No Deterioration of Cognitive Performance in an Aggressive Unilateral and Bilateral Antidepressant rTMS Add-On Trial

Armand Hausmann, M.D.; Alvaro Pascual-Leone, M.D., Ph.D.; Georg Kemmler, Ph.D.; Claudia I. Rupp, Ph.D.; Theresia Lechner-Schoner, M.D.; Karin Kramer-Reinstadler, M.D.; Michaela Walpoth, M.D.; Sergei Mechtcheriakov, M.D.; Andreas Conca, M.D.; and Elisabeth M. Weiss, M.D.

Background: Cognitive functions were assessed before and following a course of repetitive transcranial magnetic stimulation (rTMS) in patients with depression participating in a sham-controlled, randomized trial of rTMS as adjunct to antidepressant treatment.

Method: Forty-one medicated inpatients with a DSM-IV diagnosis of a depressive episode were consecutively randomly assigned to 1 of 3 groups comparing 2 active rTMS conditions with sham stimulation. The rTMS was applied either at high frequency over the left dorsolateral-prefrontal cortex (DLPFC) (10 sessions × 10 trains × 10 seconds 20 Hz at 100% motor threshold [MT], 90-second intertrain interval) or in a combined high- and low-frequency manner to the left and right DLPFC, respectively (10 sessions × 1 train × 10 minutes at 120% MT). Thirty-eight patients completed a neuropsychological test battery at baseline and following day 14. The cognitive assessment focused on motor skills, attention, executive functions, learning, and memory. Data were collected from November 1999 to August 2002.

Results: Active treatment groups did not differ with respect to assessed cognitive measures and thus were pooled. A comparison of short-term changes (baseline–day 14) in neuropsychological performance revealed a more favorable time course of the actively treated patients for encoding in the verbal memory test compared with the sham-stimulated patients.

Conclusions: Unilateral rTMS as well as bilateral combined rTMS revealed no detrimental effects on cognition, as compared with the sham group. Moreover, neither the add-on design nor the used aggressive parameters had a negative impact on cognitive measures in comparison with sham. Repetitive transcranial magnetic stimulation might have mild beneficial cognitive effects partly independent of its antidepressant efficacy.

(J Clin Psychiatry 2004;65:772–782)

Received Aug. 21, 2003; accepted Nov. 22, 2003. *From the Department of General Psychiatry, University Hospital Innsbruck, Innsbruck (Drs. Hausmann, Kemmler, Rupp, Lechner-Schoner, Kramer-Reinstadler, Walpoth, Mechtcheriakov, and Weiss); the Department of Psychiatry I, Hospital Rankweil, Rankweil (Dr. Conca), Austria; and the Laboratory for Magnetic Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass. (Drs. Hausmann and Pascual-Leone).*

This work was supported by grant BFR02/048 (Dr. Hausmann) from the Ministry of Culture, Education, and Research of the Grand-Duchy of Luxembourg, Luxembourg, Europe.

Corresponding author and reprints: Armand Hausmann, M.D., University Hospital Innsbruck, Department of General Psychiatry, Anichstrasse 35, A-6020 Innsbruck, Austria/Europe (e-mail: armand.hausmann@uibk.ac.at).

Transcranial magnetic stimulation (TMS) allows for noninvasive electromagnetic modulation of distinct cortical areas.[1] In addition, TMS is quite likely to produce a change of activation in a widely distributed transsynaptically linked neural network as demonstrated by neuroimaging methods.[2,3] Repetitive transcranial magnetic stimulation (rTMS) (≥ 1 Hz) has been extensively studied in the treatment of depression.[4,5] High-frequency-rTMS (hf-rTMS) (≥ 1 Hz) over the left dorsolateral-prefrontal cortex (DLPFC) leads to significant antidepressant effects as compared with sham stimulation, but the clinical impact remains poor.[6,7] In order to improve efficacy in antidepressant rTMS trials, different stimulation paradigms such as combined bilateral hf- and low-frequency (lf)-rTMS over the left and right DLPFC, respectively, were recently theorized to be more effective.[8]

Much clinical rTMS research in depression has been motivated by the search for an effective somatic treatment with less cognitive impairment than electroconvulsive therapy. The cognitive side effects of rTMS in depression remain insufficiently studied, and careful monitoring of patients with adequate neuropsychological test batteries is critical. This monitoring is particularly important since the effects of rTMS on behavior and cognition can outlast the initial rTMS application.[9,10]

