A 3-Month, Follow-Up, Randomized, Placebo-Controlled Study of Repetitive Transcranial Magnetic Stimulation in Depression

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Background/Objective: There is evidence for an antidepressant effect of repetitive transcranial magnetic stimulation (rTMS), but little is known about posttreatment course. Therefore, we conducted a placebo-controlled, double-blind study in depressed patients in order to investigate the effect of rTMS on depression over 12 weeks after completion of the 2-week stimulation period.

Method: 55 patients with a moderate or severe DSM-IV major depressive episode were randomly assigned to rTMS or sham treatment. rTMS was given daily for 10 days over the left dorsolateral prefrontal cortex with the following treatment parameters: 20 Hz, 20 trains of 2 seconds, 30 seconds between trains, and 80% motor threshold. The effect of rTMS on depression was rated repeatedly with the 17-item Hamilton Rating Scale for Depression (HAM-D) during the 2-week period of stimulation and the 12-week follow-up period conducted from 1997 to 2001.

Results: We found a modest, clinically nonrelevant decrease in HAM-D scores in both rTMS and sham patients over 2 weeks of treatment. However, over the subsequent 12-week follow-up, the rTMS group continued to improve significantly compared with the placebo group.

Conclusion: Decrease of depressive symptoms may continue after the cessation of rTMS stimulation.

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Repetitive transcranial magnetic stimulation (rTMS) has been investigated in a rapidly increasing number of studies as a nonpharmacologic and subconvulsive alternative for the treatment of depression.[1,2] We refer to the comprehensive review by Wassermann and Lisanby.[3] The efficacy of rTMS has thus far been the subject of several meta-analyses.[4–9]

Whereas the short-term therapeutic potential of rTMS is still under some debate, even less is known about its long-term poststimulation effects. Until now, only Dannon et al.[10] mentioned a lasting effect at 3-month and 6-month follow-up, comparable with electroconvulsive therapy (ECT). We report on a placebo-controlled, 12-week follow-up study of rTMS conducted from 1997 to 2001 in 52 patients, using random-effects analysis to correct for unbalanced data, a common problem in longitudinal medical research.

METHOD

Subjects/Design

Inpatients and outpatients older than 16 years who met DSM-IV criteria for a major depressive episode and had a score of ≥ 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) were included. Patients were referred to a specialized psychiatric department of a general teaching hospital by general practitioners, medical specialists, and mental health hospitals. Demographic and clinical characteristics are presented in Table 1.

Exclusion criteria included a history of epilepsy and any other medical disorder that precluded the administration of rTMS.[11] Patients taking psychotropic medication were accepted if the dosage of antidepressive medication had not been changed for 6 weeks and if the dosage of benzodiazepine (hypnotics and anxiolytics) had not been changed for 2 weeks prior to study inclusion. Antidepressive, hypnotic, and anxiolytic medication had to remain stable during the 14-week study, meaning that dose changes were not tolerated, and patients could maximally miss 1 dose a week. Antipsychotics or mood stabilizers were prescribed in some cases of psychotic symptoms or

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Table 1. Demographic and Clinical Characteristics of rTMS and Sham Patients

Characteristic	rTMS Group (N = 26)	Sham Group (N = 26)	p Value[a]
Age, mean (SD), y	51 (15.4)	52 (13.2)	NS
Male/female, N	14/12	9/17	NS
Patients receiving ECT before treatment, N	1	0	NS
Patients > age 65 y, N	7	5	NS
Patients left-handed/right-handed/ambidextrous, N	1/24/1	3/22/1	NS
Patients with personality disorder, N	15	13	NS
Total dropouts, N	14	11	NS

[a]$p < .05$.
Abbreviations: ECT = electroconvulsive therapy, NS = not significant, rTMS = repetitive transcranial magnetic stimulation.

a history of hypomania or mania. For an overview of all psychotropic medication taken by rTMS and sham patients, we refer to Table 2.

Written informed consent was obtained; patients were aware of the duration of their involvement and the option to drop out of the study at any moment. The ethics committee of the hospital approved the protocol. Prior to treatment, all patients were assessed with standard clinical, psychiatric, and laboratory tests. Trained medical practitioners rated depression at baseline with the 17-item HAM-D. Ratings were repeated at weeks 1, 2, 4, 8, and 14; weeks 1 and 2 were the actual weeks of treatment. Patients were randomly assigned to either rTMS or sham condition. Only the neurophysiologist applying the magnetic stimulus was aware of the chosen condition. The patient, the rater, the treating physician, and all nurses were blind to the treatment modality. Because patient and rater were blinded, the study was methodologically double-blind and placebo-controlled.

