a]	27.8 ± 3.0	−1.8	(−4.0, .1)		ns
PSQI	12.2 ± 4.5	10.4 ± 4.6	1.2	(−1.0, 4.7)		ns
Gender (F/M)	15/5	14/6			.12	ns
MATS (≤1/≥2)	8/12	6/13			.3	ns
Previous ECT (no/yes)	12/8	15/5			1.0	ns
Axis II (no/yes)	15/5	13/7			.47	ns
Inpatient (no/yes)	4/16	9/11			2.8	ns

[a] n = 19

Data are mean ± SD unless otherwise noted. ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; HRSD, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; GAS, Global Assessment of Function Scale; GDR, Global Depression Scale; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; F, female; M, male; MATS, Michigan Adequacy of Treatment Scale.

treatments) over the left dorsolateral prefrontal cortex (LDPFC). The site for stimulation was placed 5 cm anterior to, and in a parasagital plane to the site of maximal APB stimulation. The figure-eight coil, with a 70-mm wing diameter, was held by hand and kept flat over the scalp, rotated at a 45 degree angle from the midline and with the handle to the back of the head. Stimulation was done at 10 Hz and 90% MT, with a total of 1200 pulses each day (20 6-sec trains with a 30-sec interval between the trains). Patients received 24,000 magnetic pulses over the rTMS course. Patients who did not respond to rTMS were offered a course of ECT.

ECT Methods

Electroconvulsive therapy was administered following protocols approved at the Sheba Medical Center. These protocols follow the guidelines of the American Psychiatric Association. All patients signed an informed consent form for ECT after receiving thorough explanations of the procedure. All patients underwent a complete medical and psychiatric examination. Additional consultations were performed depending on clinical findings. All patients were fasting before ECT. Electroconvulsive therapy was performed in a specialized ECT suite. We used the brief-pulse MECTA Spectrum machine (MECTA Corporation, Lake Oswego, OR), British mode. The Spectrum machine at our disposal is built according to British standards and delivers double the amount of charge delivered by the average U.S. equipment (1164 millicoulombs vs. 582 millicoulombs), thus the upper limits of electrical stimulation provided in this study are larger than those available to U.S. clinicians. All patients received 100% oxygenation during the procedure. Patients received 1 mg/kg methohexital and .75–1 mg/kg succinylcholine. During the first ECT treatment, titration of electrical charge was performed in all cases following the method of limits. Additional treatments were performed at 2.5-times-threshold charge. Seizure duration was assessed both clinically and with electroencephalogram (EEG) monitoring. Charge was increased by 10%–20% whenever motor seizure duration decreased below 25 sec. All patients started with right unilateral nondominant electrode placement and were switched to bilateral electrode placement if after 6 ECT treatments a decrease of at least 30% in the HRSD was not observed. Treatments with ECT were continued until the treating physician considered that a therapeutic response had been obtained or that no further therapeutic benefit was to be expected. Patients included in this study were required to have had at least 6 ECT treatments, unless the course was suspended due to an early therapeutic response.

Thirteen patients were treated unilaterally, and seven patients were treated bilaterally. Response rates among patients treated with unilateral placement was not significantly different from that of patients treated with bilateral electrode placement (χ^2 = 1.3, ns). The seizure threshold in responders to ECT (77.5 ± 60.2 millicoulombs) was similar to that of nonresponders (84.3 ± 28.3 millicoulombs; t = .3, 95% confidence interval [CI] −41.4-55.4, ns). The mean electrical charge (not including the first, titration, treatment) was 328.8 ± 155.5 millicoulombs in responders and 481.6 ± 293.8 in nonresponders (t = 1.5, CI −65.8-371.4, ns). The electrical charge during the last ECT treatment was 561.8 ± 282.9 millicoulombs in responders and 676.6 ± 385.6 millicoulombs in nonresponders to ECT (t = .3, CI −298.7-393.7, ns). Mean clinical seizure length over all the treatments was 32.4 ± 7.8 sec, whereas the mean EEG seizure recorded was 53.2 ± 18.4 sec. Patients received an average of 10.25 ± 3.1 ECT treatments. Responders received a mean of 9.6 and the nonresponders a mean of 11.25 ECT treatments. Mean seizure duration was not significantly different between those responding (clinical 31.4 ± 6.2; EEG 50.1 ± 10.1) and those not responding to ECT (clinical 33.7 ± 10; EEG 57.9 ± 26.7) (clinical t = .6, CI −5.3-9.9, ns; EEG t = .9, CI −9.8-25.5, ns). Patients switching from unilateral to bilateral treatments received a mean of five additional bilateral treatments.