The potential risks of cognitive side effects of rTMS may well increase when rTMS is used as "add-on"

therapy for antidepressant medication, which can have neuropsychological deficits of its own. In polydrug trials, side effects can be potentiated due to interactions between drugs.[11]

Data on standard neuropsychological tests have revealed within-group improvements[3,10,12–16] or improvements in means by time × treatment interaction[12,17] on several cognitive measures in the majority of antidepressant rTMS trials (Table 1). In the present study, some patients received rTMS to both the right and the left prefrontal cortex at different stimulation frequencies. With the exception of 2 reports,[18,19] little is known about the safety of bilateral rTMS application. The aggressive stimulation parameters used, in order to enhance antidepressant outcome, have never been carefully assessed before and could have been a source of cognitive impairment. For example, Loo et al.,[19] using a simultaneous bilateral hf-rTMS, described a significant initial weak deleterious effect on problem-solving skills in patients during a 3-week trial. In consideration of the imponderability of cognitive outcome, we sought to monitor neurocognitive aspects in patients who underwent active treatment designed to enhance antidepressant outcome, in comparison with sham-stimulated patients.

METHOD

Patients

The study was designed as a single-center, prospective, double-blind, sham-controlled trial. Forty-one patients with a diagnosis of a depressive episode in the course of major depression or bipolar I disorder according to DSM-IV criteria were consecutively chosen from a sample of inpatients from a psychiatric ward at the University Hospital Innsbruck, Innsbruck, Austria. The ethics committee of the University of Innsbruck approved the study design. At admission to the ward, a washout of antidepressant medication was performed for a duration dependent on the 5-fold half-life of the drug that the patient was taking. After a complete description of the study to the subjects, written informed consent was obtained prior to participation. All patients received rTMS during a 2-week time period (2 × 5 sessions with a 2-day break). In order to speed up the expected antidepressant effect, an "add-on" study paradigm was chosen, and antidepressant medication was commenced on the first day of stimulation and maintained throughout the stimulation period. Dosage remained constant during the trial. Data were collected from November 1999 to August 2002.

The 41 patients were randomly assigned to 1 of 3 groups: A1, A2, and C (A1 = active unilateral stimulation, A2 = active bilateral stimulation, and C = control [sham group]). In addition, all patients, irrespective of randomization, received an antidepressant drug the first day of rTMS. Three patients, 1 from each group, terminated the study prematurely. One patient dropped out because she could not tolerate the uncomfortable sensation inherent to hf-rTMS, 1 patient (group A2) was excluded because she developed a manic symptomatology, and a third patient was transferred to another hospital closer to his home 1 day before terminating the stimulation protocol.

Group A1. Patients (N = 12) received hf-rTMS applied to the left DLPFC (20 Hz, 100% motor threshold (MT), 10 trains of 10 seconds' duration with a 90-second intertrain interval, resulting in a total of 2000 stimuli per session for 2 × 5 days). After a 5-minute break, a low-frequency sham stimulation was applied over the right DLPFC.

Group A2. Patients (N = 13) underwent active hf-rTMS of the left DLPFC as described for Group A1 followed by active lf-rTMS over the right DLPFC (1 Hz, 120% MT, for 10 minutes, resulting in a total of 2600 stimuli per session for 2 × 5 days).

Group C. Patients (N = 13) who served as a control group received bilateral sham stimulation, hf-rTMS to the left DLPFC, followed by lf-rTMS to the right DLPFC.

Repetitive Transcranial Magnetic Stimulation Procedure

Magnetic stimulator. Stimulation was performed with a Magstim 200 Rapid Stimulator (Magstim Company Limited, Spring Gardens, Whitland, U.K.).

Coil placement and orientation. Active stimulation was performed with a figure 8–shaped focal coil centered to the left and right DLPFC as defined by the individual's magnetic resonance imaging. Identical to the handling of the active coil, the sham coil was placed onto the patient's head; the only difference was that this coil was disconnected from the stimulator. At the same time, a second active coil was held 10 cm behind the patient's head. This coil produced the acoustic artifact as required by randomization group. This kind of sham stimulation was chosen in order to avoid a sham paradigm previously described to be somewhat active.[20]

Stimulation. Surface electromyographic electrodes were attached bilaterally over the first dorsal interosseous muscle, and the patient's individual MT at rest was determined bilaterally. The doctor-patient interaction was standardized and was consistent for all treatment groups.

