Repetitive Transcranial Magnetic Stimulation Is as Effective as Electroconvulsive Therapy in the Treatment of Nondelusional Major Depressive Disorder: An Open Study

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Background: *Repetitive transcranial magnetic stimulation (rTMS), a new method for the stimulation of the central nervous system, is being proposed as a potential new treatment in patients with major depressive disorder (MDD). We tested the hypothesis that rTMS would be as effective as electroconvulsive therapy (ECT) in patients with MDD.*

Methods: *Forty patients with MDD referred for ECT were randomly assigned to either ECT or rTMS. Repetitive transcranial magnetic stimulation was performed at 90% power of the motor threshold. The stimulation frequency was 10 Hz for either 2 sec (first eight patients) or 6 sec (final 12 patients) for 20 trains. Patients were treated for up to 20 treatment days. Electroconvulsive therapy was performed according to standard protocols.*

Results: *Overall patients responded best to ECT ($\chi^2 = 3.8$, $p < .05$). Patients with MDD and psychosis responded significantly better to ECT ($\chi^2 = 9.2$, $p < .01$), whereas MDD patients without psychosis responded similarly to both treatments ($\chi^2 = 0.0$, ns). The analysis of variance with repeated measures of clinical variables for the whole sample revealed significant treatment effects for both groups; however, interaction between group and treatment was seen only for the Global Assessment of Function and the Sleep assessment. When the psychosis–nonpsychosis grouping was considered, patients with psychosis responded dramatically better to ECT in all assessments, whereas those without psychosis responded similarly to both treatments.*

Conclusions: *Overall ECT was a more potent treatment for patients with MDD, this being particularly evident in patients with MDD and psychosis; however, in patients with MDD without psychosis the effects of rTMS were similar to those of ECT. The results we report are encouraging and support an important role for rTMS in the treatment of severe MDD; however, additional blinded studies are needed to precisely define this role.* Biol Psychiatry 2000;47:314–324 © *2000 Society of Biological Psychiatry*

Key Words: TMS, ECT, MDD, transcranial magnetic stimulation, electroconvulsive therapy

Introduction

Transcranial magnetic stimulation (TMS) was introduced by Barker et al in 1985 as a new method for noninvasive and almost painless stimulation of the central nervous system (CNS). In TMS a relatively small coil is applied to the scalp while a powerful and rapidly alternating electrical current is passed through the coil wire. This produces a magnetic field that passes unimpeded through the scalp and in turn induces ionic flow in neuronal tissue (Barker 1991). Transcranial magnetic stimulation applied over the motor cortex, for example, will induce a contralateral muscular-evoked potential (MEP) that can be used for measurements of nerve conduction. Initially TMS was used in the study of nerve conduction and cognitive function (Hallet and Cohen 1989); however, antidepressant effects in patients with mood disorders were soon reported (Conca et al 1996; Grisaru et al 1994; Hoflich et al 1993; Kolbinger et al 1995).

The development of stimulators capable of delivering stimulation frequencies of up to 60 Hz (repetitive transcranial magnetic stimulation [rTMS]) increased the potential clinical applications of rTMS. Three recently published studies (Figiel et al 1998; George et al 1997; Pascual-Leone et al 1996) involving stimulation of the left dorsolateral prefrontal cortex (LDLPFC) suggest that rTMS may have significant antidepressant properties. George et al (1997) reported on a 2-week placebo-controlled crossover trial of real and sham rTMS in 12

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patients with major depressive disorder (MDD). In that study significant, albeit mild, antidepressant effects for rTMS were found. Pascual-Leone et al reported on the effects of 1 week of either sham or real rTMS over several brain regions in 17 patients with MDD with psychotic features. They found very significant effects of 1 week of rTMS applied over the LDLPFC. Figiel et al, in the largest open study published so far, reported a 42% overall response rate to rTMS in refractory depressed patients treated with rTMS.

Electroconvulsive therapy (ECT) is considered the most powerful antidepressant treatment. Patients referred for ECT usually suffer from medication resistant MDD, have delusions or hallucinations or intense suicidal thoughts, or are very ill in general (American 1990). Electroconvulsive therapy is a safe and reliable procedure; however, it requires anesthesia, muscular relaxation, and the induction of a CNS seizure, and memory disturbances may complicate its course. A treatment that could provide a similar kind of relief while being less invasive is sorely needed.

Repetitive transcranial magnetic stimulation has been advanced as a potential nonconvulsive substitute for ECT (Belmaker and Fleishman 1995; George and Wasserman 1994; Zyss 1994), although Sackeim has argued against this hypothesis (Sackeim 1994). Studies in laboratory animals, in both behavioral and biochemical models, have shown that TMS shares some of the effects of electroconvulsive shock (Ben-Sachar et al 1997; Fleischmann et al 1994, 1995, 1996, 1999; Zyss et al 1997), particularly seizure inhibition and seizure shortening. The decrease in seizure length is one of the well-established effects of ECT in humans (Abrams 1992). These similarities between the effects of electroconvulsive shock, ECT, and TMS on seizures provided the basis for our study comparing ECT and rTMS in severe depression. Our results suggest that rTMS is as effective as ECT in the treatment of patients with MDD without psychosis; however, it appears to be ineffective in patients with MDD with psychotic features.