Table 2. Clinical Ratings in a Group of Patients with Major Depression Treated with Either ECT or rTMS

	ECT Group			TMS Group		
	Baseline	Week 2	End of Treatment	Baseline	Week 2	End of Treatment
HRSD	25.5 ± 5.9	15.9 ± 6.6	13.2 ± 6.6	24.4 ± 3.9	14.7 ± 8.8	13.3 ± 9.2
BPRS[a]	37.0 ± 5.9	31.2 ± 6.0	28.0 ± 5.8	33.4 ± 4.6	28.8 ± 6.9	27.3 ± 7.3
GAF[a]	39.8 ± 9.3	55 ± 12.4	60.6 ± 13.5	48.9 ± 10.8	58.3 ± 17.1	62.5 ± 18.8
GDR	2.5 ± .6	1.2 ± 1.0	.85 ± .93	2.4 ± .5	1.0 ± 1.1	.9 ± 1.1
PSQI	12.2 ± 4.5	8.3 ± 3.9	8.6 ± 4.9	10.4 ± 4.6	9.9 ± 5.1	9.4 ± 5.0
MMSE	25.8 ± 3.4	26.3 ± 2.9	27.1 ± 2.5	27.8 ± 3.0	28.0 ± 2.1	28.0 ± 1.8

Data are mean ± SD.

ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; HRSD, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Function; GDR, Global Depression Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini-Mental State Exam.

[a]Performed on scales with significant baseline differences

Statistical Methods

Patients were randomized either to rTMS or ECT groups based on a computer-generated list. Our primary outcome variables were treatment response and the changes in the HRSD scores. Additional outcomes variables studied included changes in the BPRS, the GAF, the GDR, the PSQI, and the MMSE.

Response to treatment was defined using two parameters: a decrease of 50% or more or a final rating of 10 or less in the HRSD, and a final GAF rating ≥ 60. Response rate was explored with χ^2, whereas the change of scores with treatment was tested using repeated measures analysis of variance (ANOVA). In those rating scales with baseline differences between the groups (BPRS and GAF), ANOVA with repeated measures of change scores was used. Remission was defined as a final HRSD of ≤ 8. Additional statistical analysis included baseline comparisons performed with either two-sample *t* tests for continuous data or χ^2 for nominal data. The extent of the clinical response in those patients who improved with treatment was tested by comparing the final ratings in both groups. These additional analyses were performed with Student's *t* tests.

Results

The overall response rate for both groups of patients was 58% (23 out of 40 patients responded to treatment); this rate of response is similar to that reported in recent studies of ECT-treated populations (McCall et al 2000; Sackeim et al 2000). The primary outcome variable of response to treatment was tested with a χ^2; in the ECT group, 12 patients responded and eight did not respond to treatment; in the rTMS group, 11 patients responded to treatment and nine did not (χ^2 = .01, ns). Thus, patients responded equally well to either ECT or rTMS.

Clinical ratings (HRSD, BPRS, GAF, GDR, PSQI, and MMSE) at baseline, 2 weeks into treatment, and at the end of treatment are presented in Table 2. For the HRSD, GDR, PSQI, and MMSE, the ANOVA with repeated measures of absolute scores showed a significant effect of treatment but no group or interaction effect, suggesting that scores change similarly with either ECT or rTMS. Identical findings were found for the ANOVA with repeated measures of change scores (BPRS and GAF) (Table 3).