Safety. The stimulation parameters used must be considered aggressive, as they are out of range of commonly used safety recommendations.[21] Patients were informed of this fact, and specific precautions were implemented. Surface electrodes remained attached during stimulation in order to enable early recognition of possible intracerebral stimulus spreading. Nonblinded psychiatrists performed stimulation, and neurophysiological monitoring was performed by a clinical neurophysiologist or by a psychiatrist trained in the particular aspects of detecting signs of seizure activity.

Table 1. Published Studies Assessing Neurocognition in Antidepressive rTMS Trials

Author	Design	Number of Patients	Medication	rTMS Parameters
Avery et al, 1999[41]	Randomized, double-blind, placebo-controlled	N = 4 (10 Hz) N = 2 (sham)	Yes (N = 4) No (N = 2)	10 Hz at 80% MT, 10 sessions × 20 trains × 5 s over LDLPFC 10,000 stimuli
Padberg et al, 1999[12]	Randomized, double-blind, placebo-controlled	N = 9 (10 Hz) N = 9 (0.3 Hz) N = 6 (sham)	Yes (N = 15) No (N = 3)	10 Hz at 90% MT, 5 sessions × 5 trains × 5 s over LDLPFC 1250 stimuli 0.3 Hz at 90% MT, 5 sessions × 10 trains over LDLPFC 1250 stimuli
Triggs et al, 1999[10]	Open	N = 10 (20 Hz)	No (N = 9) Yes (N = 1)	20 Hz at 80% MT, 10 sessions × 50 trains × 2 s over LDLPFC 20,000 stimuli
Little et al, 2000[13]	Randomized, double-blind, placebo-controlled, crossover	N = 10 (1 and 20 Hz crossover) N = 3 (sham and 20 Hz crossover)	No (N = 10) Yes (N = 3)	20 Hz at 80% MT, 10 sessions × 20 trains × 2 s over LDLPFC 8000 stimuli 1 Hz at 80% MT, 10 sessions × 20 trains × 10 s over LDLPFC 8000 stimuli
Speer et al, 2001[33]	Randomized, double-blind, placebo-controlled, crossover	N = 10 (1 Hz) N = 3 (20 Hz) N = 5 (sham and crossover to 20 Hz)	No (N = 15) Yes (N = 3)	20 Hz at 100% MT, 10 sessions × 40 trains × 2 s over LDLPFC 16,000 stimuli 1 Hz at 100% MT, 10 sessions × 1 train × 26 min over LDLPFC 16,000 stimuli
Loo et al, 2001[14]	Randomized, double-blind, placebo-controlled, 2-week evaluation	N = 9 (10 Hz) N = 9 (sham)	Yes (N = 13) No (N = 5)	10 Hz at 110% MT, 10 sessions × 30 trains × 5 s over LDLPFC 15,000 stimuli
Moser et al, 2002[17]	Randomized, blind, placebo-controlled	N = 9 (20 Hz) N = 10 (sham)	No	20 Hz at 80% MT, 5 sessions × 20 trains × 2 s over LDLPFC 4000 stimuli
Shajahan et al, 2002[3]	Randomized, double-blind	N = 5 (20 Hz) N = 5 (10 Hz) N = 5 (5 Hz)	Yes	20 Hz at 80% MT, 10 sessions × 25 trains × 1 s over LDLPFC 5000 stimuli 10 Hz at 80% MT, 10 sessions × 25 trains × 2 s over LDLPFC 5000 stimuli 5 Hz at 80% MT, 10 sessions × 25 trains × 4 s over LDLPFC 5000 stimuli