Methods and Materials

Patients included in this study were both inpatients and outpatients with MDD referred for ECT. Reasons for referral included nonresponse to antidepressant treatment and/or the diagnosis of psychotic MDD. Patients were considered for inclusion in this protocol if they met the following criteria: age over 18; a DSM-IV diagnosis of MDD; a 17-item Hamilton Rating Scale for Depression (HRSD) score of $\geq$18; no personal or first-degree relative history of seizure; and no medical, neurological, or neurosurgical disorder that would preclude the administration of ECT or rTMS (Pascual-Leone et al 1993; Wasserman 1998). Patients with additional axis-I diagnoses were excluded from the study. All protocols were approved both by the Sheba Medical Center and the Ministry of Health Human Research Committee. Patients signed an informed consent before inclusion in the study. All patients were assessed with standard clinical, psychiatric, and laboratory examinations (complete blood count, blood chemistry, and thyroid indices). All patients were assessed at baseline with a battery of rating scales that included a DSM-IV checklist, a previous history of depressive illness form, the 17-item HRSD, the Brief Psychiatric Rating Scale (BPRS), the Global Depression Scale (GDR), the Global Assessment of Function Scale (GAS), the Pittsburgh Sleep Quality Index (PSQI), and the Mini Mental State Examination (MMS). Additionally, the adequacy of the antidepressant treatment was assessed by clinical interview with a modified Michigan Adequacy of Treatment Scale (MATS; Grunhaus and Remen 1993). Ratings were repeated weekly for 4 weeks in both groups, whereas in the ECT group they were also performed in the final week of ECT treatment. All ratings were performed by the same research assistant, who was not blind to the treatment method. Raters were trained by the senior investigator through live clinical interviews. Clinical ratings were confirmed with nurses' observations in the units or collateral reports by family members. Patients were randomly allocated to either the rTMS or the ECT group according to an *a priori* generated list.

Demographics and baseline clinical variables are described in Table 1. No differences in age, gender distribution, baseline severity, proportion of psychotic patients, length of episode, proportion of patients receiving ECT in previous episodes, and proportion of patients having been treated properly (as assessed with the MATS) were identified. Most patients were inpatients; they were equally distributed between the ECT and rTMS groups. No difference between the groups was identified at the baseline clinical ratings.

ECT Methods

Electroconvulsive therapy was performed according to approved protocols at Sheba Medical Center. Electroconvulsive therapy equipment consisted of a MECTA (Lake Oswego, OR) SR-1 machine that delivers a brief-pulse bidirectional current. In brief, the methods include:

1. Titration of electrical charge during the first ECT treatment using the methods of limits (Sackeim et al 1987, 1993)—although seizure duration was assessed both by the cuff method and electroencephalographic (EEG) measurements, we used the motor response of the leg to determine seizure length.
2. Subsequent ECT treatments were performed at 2.5 times the threshold energy and charge was titrated upward every second or third treatment to maintain a seizure length of $\geq$25 sec.
3. Electrode placement was initially right unilateral (D'Iglia position; all patients were right-handed) in all patients, and patients could be switched to bilateral electrode placement if improvement (HRSD decrease of $\leq$30%) was not observed by the sixth treatment.
4. All patients received 100% oxygenation during the procedure and anesthesia with methohexital (1 mg/kg) and muscle relaxation with succinylcholine (1 mg/kg).

Table 1. Demographics and Baseline Assessments—All Samples

	ECT group $X \pm SD$ (N = 20)	rTMS group $X \pm SD$ (N = 20)	t	CI	χ^{2a}	p
Age	63.6 ± 15.0	58.4 ± 15.7	1.1	(−4.7, 15.0)		ns
Duration of episode (months)	6.9 ± 7.9	8.3 ± 7.4	−0.6	(−6.4, 3.5)		ns
Previous episodes	2.4 ± 3.05	2.3 ± 2.85	0.033	(−1.88, 1.95)		ns
HRSD	28.4 ± 9.3	25.8 ± 6.1	1	(−2.5, 7.6)		ns
BPRS	39.5 ± 12.7	37.8 ± 8.3	0.5	(−5.2, 8.6)		ns
GAS	31.0 ± 8.5	34.1 ± 11.7	−0.9	(−9.6, 3.5)		ns
GDR	2.6 ± 0.6	2.4 ± 0.7	1.2	(−0.2, 0.7)		ns
MMS[b]	25.9 ± 4.1	24.8 ± 4.1	0.8	(−1.7, 4.0)		ns
PSQI[c]	12.5 ± 4.4	11.7 ± 5.7	0.5	(−2.6, 4.1)		ns
Sex (F/M)	14/6	12/8			0.1	ns
MATS (≤1, ≥2)	10/10	5/15			1.7	ns
Previous ECT (N/Y)	11/9	14/6			0.4	ns
Psychosis (N/Y)	10/10	11/9			0	ns
Axis II (N/Y)	18/2	14/6			1.4	ns
Inpatient (N/Y)	3/17	5/15			0.2	ns

ECT = electroconvulsive therapy, rTMS = repetitive transcranial magnetic stimulation, CI = confidence interval, HRSD = Hamilton Rating Scale, BPRS = Brief Psychiatric Rating Scale, GAS= Global Assessment of Function Scale, GDR = Global Depression Scale, MMS = Mini Mental State Examination, PSQI = Pittsburgh Sleep Quality Index, MATS = Michigan Adequacy of Treatment Scale.

[a] Chi-square with continuity correction.

[b] $N = 35$ ($n = 16$ ECT group, $n = 19$ rTMS group).

[c] $N = 39$ ($n = 19$ ECT group, $n = 20$ rTMS group).

5. Post-ECT monitoring according to established anesthesia procedures was performed. ECT treatments were given twice-weekly.

Psychotropic medications were continued during the course of ECT according to physicians preference; however, they remained stable across the course of ECT. The use of benzodiazepines was limited to ≤3 mg of lorazepam equivalents a day and were held the night before the ECT. We were interested in testing the efficacy of rTMS in the context of an average ECT practice. Additional medications included neuroleptics alone (four patients), neuroleptics with antidepressants (six patients), antidepressants alone (five patients), and neuroleptics and anticonvulsants (one patient). Four patients did not receive any additional medications.