To compare the degree of the clinical response, we analyzed the final rating scale scores of those patients who responded to treatment. Results for this comparison are presented in Table 4. The final scores were similar between the groups, with the exception of the GAF in which the rTMS treated group had higher scores. Although final GAF scores were higher in the rTMS group, change scores (final score − baseline score) were similar in both groups (t:1.1, CI:-4.1, 14.5, NS). The rate of remission (final HRSD ≤ 8) was 30%, equal in both groups.

The side effects reported by the rTMS treated patients were very mild. Three patients reported mild headache responsive to paracetamol and two patients required the addition of brotizolam for sleep disturbances. The ECT-treated group was handled clinically and no special recording of side effects was done. No patient in the ECT-treated group had their course interrupted because of side effects of the treatment.

Discussion

The findings from this study support the following conclusions:

1. the clinical responses to rTMS and ECT were indistinguishable, suggesting that both treatments were effective for severe and resistant nonpsychotic MD This suggestion is supported by the findings in primary (response rate and HRSD changes) and secondary (BPRS, GAF, GDR, PSQI, and MMSE) outcome variables.
2. the extent of the clinical response, as assessed by the final ratings of the responders to treatment only, was similar in both groups The GAF was higher for the rTMS-treated patients; however, when delta scores are calculated this difference disappears.
3. the rate of remission (final HRSD ≤ 8) was 30%, equal in both groups.

In this randomized, controlled study, both ECT and rTMS were associated with a significant response to

Table 3. ANOVAs for Clinical Ratings in a Group of Patients with Major Depression Treated with Either ECT or rTMS

	Group Effect		Time Effect		Interaction	
Rating Scale	*F* (df)	*p*	*F* (df)	*p*	*F* (df)	*p*
ANOVA with Repeated Measures of Absolute Scores						
HRSD	.1 (1, 38)	ns	60.9 (2, 76)	.01	.1 (2, 76)	ns
GDR	.1 (1, 38)	ns	69.3 (2, 76)	.01	.3 (2, 76)	ns
PSQI	.02 (1, 38)	ns	5.3 (2, 76)	.01	2.5 (2, 76)	ns
MMSE	3.1 (1, 34)	ns	.9 (2, 68)	ns	.5 (2, 68)	ns
ANOVA with Repeated Measures of Change Scores[a]						
BPRS	1.9 (1, 38)	ns	3.7 (1, 38)	.05	.05 (1, 38)	ns
GAF	2.7 (1, 38)	ns	5.0 (1, 38)	.05	.3 (1, 38)	ns

ANOVA, analysis of variance; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; HRSD, Hamilton Depression Rating Scale; GDR, Global Depression Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini-Mental State Examination; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Function.

[a]Performed on scales with significant baseline differences.

treatment. The primary outcome variables (response to treatment and HRSD score changes) and all of the secondary outcome variables (BPRS, GAF, GDR, PSQI, and MMSE) demonstrated similar improvements between the groups. In all of the variables a significant effect of treatment was found, but no significant group or interaction effect was discovered. The results presented provide further support for the claim that left dorsolateral prefrontal rTMS exerts significant antidepressant effects (Epstein et al 1998; Figiel et al 1998; Garcia-Toro et al 2001; George et al 2000; Grunhaus et al 2000; Janicak et al 2002; Menkes et al 1999; Pascual-Leone et al 1996; Pridmore et al 2000), and that in patients with nonpsychotic MD these therapeutic effects are similar to those seen with ECT (Grunhaus et al 2000; Janicak et al 2002; Pridmore et al 1998). This conclusion needs to be limited to the acute effects of treatment, because reports on the long-term effects of rTMS have yet to be published. In a study by our group (Dannon et al 2002) the 6-month outcome following rTMS compares well to that seen following ECT (30% relapse rate at 6 months post-ECT or -rTMS).