Repetitive Transcranial Magnetic Stimulation Procedure

Subjects received rTMS daily on 10 consecutive weekdays (5 sessions per week). We used the Magpro[12] with a circular stimulating coil (MC-125; Dantec Medical A/S, Skovlunde, Denmark) for biphasic pulses. The windings of this coil have an inner radius of 10 mm and an outer radius of 60 mm, and the coil induced an electric field maximal at 4 to 5 cm radial distance from the coil center in a previous study.[13] Stimulation parameters were in accordance with standards when the study was started (20 Hz, 20 trains of 2 seconds, 30 seconds between trains, and 80% motor threshold).[14] The parameters were kept constant during the study. Before the first session, the optimal motor point and the stimulation threshold for right thenar muscle activation were determined for each patient. The left dorsolateral prefrontal cortex (DLPFC) stimulation site was defined as 5 cm anterior to this optimal motor point, according to the technique of George et al.[15] and Pascual-Leone et al.,[16] and was marked. During the rTMS session, the coil was centered flat over the left DLPFC. The small hole in the center of the coil permitted exact positioning by visual control of the mark. Sham treatment was performed by angling the outer edge of the coil 45°, with the other outer edge resting on the vertex, thereby inducing a contraction of the scalp and face muscles by direct stimulation. We will comment on technical, stimulation, and sham aspects of the study in the Discussion section.

Statistics

Independent sample t tests were used to investigate differences between rTMS and sham treatment for age and HAM-D scores. Chi-square tests were performed to check whether the rTMS and sham groups differed in electroconvulsive therapy ECT before rTMS treatment, age older than 65 years, and personality disorder.

A hierarchical linear model was used to analyze the change in HAM-D scores over time and the difference between sham and rTMS treatment, as well as the influence of other characteristics. This model is also known as a multilevel or random-effects regression model.[17,18] Contrary to the standard repeated-measures analysis of variance (as, for instance, implemented in the SPSS GLM module [SPSS release 10.0.0; SPSS, Inc., Chicago, Ill.]), the random-effects regression model can handle unbalanced data because it does not require the same number of measurements for each subject. Therefore, subjects with incomplete data were not omitted from analysis, nor were measurement points discarded (typically, the later time points because of dropout) that normally result in loss of power and disregard of the effect of dropout.

The 5 HAM-D scores at weeks 1, 2, 4, 8, and 14 were entered into the hierarchical linear model, using the HAM-D score at baseline (week 0) as covariate. The change in HAM-D score over time was modeled with a piecewise linear model distinguishing between treatment (weeks 1 and 2) and posttreatment periods. First, we investigated the relation between decrease in HAM-D scores over treatment and posttreatment periods and rTMS or sham conditions. Second, we looked for possible influences of several covariates, such as sex, age, or left-handedness.

RESULTS

Fifty-five patients originally entered the study. Two patients dropped out after 1 rTMS session: the first patient received emergency ECT because of suicidal ideation, and the second patient complained of extreme dizziness. One patient dropped out after 5 sessions (because of extra medication due to suicide risk). Because we intended to investigate late effects of a completed stimulation, these patients were excluded. Therefore, data were analyzed for

Table 2. Psychotropic Medications Taken by rTMS and Sham Patients During the Study[a]

Group	MAOIs	TCAs	SSRIs	Mood Stabilizers	Neuroleptics	Hypnotics	Tranquilizers	Anticholinergics
rTMS	0	0	10	3	6	13	14	2
Sham	0	4	17	2	9	14	16	0
Total	0	4	27	5	15	27	30	2

[a]Some patients were taking more than 1 medication.
Abbreviations: MAOI = monoamine oxidase inhibitor, rTMS = repetitive transcranial magnetic stimulation, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Reasons for Patient Dropout in rTMS and Sham Groups After Completion of Stimulation Sessions (by week of HAM-D measurement)[a]

	Week 2		Week 4		Week 8		Week 12	
Reason	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham
Increase of symptoms			1		2	2	2	1
Strong increase of symptoms								1
Decrease of symptoms		2	1		2	1	2	
Strong decrease of symptoms	1			1				
Other[a]						1	3	2
Total	3		3		8		11	