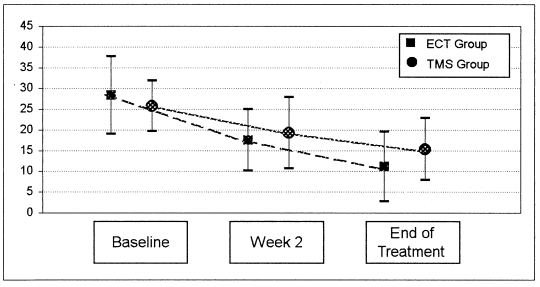
Patients treated with ECT received a mean of 9.6 treatments (range 7 to 14). Patients responding to ECT had mean seizure duration similar to that of those patients unresponsive to ECT (clinical seizure in responders 42 ± 24.2 vs. in nonresponders 26 ± 6.1, $t = -1.3$, ns; EEG seizure in responders 66.2 ± 26.8 vs. 47.4 ± 13.9 in nonresponders, $t = 1.9$, ns). Twelve patients received unilateral ECT for the whole course of ECT, whereas eight patients were switched to bilateral electrode placement because of insufficient response to ECT. Response rates were similar in both groups.

rTMS Methods

We used MAGSTIM (New York) rapid equipment with four booster modules. Motor threshold (MT) over the left motor cortex (area controlling the abductor pollicis brevis [APB]) was determined by electromyographic method, looking for the lowest machine power output that would provide in five of 10 stimulations an MEP of at least 50 μV. Motor threshold was determined daily in all cases. Stimulations were given at 90% MT with continuous electromyographic monitoring. Repetitive transcranial magnetic stimulation was administered over the LDLPC. Placement of the electrode over the LDLPFC was determined following the method of Pascual-Leone et al (1996): placing the coil 5 cm forward, and in a 45° angle from the vertex, from the best spot for the APB control. We used a 10-cm wingspan figure-eight coil cooled in ice for the rTMS administration. During stimulation the coil was held with the handle towards the back of the head and at a 45° angle. Repetitive transcranial magnetic stimulation was administered five times a week for 4 weeks (for a total of 20 stimulations). Although limiting the time period for administration of rTMS while leaving the length of the ECT at the discretion of the clinician may introduce a bias against rTMS, our human use approval required this limitation. To the first eight patients we administered 20 trains of rTMS at 10 Hz for 2 sec (total of 400 magnetic pulses per treatment day). To the final 12 patients we administered 20 trains of rTMS at 10 Hz for 6 sec (total of 1200 magnetic pulses per treatment day). This was the first rTMS protocol performed at our center, so the authors opted for a more cautious approach at the outset of the study. All psychiatric medications were discontinued before the administration of rTMS; clonazepam (1–2 mg/day, given in twice-daily doses) was started in all patients to decrease anxiety, provide relief of severe insomnia, and have an additional protective element regarding seizures. Patients who did not respond to the course of rTMS were offered a course of ECT. The response to ECT of rTMS nonresponders will be the subject of another communication.

The statistical analyses were performed for the whole sample ($N = 40$), psychotic patients ($n = 19$), and nonpsychotic patients only ($n = 21$). This study was considered preliminary, so power

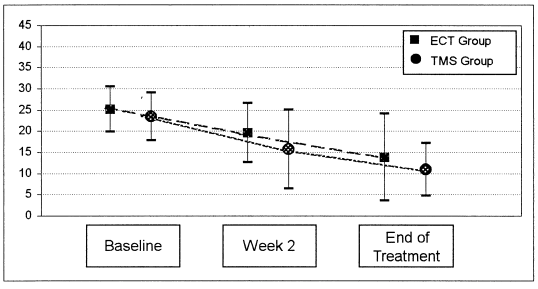
HRSD Ratings at Baseline, Week 2, and End of Treatment for The Whole Sample of MDD Patients



HRSD Ratings	ECT Group	TMS Group
Baseline	28.4 ± 9.3	25.8 ± 6.1
Week Two	17.6 ± 7.4	19.3 ± 8.6
End of Treatment	11.2 ± 8.4	15.4 ± 7.5

ANOVA Table	F	(df)	p
Group Effect	0.4	(1,38)	NS
Time Effect	41.5	(2,76)	0.000
Interaction	2.5	(2,2)	0.090

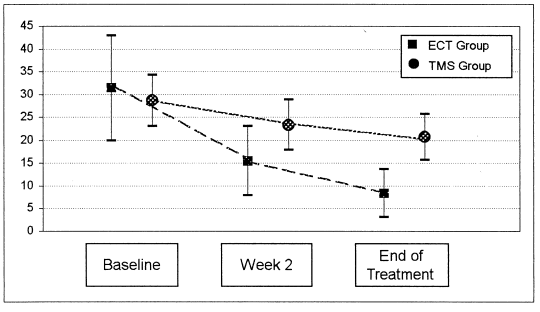
HRSD Ratings at Baseline, Week 2, and End of Treatment for The MDD Non- Psychotic Patients Only



HRSD Ratings	ECT Group	TMS Group
Baseline	25.2 ± 5.3	23.5 ± 5.6
Week Two	19.7 ± 7.0	15.8 ± 9.3
End of Treatment	13.9 ± 10.3	11.0 ± 6.2

ANOVA Table	F	(df)	p
Group Effect	1.4	(1,19)	NS
Time Effect	19	(2,38)	0.000
Interaction	0.2	(2,2)	NS

HRSD Ratings at Baseline, Week 2, and End of Treatment for The MDD Psychotic Patients Only



HRSD Ratings	ECT Group	TMS Group
Baseline	31.5 ± 11.5	28.7 ± 5.6
Week Two	15.5 ± 7.6	23.4 ± 5.5*
End of Treatment	8.4 ± 5.3	20.8 ± 5.0**