Tests	Time × Treatment Interaction	Within-Group Findings
Controlled Oral Word Association Test[42,43] Galveston Orientation and Amnesia Test[44] Lateral Dominance Examination[45] Rey Auditory Verbal Learning Test[46] Stroop Color Word Test[27] Trail Making Test A and B[26] Digit Span and Digit Symbol subtests of Wechsler Adult Intelligence Scale[47]	No significant differences	No significant findings
Verbal Learning Task[48]	Treatment groups (10 and 0.3 Hz) performed significantly better on memory scores in comparison with sham group.	Significant improvement in verbal memory in the 10-Hz group but not in the 0.3-Hz group Trend to decreased memory performance in the sham group
Boston Naming Test[49] Controlled Oral Word Association Test Digit Span subtest Hopkins Verbal Learning Test[50] Mini-Mental State Examination[51] State Trait Anxiety Inventory[52]	Open trial	Significant improvement of Digit Span subtest and Controlled Oral Word Association Test following day 10 Improvement of Controlled Oral Word Association Test, Boston Naming Test, and Hopkins Verbal Learning Test after 3 months
Battery A: (immediately before and after each rTMS session) Buschke Selective Reminding Test of Episodic Memory[53] Colorado Neuropsychology Battery (memory cards)[54] Meta-Memory Task (recall, recognition)[55] Battery B: (pre- and post-rTMS after each treatment condition) Buschke Selective Reminding Test of Episodic Memory Category Fluency Task[56,57] Continous Performance Task[58] Letter Fluency Task[42]	No data	Significant improvement in List Recall Test from pre- to post-rTMS after 1 week for 1 and 20 Hz
Buschke Selective Reminding Test of Episodic Memory Colorado Neuropsychology Battery (memory cards)[54] Continous Performance Task Shipley Institute of Living Scale[59] Word and Category Fluency Test[43]	Analysis missing	No deterioration in measures comparing treatment condition with baseline Significant improvement in sham condition concerning Buschke Selective Reminding Test relative to baseline
Autobiographical Memory Interview[60] Controlled Oral Word Association Test Digit Span subtest (backward/forward) Tapping Speed Test[61] Rey Auditory Verbal Learning Test Mini-Mental State Examination Tower of London[62] Visual Paired Associates Learning[63]	No significant time × group interaction in any of the evaluated tests	…
Boston Naming Test[49] Trail Making Test A and B Stroop Test Controlled Oral Word Association Test Digit Symbol Substitution Test[47] Rey Auditory Verbal Learning Test Line orientation Sentence repetition	Significant improvement of the actively treated group on Trail Making Test B in comparison with sham	…
Daily tests Auditory Verbal Learning Test[64] Simple and complex motor speed Stress Arousal Inventory[65] Traffic Lights Test[3] Weekly tests Auditory Verbal Learning Test[64] Digit Symbol Substitution Test Test of Everyday Attention[66] Traffic Lights Test Wechsler Memory Scale[67]	No data with respect to treatment condition	Pooled patients performed significantly better in Digit Span forward and a sub-item of Test of Everyday Attention (visual elevator: time scored) over time.

continued

Table 1. Published Studies Assessing Neurocognition in Antidepressive rTMS Trials (cont.)

Author	Design	Number of Patients	Medication	rTMS Parameters
Loo et al, 2003[19]	Randomized, double-blind, placebo-controlled	N = 9 (active) N = 10 (sham)	Yes (N = 14) No (N = 5)	15 Hz at 90% MT, 15 sessions × 24 trains × 5 s over LDLPFC and RDLPFC 27,000 stimuli
Cohen et al, 2003[18]	Open	N = 5 (20 Hz) N = 5 (1 Hz)	Yes	20 Hz at 100% MT up to 10 sessions × 20 trains × 1.5 s over LDLPFC Up to 6000 stimuli 1Hz at 100% MT up to 10 sessions × 2 trains × 60 s over RDLPFC Up to 1200 stimuli
O'Connor et al, 2003[15]	ECT: open rTMS: open	N = 14 (ECT) N = 14 (rTMS)	No	10 Hz at 90% MT, 10 sessions × 20 trains × 8 s over LDLPFC 16,000 stimuli
Martis et al, 2003[16]	Open	N = 15	No	10 Hz at 110% MT, 10–20 sessions × 20 trains × 5 s over LDLPFC 10,000–20,000 stimuli
Hoeppner et al, 2003[32]	Placebo-controlled	N = 10 (20 Hz) N = 10 (1 Hz) N = 10 (sham)	Yes	20 Hz at 90% MT, 10 sessions × 20 trains × 2 s over LDLPFC 8000 stimuli 1 Hz at 110% MT, 10 sessions × 2 trains × 60 s over RDLPFC 1200 stimuli

Abbreviations: ECT = electroconvulsive therapy, LDLPFC = left dorsolateral-prefrontal cortex, MT = motor threshold,

Ratings for Depression

Patients were evaluated using the 21-item Hamilton Rating Scale for Depression (HAM-D-21)[22] and the Beck Depression Inventory (BDI)[23] at baseline (day 0) and following stimulation (day 14). Between day 0 and day 14, patients were evaluated at days 1, 3, 5, 7, and 10. Blinded trained psychiatrists who underwent biweekly interrater training performed all ratings.