[a]Other = electroconvulsive therapy, holiday, no-show, or moved to other treatments.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Table 4. Mean HAM-D Score Decrease in rTMS and Sham Groups by Week

	rTMS		Sham		
Week	N	HAM-D Score, Mean (SD)	N	HAM-D Score, Mean (SD)	p Value
0	26	25.9 (4.33)	26	25.9 (5.59)	.99
1	26	22.1 (6.83)	26	23.8 (6.54)	.36
2	25	21.1 (7.47)	24	21.9 (7.08)	.71
4	23	20.6 (9.25)	23	20.2 (8.14)	.88
8	19	15.5 (7.45)	19	21.2 (9.59)	.06
14	12	14.7 (7.96)	15	18.7 (8.21)	.21

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

the 52 patients who completed the 2-week stimulation period, randomly divided into 26 sham and 26 rTMS patients. At week 14, the total number of dropouts was 11 of 26 sham patients and 14 of 26 rTMS patients. Reasons for patient dropout are shown in Table 3.

Sham and rTMS patients did not differ significantly in age and HAM-D score at baseline (week 0). No pretreatment differences between groups were found for sex; left-handedness, right-handedness, or ambidexterity; type of depression according to DSM-IV criteria; personality disorder; time or reason for dropout; ECT before treatment; medication; side effects of treatment; inpatient or outpatient status; or age older than 65 years.

During the treatment period, the mean HAM-D score decreased in both groups by approximately 2.5 points in the first week and 1 point in the second week. So, there was some improvement of depressive symptoms in both groups. However, the mean HAM-D score decrease never surpassed 20% in either group. Moreover, the random-effects model revealed no statistically significant difference between groups during treatment. Application of the random-effects model, however, showed that posttreatment HAM-D scores dropped in both groups, progressively diverging from each other, resulting in a significant mean difference of more than 4 points in favor of the rTMS group over the sham group (Tables 4 and 5).

As can be seen in Figures 1 and 2, patterns of individual posttreatment HAM-D scores were markedly different. So, the better posttreatment outcome of the rTMS group does not allow for any prediction in individual cases.

With respect to benzodiazepine comedication (anxiolytics as well as hypnotics), we looked at a possible influence on changes in HAM-D scores. After both weeks 1 and 2, benzodiazepine users showed a significantly smaller decrease in HAM-D scores than did nonusers, the difference being 2.5 points ($p = .04$) after the first week and 2.6 points ($p = .02$) after the second week. However, this effect was not significantly different for rTMS-treated patients, compared with the sham group. At week 14, benzodiazepine users still showed a smaller but no longer significant decrease of HAM-D scores (2.2 points, $p = .20$). Again, no difference was found between the rTMS and sham groups.

DISCUSSION

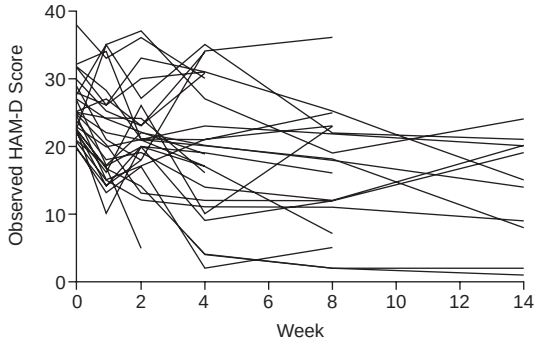
Obviously, technical and stimulation parameters used in this study were actual at its start, but they do not fit into current views.[19] Therefore, the reason to present these data for scientific discussion is found in our findings from a 3-month follow-up after stimulation. First, we will discuss the possible influence of technical factors. Next, we will comment on our posttreatment data.