*p<0.1
**p<0.001

ANOVA Table	F	(df)	p
Group Effect	7.9	(1,17)	0.01
Time Effect	25.1	(2,34)	0.000
Interaction	6.1	(2,2)	0.005

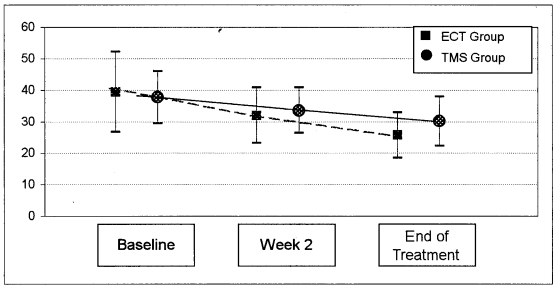
Figure 1. Hamilton Rating Scale for Depression (HRSD) ratings at baseline, 2 weeks into the treatment, and the end of the treatment for the repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) groups for the whole sample and for the psychotic and nonpsychotic groups.

calculations to determine the minimal sample needed to detect a difference between the groups were not done (Cohen and Cohen 1975). In general, to detect mean differences of .3 with a power of 80%, over 50 patients are required. The main hypothesis was tested with analysis of variance (ANOVA) with repeated measures, with additional post hoc analysis performed with two-sample *t* tests and chi-squares. Time points taken into consideration for the analysis were baseline, week 2, and end of treatment (week 4 for the rTMS group and the week when the clinician considered that the ECT course had ended for the ECT group). Response to treatment was categorized using a dual definition. Patients were considered to be responders to treatment if the final HRSD had decreased to ≥50% or more from baseline and the final GAS of ≥60. A repeated-measures ANOVA of the HRSD [group effect $F(1,18) = 0.36$, ns; treatment effect $F(2,36) = 18.9$, $p < .001$; interaction $F(2,2) = 2.0$, ns] and BPRS ratings [group effect $F(1,18) = 0.99$, ns; treatment effect $F(2,36) = 6.9$, $p < .01$; interaction $F(2,2) = 1.3$, ns] was performed comparing the rTMS patients treated with 400 daily stimulations with those treated with 1200 daily stimulations. No difference in HRSD or BPRS ratings was found. We therefore pooled the sample.

Results

Results are presented first for the whole sample, then for the nonpsychotic patients, and finally for the psy-

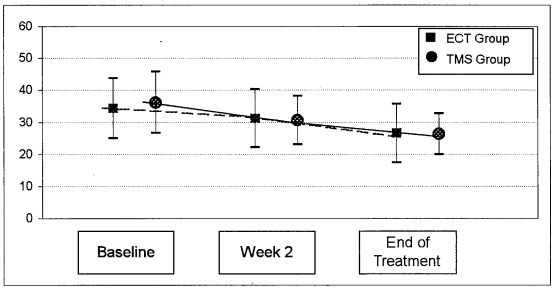
BPRS Ratings at Baseline, Week 2, and End of Treatment for The Whole Sample of MDD Patients



BPRS Ratings	ECT Group	TMS Group
Baseline	39.5 ± 12.7	37.8 ± 8.3
Week Two	32.0 ± 8.8	33.6 ± 7.2
End of Treatment	25.8 ± 7.2	30.2 ± 7.8

ANOVA Table	F	(df)	p
Group Effect	0.4	(1,36)	NS
Time Effect	22.1	(2,72)	0.000
Interaction	1.7	(2,2)	NS

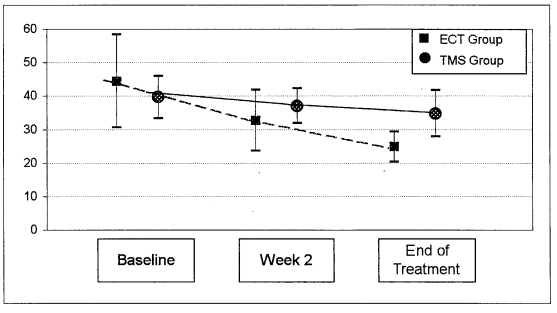
BPRS Ratings at Baseline, Week 2, and End of Treatment for The MDD Non- Psychotic Patients Only



BPRS Ratings	ECT Group	TMS Group
Baseline	34.4 ± 9.4	36.2 ± 9.6
Week Two	31.3 ± 9.1	30.7 ± 7.6
End of Treatment	26.6 ± 9.2	26.4 ± 6.4

ANOVA Table	F	(df)	p
Group Effect	0.0	(1,19)	NS
Time Effect	7.2	(2,38)	0.002
Interaction	0.2	(2,2)	NS

BPRS Ratings at Baseline, Week 2, and End of Treatment for The MDD Psychotic Patients Only



BPRS Ratings	ECT Group	TMS Group
Baseline	44.5 ± 13.9	39.7 ± 6.3
Week Two	32.8 ± 9.1	37.1 ± 5.2
End of Treatment	24.9 ± 4.5	34.8 ± 6.9*

*p<0.01

ANOVA Table	F	(df)	p
Group Effect	0.6	(1,15)	NS
Time Effect	24.5	(2,30)	0.000
Interaction	9.2	(2,2)	0.001

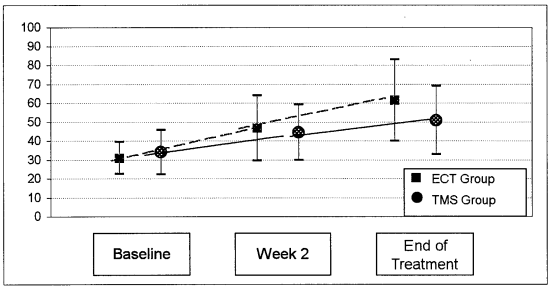
Figure 2. Brief Psychiatric Rating Scale (BPRS) ratings at baseline, 2 weeks into the treatment, and the end of the treatment for the repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) groups for the whole sample and for the psychotic and nonpsychotic groups.

chotic patients in Figures 1–5. In Figure 1 we can see that HRSD ratings for the whole sample are not significantly different between the groups, although the interaction between time and group was almost significant ($p < .1$). In nonpsychotic patients the HRSD decreased similarly in both groups (significant treatment effect); however, in patients with psychosis the improvement is strikingly better with ECT than with rTMS (significant time and treatment effects, and of the interaction). In Figures 2–5 we observe that the effects of ECT and rTMS on the BPRS, GAS, GDR, and PSQI closely mimic the effects on the HRSD.