The current study improves on our previous report by using a more refined standardization of rTMS methods (all patients stimulated with one rTMS paradigm), by the use of blind raters, and by limiting the amount of psychotropic medications allowed to patients. It would be preferable to perform these studies with patients being totally medication free; however, the severity of illness precludes such an option. An additional strength of this study was that we performed rTMS for up to 20 days. In most studies published so far, rTMS has been performed for just 1 or 2 weeks, and some studies have applied only 80% of MT. It is very plausible that shorter periods of stimulation or less intense paradigms of stimulation will be associated with weaker response rates. Gershon et al (in press) have performed a review of studies of rTms and found that intensity of stimulation (higher number of stimulation increased power and more treatments) is a factor in outcome. Those studies using higher-intensity schedules report more positive results. A recent report describing the effects of twice-daily TMS in Parkinson's disease supports the improved effects of a more intense paradigm (Mally and Stone 1999).

Table 4. Final Ratings for Responders Only[a]

	ECT Group (n = 12)	TMS Group (n = 11)	*t*	CI	*p*
HRSD	9.0 ± 3.8	6.8 ± 2.7	1.6	(−.6, 5.1)	ns
BPRS	24.3 ± 3.2	22.4 ± 2.2	1.5	(−.5, 4.3)	ns
GAF	69.3 ± 7.4	77.2 ± 4.1	−3.0	(−13.2, −2.5)	.006
GDR	.25 ± .45	0 ± .3	.9	(−.1, .4)	ns
PSQI	5.5 ± 3.2	8.5 ± 4.6	−1.7	(−6.4, .4)	ns
MMSE[b]	27.4 ± 2.1	28.8 ± .7	−2	(−2.8, .1)	ns

Data are mean ± SD. ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; HRSD, Hamilton Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Function; GDR, Global Depression Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini-Mental State Examination.

[a]HRSD decreased ≥50% or more from baseline or HRSD ≤ 10, and the final GAS ≥ 60.

[b]n = 11.

Six Limitations of This Study Need to be Addressed

The initial ECT energy level administered to our patients was just 2.5 times the seizure threshold. In this regard it could be argued that we used insufficient charge and therefore compromised the outcome of the ECT-treated patients. In reality, we provided energy levels similar, and even higher, than those given to the high-energy groups by Sackeim et al (2000) and McCall et al (2000). For example, the mean electrical charge reported by Sackeim in his high-dosage group was 348.5 millicoulombs, and that reported by McCall in his fixed-dose group was 339 millicoulombs. In our sample, the nonresponders to ECT received an average charge of 481.6 millicoulombs, actually higher than that administered in either the Sackeim or McCall studies. These comparisons, together with the ECT parameters previously described, suggest that patients in our study, especially the nonresponders, received adequate ECT courses.

Although our study was randomized and controlled, we did not have a masked or sham comparison group. Thus, the effects of rTMS could conceivably be secondary to placebo effects or to interactions between the treating psychiatrist and the patient. A masked or sham comparison was felt to be unethical for these patients because of the severe, long, and resistant nature of their illness. The recent decision by the World Medical Association (2000) severely limiting the use of placebo treatment in patients with significant illness bears directly on this decision. It could be argued that interactions between the treating physician and the patient may have a significant psychological effect on patients and therefore mask the effects of rTMS treatment itself. This cannot be solved without a sham comparison group; however, it could also be argued that ECT itself, with all the instrumentation involved in the treatment and the medical attention received by the patients, also has a significant placebo effect. This is no reason however, to require that all ECT studies have a sham comparison group. To limit to some extent the psychological influences of the treatment team in this study, the team was instructed to limit interactions with the patients during the treatments. In general, the issue of a "true" sham rTMS has yet to be finalized (Bohning et al 1997; Lisanby and Sackein 2000; Loo et al 2000). Sham positioning of rTMS coils (placing the rTMS coil wings at a 45 or 90 degree angle) have been found to create excitability changes at cortical levels. New coils specifically developed to mask the delivery of the magnetic pulse while still generating the characteristic noise of the magnetic stimulator are currently being tested.