Table 5. Statistical Results From the Random-Effects Regression Model for rTMS and Sham Groups

Variable	Parameter Estimate	Standard Error	p Value
Fixed-effects			
HAM-D score percentage compared with baseline	0.886	0.129	< .00001
Improvement (wk 0–1)			
Overall	–2.503	3.476	.24
Difference rTMS vs sham	–0.562	1.289	.33
Improvement (wk 1–2)			
Overall	–1.097	1.838	.28
Difference rTMS vs sham	0.562	1.289	.33
Improvement posttreatment (wk 4–14)			
Overall	–1.10	1.84	.27
Difference rTMS vs sham	–4.400	2.680	.05
Covariate			
Women vs men	2.129	1.297	.05
> age 65 y vs younger	3.371	1.504	.01
Left/ambidextrous vs right	–2.88	1.899	.06
Random-effects			
Between-patient variance			
Overall	12.42	3.722	< .00001
Wk 4, 8, and 14	6.046	4.608	< .0001
Posttreatment improvement	52.49	23.50	.006
Measurement variance	11.46	1.818	

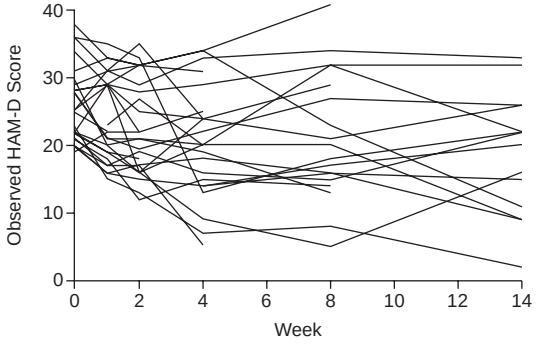
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Figure 1. Observed HAM-D Scores for Patients in the rTMS Group (N = 26)



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Figure 2. Observed HAM-D Scores for Patients in the Sham Group (N = 26)



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Four aspects of technical methodology must be taken into account in order to adequately weigh the presented data. First, at the start of this study, we searched for alternatives to the so-called "halo" type of round coil. Our choice of the Magpro and MC-125 was based on the small inner diameter of the coil's windings. Second, disadvantages of angling the coil 45° in order to create a sham condition are now well known[20,21]; however, at the start of the study, this was a standard procedure. Third, blinding of patients and raters was sufficiently strict to warrant a double-blind protocol. Fourth, compared with current standards regarding safe "dosage" of the magnetic stimulation, our study, although in line with the standards of the time, was "underpowered."[19] However, with respect to the interpretation of our data, this fact only underscores the possible importance of any effect found, provided that confounding factors were optimally excluded. As we have argued, we believe that the confounding factors were at least sufficiently controlled to allow for further scrutiny of our data.

During the 2-week stimulation period, some amelioration of depressive complaints as compared with baseline was found. However, statistical difference between the rTMS and sham groups did not emerge, nor could this change be considered a clinical response. Although positive short-term results have been reported from studies using the same stimulation parameters,[14,22] our finding is hardly surprising. The relatively low total amount of magnetic energy applied should be taken into account, as well as the undeniable fact that the bustle of the rTMS or sham procedure easily creates placebo effects, even apart from any influence of angling the coil.

In fact, our study was primarily set up to look for "late" effects, since immediate effects may not be the whole story, as is the case with medication and ECT. George et al.[14] and Berman et al.[22] did not find continuing benefits after 2 weeks of rTMS treatment. Dannon et al.[10] found a lasting effect of rTMS at 3- and 6-month follow-up, comparable with ECT. Only 3 of 21 patients who completed the 6-month follow-up after rTMS relapsed, whereas all patients who remained well had low levels of depressive symptomatology. Nevertheless, since follow-up studies are still rare, our data might be of interest because they show that depression may continue to improve after cessation of stimulation. With the aid of the random-effects regression model, this tendency was seen in both groups, but became clearer over time in favor of the rTMS group as compared with the sham group. Our 3-month observation resulted in a significant difference of more than 4 points on the HAM-D in the rTMS group.

Our finding of an increasing effect after a nonsignificant and clinically nonrelevant outcome of the treatment period requires explanation. First, our statistical analysis may have revealed a tendency that would otherwise have stayed hidden. Second, placebo effects may have played a role in inducing some "real" effect.[23] Although the change from baseline was modest in both groups during treatment, all activities concerning measurements during follow-up may have suggested to subjects that improvement was still to be expected. Also, the sham technique of angling the coil may have influenced results. However, irrespective of the technical specifications of the coil referred to previously, such an unwanted "real" late effect of the sham condition would call for an explanation in itself. Moreover, that improvement during follow-up was significantly more pronounced in the rTMS group than in the sham group puts that argument into perspective.