The cognitive effects of both treatments were explored with the MMS. No difference between the groups (ECT baseline 25.9 ± 4.1, ECT end of treatment 24.5 ± 7.6; rTMS baseline 24.8 ± 4.1, rTMS end of treatment 26.3 ± 3.9, repeated measures ANOVA [group effect $F(1,29) = 0.1$, ns; time effect $F(2,58) = 1.3$, ns; interaction $F(2,2) = 2.3$, ns]) was observed. The analysis was also performed for the psychotic–nonpsychotic groups with similar results.

To explore further the clinical effects of these treatment modalities we defined the overall response rate using the previously described definitions (see Methods and Mate-

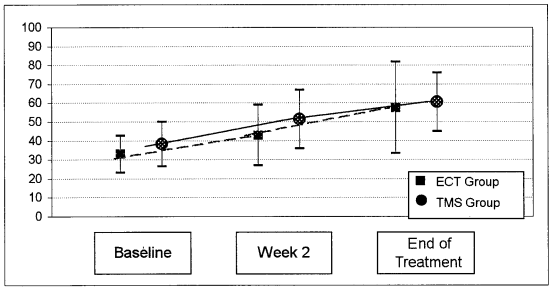
GAS Ratings at Baseline, Week 2, and End of Treatment for The Whole Sample of MDD Patients



GAS Ratings	ECT Group	TMS Group
Baseline	31.0 ± 8.5	34.1 ± 11.7
Week Two	46.8 ± 17.2	44.5 ± 14.7
End of Treatment	61.5 ± 21.5	51.0 ± 18.2

ANOVA Table	F	(df)	p
Group Effect	0.7	(1,38)	NS
Time Effect	40.8	(2,76)	0.000
Interaction	3.4	(2,2)	0.040

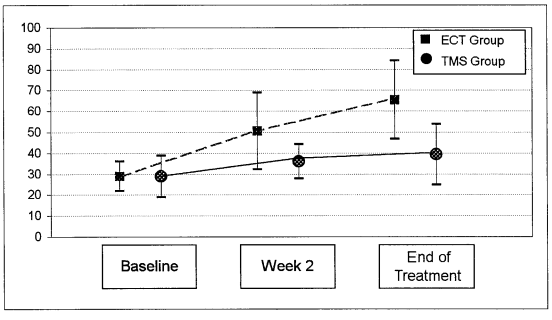
GAS Ratings at Baseline, Week 2, and End of Treatment for The MDD Non- Psychotic Patients Only



GAS Ratings	ECT Group	TMS Group
Baseline	33.0 ± 9.8	38.3 ± 11.8
Week Two	43.0 ± 16.0	51.4 ± 15.5
End of Treatment	57.5 ± 24.2	60.5 ± 15.6

ANOVA Table	F	(df)	p
Group Effect	1.0	(1,19)	NS
Time Effect	19.8	(2,38)	0.000
Interaction	0.3	(2,2)	NS

GAS Ratings at Baseline, Week 2, and End of Treatment for The MDD Psychotic Patients Only



GAS Ratings	ECT Group	TMS Group
Baseline	29.0 ± 7.0	28.9 ± 9.9
Week Two	50.6 ± 18.3	36.1 ± 8.2*
End of Treatment	65.5 ± 18.8	39.4 ± 14.5**

*p<0.1
**p<0.01

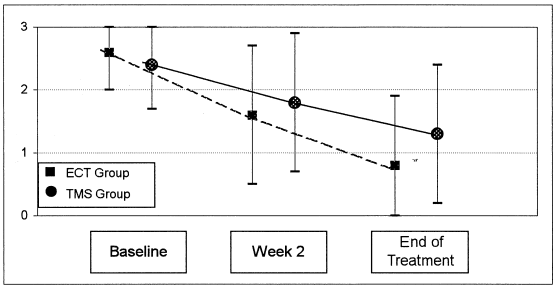
ANOVA Table	F	(df)	p
Group Effect	8.2	(1,17)	0.01
Time Effect	21.4	(2,34)	0.000
Interaction	6.4	(2,2)	0.004

Figure 3. Global Assessment of Function Scale (GAS) ratings at baseline, 2 weeks into the treatment, and the end of the treatment for the repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) groups for the whole sample and for the psychotic and nonpsychotic groups.

rials). We compared the response at week 4 for patients treated with rTMS and at the end of treatment for patients treated with ECT. When the whole sample is considered, ECT-treated patients responded significantly better than patients treated with rTMS (ECT group responders 16 of 20; rTMS group responders 9 of 20; $\chi^2 = 3.8$, $p < .05$). For the patients with psychosis this difference is striking, with all patients treated with ECT responding and only two of the rTMS-treated patients responding (ECT group responders 10 of 10; rTMS group responders 2 of 9; $\chi^2 = 9.2$, $p \leq .01$). In the group of nonpsychotic patients this difference disappears and patients respond to both interventions (ECT group responders 6 of 10; rTMS group responders 7 of 11; $\chi^2 = 0.02$, ns).