Neuropsychological Measures

Neuropsychological assessment was done before (baseline, day 0) and following (day 14) rTMS using standardized psychometric testing procedures focusing on motor skills, attention, executive functions, learning, and memory. Verbal memory functions were evaluated with the Muenchner Verbaler Gedaechtnistest (MVG),[24] a German equivalent of the California Verbal Learning Test.[25] This test measures learning, short-term and long-term verbal memory, and word recognition. In order to minimize practice effects, a paired alternate test form of the MVG was used. To test psychomotor speed, attention, and cognitive flexibility, the Trail Making Test (TMT)[26] was administered. Selective attention, set shifting, and suppression of distraction were evaluated using the Color-Word Interference Test (Stroop Test).[27] The Stroop Test is suitable for evaluating special aspects of selective attention, namely susceptibility to interference, and examines conflicts between automated and controlled information processing.[28,29] The verbal fluency test was adapted from the Controlled Oral Word Association Test.[30] Letter fluency (F, A, S) and category fluency (supermarket, animals, vegetables) were each tested in 60-second trials. The mean number of words produced in each of the 2 trials was the outcome of interest.

Statistical Analysis

The 3 treatment groups (A1, A2, C) were compared with respect to patient characteristics and baseline neuropsychological performance and depression scores (HAM-D-21 and BDI) by 1-way analysis of variance (ANOVA) or χ^2 test, depending on the variable type. The 2 actively treated groups (A1, A2) were then compared regarding neuropsychological performance, both at baseline and day 14, using 1-way ANOVA and, due to a lack of group differences, were pooled for all further parts of the analysis.

Changes in neuropsychological parameters (day 0 vs. day 14) were analyzed both within and between groups (active treatment vs. sham), using paired t tests for the

Tests	Time × Treatment Interaction	Within-Group Findings
Core-measure of psychomotor retardation[68] Controlled Oral Word Association Test Expanded Paired Associate Test[69] Mini-Mental State Examination Rey Auditory Verbal Learning Test Tower of London Visual Learning[70] Visual Paired Associates Learning	No significant difference between sham and active treatment over time Difference between groups in Tower of London with sham group improving and actively treated group worsening (not significant after correction)	…
Mini-Mental State Examination	Open trial	No significant outcome in Mini-Mental State Examination relative to baseline
Rey Auditory Verbal Learning Test Letter Number Sequencing Task[67] Transient News Events Test[71]	Open trial	Mild improvement in Letter Number Sequencing Task and Transient News Events Test
Simple and Choice Reaction Time[43] Stroop Test Wechsler Adult Intelligence Scale-3[47] Wechsler Memory Scale-Revised[67] Controlled Oral Word Association Test Tests grouped into 3 cognitive domains such as attention and mental speed, working memory-executive function, and objective memory	Open trial	Tests showed a significant improvement over time in attention and mental speed, working memory–executive function, and objective memory.
Motor Agitation and Retardation Scale[72] D2-Test[73]	Significant improvement of slight motor retardation following active treatment (20 Hz or 1 Hz)	…

RDLPFC = right dorsolateral-prefrontal cortex, rTMS = repetitive transcranial magnetic stimulation, … = no data.

former and repeated-measures ANOVA for the latter analyses. Group differences in the short-term course of neuropsychological measures are indicated by significant group-by-time interactions. The distribution of several neuropsychological measures (in particular TMT A and B as well as Stroop 2 and 3) showed marked non-normality and were therefore subjected to an appropriate normalizing transformation before performing the ANOVAs. The relationship between neuropsychological performance measures and depression, both at fixed time points and in the course of time, was analyzed using Spearman correlation coefficients (Pearson correlation coefficients would have yielded very similar results). Data on dropouts were analyzed using the last observation carried forward method. Observations were carried forward for a maximum time span of 4 days. All significance levels reported are 2-tailed without adjustment for multiple testing. However, for scrutinizing group differences, Bonferroni-corrected significance levels were calculated additionally for group-by-time interactions.

Power Analysis

The sample size of 25 subjects receiving active treatment (groups A1 + A2) and 13 control subjects (group C) was large enough to detect, under standard assumptions (80% power, significance level of $\alpha = .05$), between-group differences exceeding an effect size of 1.01 and within-group differences (day 0 vs. day 14) beyond an effect size of 0.58 for the active treatment group and beyond an effect size of 0.88 for the sham group. The sample size, which is larger than those in most other rTMS studies,[17] is therefore sufficiently high to reveal moderate within-group differences, especially in the active treatment group, but allows only for the detection of marked between-group differences.