Therefore, as far as we can judge, our finding of a late effect of rTMS in depression surpassing the effect of the possible placebo condition is probably not attributable to a clear methodological flaw, although we present our data for discussion on this topic. Placebo effects may have played a mediating role[24] but cannot explain the posttreatment difference between rTMS and sham patients that we found. Perhaps a late effect of rTMS through long-term potentiation is at stake—even with the "old" stimulation parameters used—because of, for instance, a slow activation of gene expression.[25] The late onset of antidepressant effects of vagus nerve stimulation comes to mind as a possible analogy.[26]

With regard to comedication, our data do not yield an indication that benzodiazepines hamper the effect of rTMS, because no significant difference in the effect of benzodiazepines appeared between the rTMS and sham groups. That HAM-D scores dropped less in benzodiazepine users than in nonusers, independently from their receiving rTMS or sham stimulation, is not easy to explain. This finding might reflect the very reason for which these patients were prescribed anxiolytic medication: probably as a group they were more anxious or distressed. However, this hypothesis is not reflected by a difference in pretreatment HAM-D scores. So, one could hypothesize that a higher level of anxiety in benzodiazepine users manifested itself in an attenuated response to any intervention, be it real or sham. Obviously, this specific issue is in need of more research.

CONCLUSION

In conclusion, although our study was performed with stimulation parameters that may have been insufficient according to current knowledge, our findings from a 3-month posttreatment course might be interpreted as an indication that rTMS may also act via slow mechanisms. Future studies with more modern treatment settings and rigorous control of confounding factors are needed to shed light on this hypothesis.

REFERENCES

1. Kirkcaldie M, Pridmore S, Reid P. Bridging the skull: electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) in psychiatry. Convuls Ther 1997;13:83–91
2. George MS, Nahas Z, Kozel FA, et al. Mechanisms and state of the art of transcranial magnetic stimulation. J ECT 2002;18:170–181
3. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 2001;8:1367–1377
4. Holtzheimer PE III, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull 2002;35:149–169
5. Janicak PG, Dowd SM, Martis B, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry 2002;51:659–667
6. Hasey G. Transcranial magnetic stimulation in the treatment of mood disorder: a review and comparison with electroconvulsive therapy. Can J Psychiatry 2001;46:720–727
7. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta-analysis. Int J Neuropsychopharmacol 2002;5:73–103
8. McNamara B, Ray JL, Arthurs OJ, et al. Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychol Med 2001;31:1141–1146
9. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. Am J Psychiatry 2003;160:835–845
10. Dannon PN, Dolberg OT, Schreiber S, et al. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals: preliminary report. Biol Psychiatry 2002;51:687–690
11. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–6
12. Magpro. Dantec Magnetic Stimulator [instruction manual], reg no 9150B5311. Skovlunde, Denmark: Dantec Medical A/S; 1992
13. Nielsen JF, Klemar B, Kiilerich H. A new high-frequency magnetic stimulator with an oil-cooled coil. J Clin Neurophysiol 1995;12:460–467
14. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752–1756
15. George MS, Wasserman EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression.

Neuroreport 1995;6:1853–1856
16. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233–237
17. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Arch Gen Psychiatry 1993;50:739–750
18. Snijders T. Analysis of longitudinal data using the hierarchical linear model. Quality & Quantity 1996;30:405–426
19. Wassermann EM. Safety and side-effects of transcranial magnetic stimulation and repetitive transcranial magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, et al, eds. Handbook of Transcranial Magnetic Stimulation. London, England: Arnold; 2002:39–49
20. Lisanby SH, Gutman D, Luber B, et al. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry 2001;49:460–463
21. Lisanby SH, Kinnunen LH, Crupain MJ. Applications of TMS to therapy in psychiatry. J Clin Neurophysiol 2002;19:344–360
22. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry 2000;47:332–337
23. Leuchter AF, Cook IA, Witte EA, et al. Changes in brain function of depressed subjects during treatment with placebo. Am J Psychiatry 2002;159:122–129
24. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 2002;59:877–883
25. Lappin JM, Ebmeier KP. Transcranial magnetic stimulation in psychiatric disorders: does TMS affect cortical functions by long-term potentiation? In: Pascual-Leone A, Davey NJ, Rothwell J, et al, eds. Handbook of Transcranial Magnetic Stimulation. London, England: Arnold; 2002: 361–375
26. George MS, Nahas Z, Bohning DE, et al. Vagus nerve stimulation therapy: a research update. Neurology 2002;59(suppl 4):S56–S61