A repeated-measures ANOVA using the responder–nonresponder groupings was used to compare the HRSD ratings of both groups at week 2 and at the end of the treatment. The ANOVA was significantly different for time effect [$F(1,18) = 7.3$, $p = .01$], group effect [$F(1,18) = 172.4$, $p < .001$], and interaction [$F(1,1) = 6.2$, $p = .02$]. The group means for the responders were 16.8 ± 11.0 at week 2 and 9.4 ± 4.7 at the end of the treatment. The group means for the nonresponders were 21.7 ± 4.5 at week 2 and 21.4 ± 4.1 at the end of the treatment.

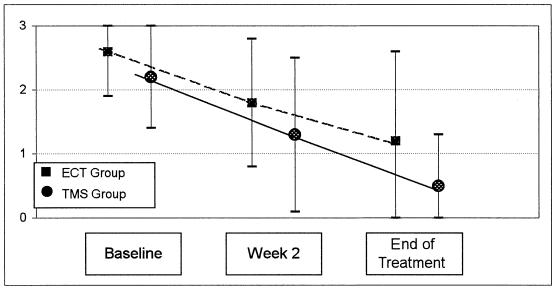
GDR Ratings at Baseline, Week 2, and End of Treatment for The Whole Sample of MDD Patients



GDR Ratings	ECT Group	TMS Group
Baseline	2.6 ± 0.6	2.4 ± 0.7
Week Two	1.6 ± 1.1	1.8 ± 1.1
End of Treatment	0.8 ± 1.1	1.3 ± 1.1

ANOVA Table	F	(df)	p
Group Effect	0.3	(1,38)	NS
Time Effect	36.1	(2,76)	0.000
Interaction	2.2	(2,2)	NS

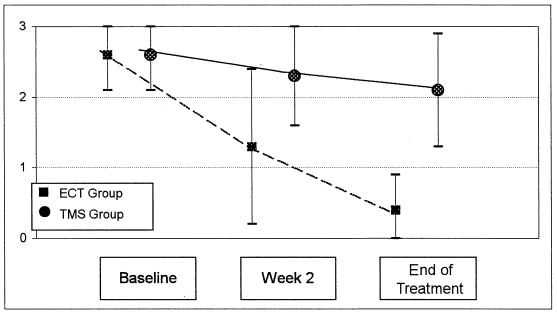
GDR Ratings at Baseline, Week 2, and End of Treatment for The MDD Non- Psychotic Patients Only



GDR Ratings	ECT Group	TMS Group
Baseline	2.6 ± 0.7	2.2 ± 0.8
Week Two	1.8 ± 1.0	1.3 ± 1.2
End of Treatment	1.2 ± 1.4	0.5 ± 0.8

ANOVA Table	F	(df)	p
Group Effect	2.6	(1,19)	NS
Time Effect	17.7	(2,38)	0.000
Interaction	0.1	(2,2)	NS

GDR Ratings at Baseline, Week 2, and End of Treatment for The MDD Psychotic Patients Only



GDR Ratings	ECT Group	TMS Group
Baseline	2.6 ± 0.5	2.6 ± 0.5
Week Two	1.3 ± 1.1	2.3 ± 0.7*
End of Treatment	0.4 ± 0.5	2.1 ± 0.8**

*p<0.1
**p<0.001

ANOVA Table	F	(df)	p
Group Effect	15.4	(1,17)	0.001
Time Effect	21.3	(2,34)	0.000
Interaction	9.5	(2,2)	0.001

Figure 4. Global Depression Scale (GDR) ratings at baseline, 2 weeks into the treatment, and the end of the treatment for the repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) groups for the whole sample and for the psychotic and nonpsychotic groups.

To compare whether the clinical response was as sound in those patients responding to each treatment modality we compared the final HRSD and GAS ratings for those patients responding to either treatment modality. Twenty-five patients were included in this analysis (ECT group $n = 16$, rTMS-treated group $n = 9$). The final HRSD ratings (ECT group 7.6 ± 4.8; rTMS group 8.6 ± 4.1; $t = -0.5$, ns) and GAS ratings (ECT group 68.8 ± 16.9; rTMS group 67.2 ± 10.6; $t = 0.24$, ns) were similar in both groups.

The side-effect profile of rTMS was considerably mild. Five patients in the rTMS complained of mild headache, which responded to analgesics. In one patient, and only during one of the treatment sessions, we noted that 20 msec following each magnetic pulse an MEP discharge was observed. This patient was being stimulated with 2-sec trains. The patient was receiving 2 mg of clonazepam. In this case spread was controlled by decreasing stimulation power by 10%. As in other cases the MT of this patient was determined daily. On the day of this event MT was identical to that obtained on the previous day. The course of treatment in the ECT group was as expected: all patients concluded the course.