The clinical method used for determining the location of the LDPFC, although common to all published studies, is far from ideal. Anatomical differences between patients may create positioning effects that may impact negatively on outcome. This problem may be compounded by the focal nature of the magnetic field created by the figure-eight coil. The use of a lycra swim cap may help in reproducing the area of stimulation; however, it is not a precise enough method. Using external anatomical landmarks (Krings et al 1997) or neuronavigational methods based on MRI imaging may help avoid this confounding variable in future studies (Herwig et al 2001a, 2001b).

The matching of the sample was appropriate on a number of variables, such as age, inpatient/outpatient status, and HRSD ratings; however, the BPRS and GAF scores favored patients in the rTMS group. Future studies, particularly those in severely ill individuals, may need to incorporate matching strategies using scores of depression, agitation/psychosis, and of functional state.

The power of stimulation used in this study was based on the determination of the MT in each individual case. Recent studies are suggesting that this method for calculating power of stimulation is inadequate, especially in elderly populations (Kozel et al 2000; McConnell et al 2001). These authors have found that the scalp-to-cortex distance increases with age, especially in frontal cortex. As a consequence, rTMS studies delivering power based on the MT only may be underpowered. Future studies will undoubtedly have to calculate power of stimulation corrected for the scalp-to-cortex ratio.

The sample size was relatively small; thus, the power of the statistics could have been insufficient. Based on the results, a univariate, two-group, repeated-measures ANOVA would only have a 5% power to detect an interaction between groups and time before and after treatment. With 20 subjects per group with very small differences in the means of the main variables, we would have required extraordinarily large samples (over 5000 patients) to demonstrate differences between the groups.

The data reported in this study adds to that of our previous report (Grunhaus et al 2000), in which we suggested a significant therapeutic effect for rTMS in severe MD. In that study we found that rTMS was as effective as ECT in patients with nonpsychotic MD. If we add the populations of nonpsychotic MD patients treated with either ECT or rTMS in both studies ($n = 61$), we do not find differences in the response rates between ECT and rTMS (responders/non responders ECT group 18/12, and rTMS group 18/13, $\chi^2 = .02$, ns). These results suggest that it is very likely that rTMS will play a significant role in the treatment of patients with severe MD in the future. Pridmore et al (2000) and Janicak et al (2002) have also published studies comparing the effects of ECT and rTMS in patients suffering from MD and have found that both treatments have similar effects.

Electroconvulsive therapy is associated with significant and potentially irreversible cognitive effects (Lisanby et al 2000b; Sackeim et al 2000; Squire 1979, 1986). The negative cognitive effects of rTMS, on the other hand, are very mild and short lived (Loo et al 2001), although long-term studies have not been done. This difference in cognitive side effects could be an issue when deciding whether to introduce TMS and rTMS as a clinical tool. In this study, we performed only the MMSE, which is a crude measure of the cognitive effects of a treatment. The MMSE results were similar between the rTMS and ECT groups, both at baseline and following the course of treatment. Studies with more thorough cognitive batteries are needed.

Is it then time to consider TMS and rTMS as a treatment for patients with MD? In a recently published editorial, Sackeim (2000) called for additional research to be performed before TMS and rTMS is offered to patients outside of the research setting. Sackeim claims that too many questions regarding both the actual administration of TMS and its mechanisms of action remain unanswered. It is difficult to argue against the need for additional studies; however, as mentioned previously, recent clinical studies (Garcia-Toro et al 2001; George et al 2000; Grunhaus et al 2000; Janicak et al 2002; Klein et al 1999; Pridmore et al 2000) are reporting significant antidepressant effects of rTMS in severe depression, even when compared with ECT.

The beneficial clinical effects of rTMS in populations referred for ECT is quite encouraging. There is no doubt that as a treatment modality rTMS is much less invasive than ECT. The significant cognitive effects of ECT (American Psychiatric Association 2001; Lisanby et al 2000b; Sackeim et al 2000; Squire et al 1983) and the apparent lack of negative cognitive effects of rTMS (Speer et al 2001), if proven in additional studies, will also constitute an important consideration in the decision of whether to offer rTMS to clinically depressed patients.

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