RESULTS

The 3 groups did not differ significantly with regard to age, gender, and disease characteristics (Table 2). There were no significant differences between the 3 groups (A1, A2, and C) or between the pooled treatment groups (A1 + A2) and the sham group in terms of HAM-D-21 and BDI scores at baseline (day 0).

Safety

In general, given the seizure-induction potential of the used paradigm, treatment conditions were well tolerated

Table 2. Sociodemographic Data and Patient Characteristics[a]

Variable	Group A1 (LDLPFC), N = 12	Group A2 (L + RDLPFC), N = 13	Group C (Sham), N = 13	Total, N = 38	Significance
Age, mean ± SD, y	47.33 ± 13.34	45.23 ± 11.95	47.00 ± 11.31	46.50 ± 11.90	NS
Gender, N (%)					
Male	6 (50.0)	5 (38.5)	4 (30.8)	15 (39.5)	NS
Female	6 (50.0)	8 (61.5)	9 (69.2)	23 (60.5)	
Diagnosis/course of illness					
Unipolar (%)	10 (83.3)	11 (84.6)	11 (84.6)	32 (84.2)	NS
Bipolar (%)	2 (16.7)	2 (15.4)	2 (15.4)	6 (15.8)	
Duration of illness, N (%)					
≤ 5 years	5 (41.7)	4 (33.3)	7 (53.8)	16 (43.2)	NS
> 5 years	7 (58.3)	8 (66.7)	6 (46.2)	21 (56.8)	
HAM-D-21 score, mean ± SD					
Baseline	31.6 ± 4.6	32.9 ± 7.1	33.7 ± 3.7		
Day 14	16.8 ± 10.0	18.4 ± 8.2	21.8 ± 8.2		

[a]Recordings of 1 patient concerning data on chronicity, number of episodes, and duration of illness are missing.
Abbreviations: HAM-D-21 = 21-item Hamilton Rating Scale for Depression, LDLPFC = left dorsolateral-prefrontal cortex, NS = not significant, RDLPFC = right dorsolateral-prefrontal cortex.

overall. With the exception of 2 patients complaining of headache (group A1 and C) and 1 patient exerting a manic symptomatology (group A2), there were no adverse events, including seizures.

Cognitive Outcomes

Unilaterally stimulated group (A1) compared with the bilaterally stimulated group (A2). Our analysis revealed no difference in any of the neuropsychological measures between the 2 active treatment groups. Thus, data from the 2 actively treated groups were pooled in order to increase statistical power (Table 3).

Changes within the active treatment groups (A1 + A2). After 2 weeks of treatment, a statistically significant improvement in 2 neuropsychological variables, namely Stroop 2 ($p = .008$) and Stroop 3 ($p = .001$), was seen in the actively treated group (A1 + A2) but not in the control group. In addition, a significant improvement could be observed in TMT A and B, which reflects an amelioration of psychomotor speed and set shifting ability. A trend toward better performance was also found in verbal fluency (letter). No other significant changes in neuropsychological performance were observed within the treated groups, neither in terms of an increase nor a decrease in performance (Table 3).

Active treatment groups (A1 + A2) compared with the sham-stimulated group (C). When comparing the actively treated patients with the sham-stimulated controls, only 1 of the neuropsychological measures showed a statistically significant group-by-time interaction, namely MVG encoding trial 5 ($p = .028$). Data indicate that actively treated patients showed a significantly more favorable time course in this parameter than sham-stimulated patients. This result remained significant after adjustment for changes in depression scores (HAM-D-21, BDI) by analysis of covariance ($p = .037$). However, there was no other significant group × time interaction effect, and the statistical significance in the MVG measure is not retained after a Bonferroni correction for multiple testing.