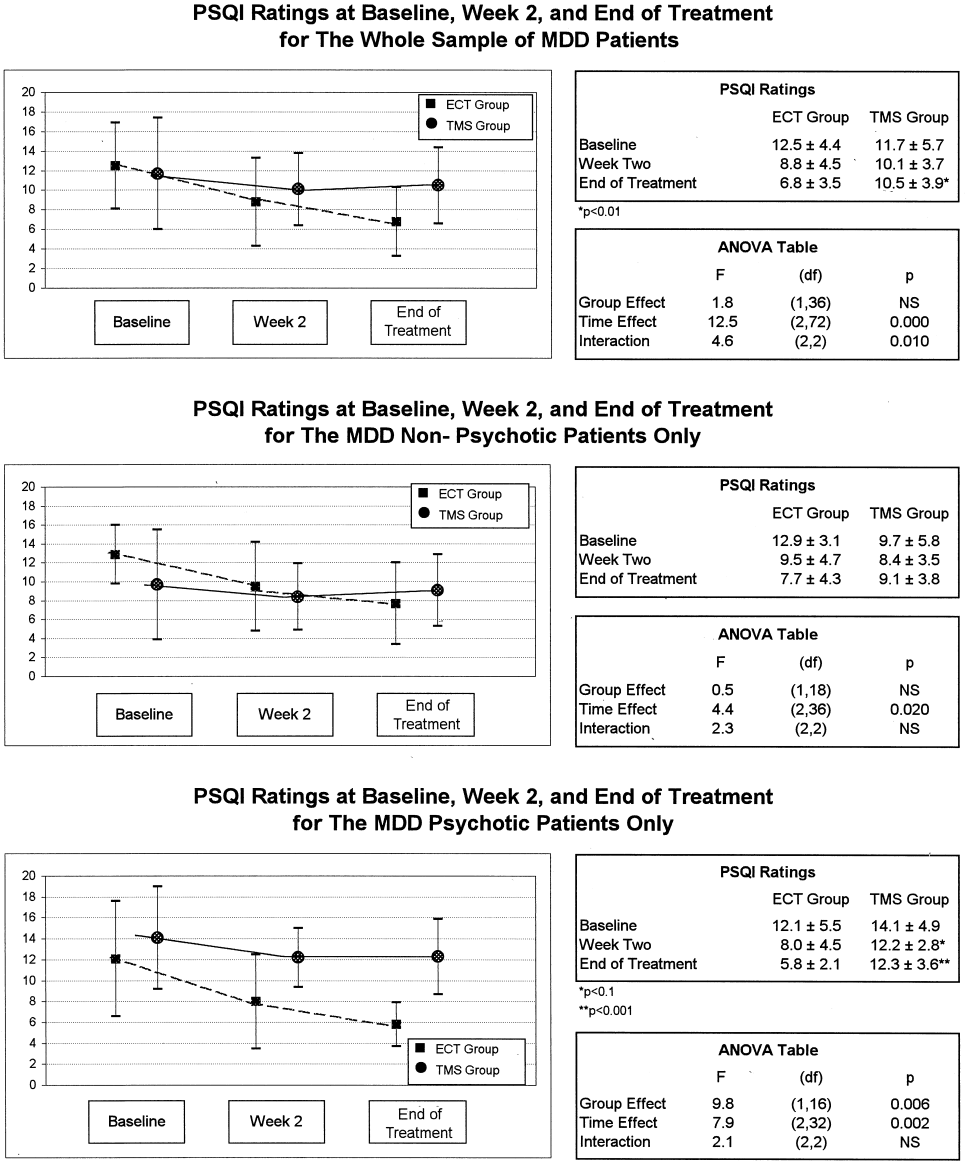


Figure 5. Pittsburgh Sleep Quality Index (PSQI) at baseline, 2 weeks into the treatment, and the end of the treatment for the repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) groups for the whole sample and for the psychotic and nonpsychotic groups.

Discussion

The findings of this study support the following conclusions:

1. Some measures of clinical response ($\chi^2 = 3.8$, $p < .05$), but not others (ANOVA with repeated measures, ns), suggest that patients treated with ECT had a more consistent antidepressant treatment response than those treated with rTMS.
2. Electroconvulsive therapy is clearly superior to rTMS in patients with MDD and psychosis, as shown both by categorical analysis and in almost all clinical variables tested.
3. The response to rTMS was similar to that observed with ECT in patients with MDD without psychosis.
4. In those patients who responded to either treatment modality, the depth of the clinical response, as measured by the final clinical ratings, was similar in both groups.
5. Repetitive transcranial magnetic stimulation was well tolerated, with only minor side effects de-

scribed. Older patients tolerated the procedure as well as their younger counterparts.

6. The data presented strongly suggest that continuing rTMS for 4 weeks increased the efficacy of this treatment. On the other hand, it also suggests that if there was minimal improvement by 2 weeks the additional weeks of treatment provided little added relief.
7. Although it was not formally tested, there were no age differences in treatment response. Older patients responded as well as younger ones. In this regard our study differs from that of Figiel et al 1998. The response of older patients to rTMS will be the subject of another communication.

However, our conclusions need to be tempered because of several considerations:

1. *Absence of a sham group:* Our treatment groups did not include a sham comparison because of the ethical concerns of including severely ill hospitalized patients in a sham protocol. The lack of a sham control may constitute a problem in rTMS studies. The placebo components of this treatment (daily contact, popular beliefs on the effects of magnets, etc.) could be powerful. Similar psychological issues, however, could be in effect in the ECT-treated patients in whom an aversion to the treatment may constitute a strong factor for an "escape into health."
2. *Nonblind assessments:* Our raters were not blind to treatment allocation; however, patient ratings were always corroborated with nurses' observations in the units and/or collateral information from relatives.
3. *Use of two treatment paradigms:* The first eight patients were treated with only 400 stimulations per treatment day, whereas the final 12 patients received 1200 stimulations per treatment day. The indications for lower and higher frequency paradigms should be explored further.
4. Patients in the ECT group were allowed psychotropics as indicated by their treating physicians, whereas rTMS patients were restricted to clonazepam only. It is unclear whether clonazepam may impact negatively on rTMS. However, these patients are severely ill, with significant agitation and or insomnia. It is very difficult to totally avoid additional medications particularly during the first week of treatment.

   The basic concept of this study was to compare rTMS and ECT as ECT is done in regular treatment facilities. Whether this was a bias against rTMS cannot be determined from this study.

The suggestion that rTMS may have a role in the treatment of MDD originated with the works by Pascual-Leone et al, George et al, and Figiel et al. Pascual-Leone et al (1996) reported that rTMS (90% MT, 10 Hz for 10 sec, 20 trains/day for a total of 2000 pulses/day) over the LDLPFC had antidepressant effects in 11 of 17 outpatients with recurrent unipolar MDD with psychosis who "had been resistant to medications, despite combinations and high dosage" (p. 233). The protocol described in the study by Pascual-Leone et al differs from standard psychiatric treatment protocols because patients received rTMS for 5 days over the various brain regions (real vs. sham rTMS over LDLPFC, right dorsolateral prefrontal cortex [RDLPFC], and vertex) and remained free from additional treatment for the rest of the month. For the whole 5-month period of the study the patients received only 5 days of an active treatment, rTMS over the LDLPFC. Thus, although from a diagnostic point of view the patients met criteria for MDD with psychotic features, the clinical severity, however, must have been significantly lower than that of the cases we are reporting, most of our sample being inpatients referred for ECT. Whether the more intense stimulation paradigm used by Pascual-Leone et al was a factor in the outcome needs to be considered.

George et al (1997) reported on 12 patients with recurrent MDD treated with rTMS in a randomized crossover real-versus-sham comparison. The authors described a significant, albeit mild, effect of real LDLPFC rTMS on depression ratings (80% MT at 20 Hz, for 2 sec, 20 trains for a total of 800 pulses/day). Figiel et al (1998), in the largest rTMS study published so far, reported on an open trial of LDLPFC rTMS administered for 5 days (110% MT at 10 Hz, for 5 sec, 10 trains for a total of 500 pulses/day), finding a 43% response rate. Figiel et al noted that older patients, particularly those with late-onset depression, and patients with psychosis responded poorly. The main difference between the George et al and Figiel et al studies and ours relates to the length of the treatment period. We extended our protocol to 20 stimulation days (4 weeks) in consideration of the fact that on average it takes between six and eight ECT treatments to reach therapeutic results (Grunhaus et al, unpublished observations). From our results it is quite clear that the 4-week paradigm we used provided additional improvement on depression ratings.

Whether higher frequency TMS (rTMS) with a figure-eight coil over the LDLPFC is superior to TMS at lower frequencies with a round coil and over other brain areas, especially the RDLPFC, is unknown. Studies have shown antidepressant response to TMS administered at low stimulation frequencies (<1 Hz) with a round coil over the vertex, or the RDLPFC position (Conca et al 1996; Grisaru et al 1994; Hoflich et al 1993; Klein et al 1999; Kolbinger et al 1995). Grisaru et al (1998) have reported that treatment with rTMS at 20 Hz over the LDLPFC may worsen the clinical course of manic patients, whereas a

similar stimulation paradigm over the RDLPFC seems to lead to clinical improvement.

The support for the application of rTMS pulses over the LDLPFC was derived from the evidence accumulated over the past 10 years pointing towards involvement of the fronto–limbic–subcortical circuits in MDD (Cummings 1993; Drevets et al 1997; George et al 1994), particularly in the LDLPFC. Most brain-imaging studies (Baxter et al 1989; Bench et al 1993; Bonne et al 1996; Martinot et al 1990; Mayberg et al 1991) suggest decreased cerebral blood flow (CBF) or decreased metabolic rates (Baxter et al 1989; Martinot et al 1990) in the LDLPFC and other frontal areas in MDD. Drevets et al (1992), however, reported increased CBF in the left prefrontal cortex using ^{15}O–positron emission tomography (^{15}O-PET). It is unclear whether these changes are state related or demonstrate a more stable, trait type of abnormality. Drevets et al (1997) proposed that changes seen in the subgenual portion of the left prefrontal cortex of patients with either familial bipolar or unipolar depressive disorder (seen with PET scans and with magnetic resonance imaging) are either an "abnormality of brain development or a degenerative change resulting from recurrent illness" (p. 826).

The neurophysiological responses to rTMS are pleomorphic and may depend on a significant number of parameters. Type of coil (figure eight and round), coil location, size of the coil, stimulation frequency, number of magnetic pulses, metabolic state of the brain, and brain circuitry affected, all influence response to rTMS. The magnetic pulses stimulate both cortico-cortical connections and corticofugal fibers (George and Wasserman 1994; George et al 1995). The cortico-cortical activation is not limited to local neuronal networks. Distant activation following rTMS has been demonstrated. Pulse-dependent increases in CBF measured with ^{15}O-labeled H_20, as seen in parietal regions after TMS stimulation on the orbitofrontal cortex (Paus et al 1997), or the EEG activation seen in the contralateral motor cortex following rTMS demonstrate cortical reactivity and connectivity (Illmoniemi et al 1997). Thus, TMS applied to a rather limited area of the brain (the LDLPFC) could lead to activation or inhibition of much broader areas through both cortico-cortical and cortico–basal ganglia connections.

It is evident from this discussion that the variables affecting the interactions between rTMS and the brain are multiple and may involve a significant amount of individual phenotypic variability. Patients may require different stimulation paradigms according to their neurophysiological status. For example, increased CBF or metabolic rates may require low-frequency stimulations, whereas decreased CBF or metabolic rates may require higher frequency stimulation paradigms (McCann et al 1998). Thus, clinical response could depended on a large number of variables that we are just beginning to understand. We propose that state of brain function, type of coil, coil location, stimulation paradigm, and diagnosis are factors that need to be considered when exploring the therapeutic response to TMS.

The suggestion that rTMS may have effects similar to those seen with ECT in the treatment of MDD without psychosis is very exciting; however, it needs to be tempered by the paucity of clinical data and the novelty of rTMS as a treatment. Electroconvulsive therapy is currently used very late in the treatment algorithms of MDD; TMS, with its much less invasive profile and possibly milder side-effect profile could become a much earlier alternative for patients with MDD without psychosis. However, additional blinded studies are needed before this suggestion becomes a specific clinical recommendation.

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