Depression Outcomes

Both HAM-D-21 and BDI scores decreased significantly from baseline to day 14 in the 2 active groups as well as in the sham group (Table 2). However, there was no significant difference between the active treatment groups (N = 25) and the sham-stimulated group (N = 13) in terms of a decrease in HAM-D-21 and BDI scores over time (days 0–14).[31]

Correlation Between Measures of Cognition and Depression

At baseline, only a single significant correlation between a cognitive measure and depression was found in the total sample, namely a positive correlation between BDI and Stroop 3 (Spearman correlation $r = 0.34$, $p = .050$). As this result does not withstand a Bonferroni correction for multiple testing, the possibility of a chance finding cannot be ruled out. Improvement in BDI total score (days 0 to 14) correlated significantly with improvements in Stroop 2 and 3 in the same period of time, both in the total sample ($r = 0.47$, $p = .012$ and $r = 0.40$, $p = .037$, respectively) and in the pooled active treatment groups A1 and A2 ($r = 0.61$, $p = .012$ and $r = 0.52$, $p = .041$, respectively). Moreover, in the latter group, a significant association between improvement in HAM-D-21 scores and improved memory performance was observed (for MVG encoding trial 1 as well as MVG encoding trial 5 and MVG encoding trials 1–5: $r > 0.5$, $p \leq .046$).

DISCUSSION

We analyzed neurocognitive data from 38 patients with depression who underwent a neuropsychological test battery at baseline and following a 2-week unilateral and

Table 3. Neuropsychological Measures in Inpatients With Depression: Active rTMS (groups A1 and A2) vs. Sham Stimulation (group C)[a,b]

Tests and Parameters	Active rTMS (Groups A1 + A2), N = 25			Sham (Group C), N = 13			Time-by-Treatment Interaction[c]
	Day 0	Day 14	Day 0 vs 14	Day 0	Day 14	Day 0 vs 14	
TMT, mean ± SD							
TMT A	57.5 ± 37.1	46.4 ± 27.9	p = .032	44.3 ± 25.9	41.1 ± 21.0	NS	NS
TMT B	141.7 ± 68.1	119.9 ± 70.7	p = .042	119.8 ± 55.4	119.9 ± 56.0	NS	NS
Stroop Test, mean ± SD							
Stroop 1 (mean time of reading color words and naming of colors)	47.5 ± 5.6	48.6 ± 14.2	NS	47.2 ± 18.4	53.1 ± 31.0	NS	NS
Stroop 2 interference	119.6 ± 30.3	102.8 ± 25.5	p = .008	114.1 ± 44.4	117.3 ± 53.0	NS	NS
Stroop 3 cognitive time	72.0 ± 27.1	54.5 ± 21.4	p = .001	66.9 ± 29.5	64.1 ± 34.3	NS	NS
MVG, mean ± SD							
Encoding trial 1	5.3 ± 1.8	6.1 ± 2.3	NS	5.4 ± 2.4	5.6 ± 2.1	NS	NS
Encoding trial 5	11.2 ± 2.9	11.9 ± 3.3	NS	12.1 ± 3.1	10.6 ± 2.8	p = .034	p = .028
Encoding trial (1–5)	43.8 ± 12.4	48.9 ± 13.1	NS	45.6 ± 10.7	44.0 ± 10.0	NS	NS
Short delay-free recall	8.0 ± 3.7	8.6 ± 3.9	NS	9.2 ± 2.9	8.1 ± 3.4	NS	NS
Long delay-free recall	8.6 ± 3.6	7.9 ± 4.1	NS	10.1 ± 3.1	8.0 ± 3.6	NS	NS
Recognition	14.7 ± 1.3	14.3 ± 2.6	NS	15.5 ± 0.7	14.4 ± 1.4	p = .019	NS
Verbal fluency, mean ± SD							
Verbal fluency-letter	27.5 ± 12.9	31.1 ± 13.5	p = .075	28.3 ± 13.1	31.4 ± 12.8	NS	NS
Verbal fluency-category	37.7 ± 8.1	37.3 ± 7.8	NS	39.5 ± 8.3	40.6 ± 7.9	NS	NS

[a]Only cases with nonmissing values at day 0 and day 14 are included.
[b]NS = p > .10.
[c]Interaction between the factors time (day 0 vs. day 14) and treatment (active rTMS vs. sham) in a repeated-measures analysis of variance.
Abbreviations: MVG = Muenchner Verbaler Gedaechtnistest, NS = not significant, rTMS = repetitive transcranial magnetic stimulation, TMT = Trail Making Test.

bilateral rTMS add-on trial using aggressive stimulation parameters. The main finding in our study was that patients showed no deterioration in cognitive functions after 2 weeks of unilateral and bilateral rTMS compared with sham stimulation. As revealed in Table 3, the short-term course (day 0 vs. day 14) of all cognitive parameters was slightly better for group A1 + A2 than for group C, surely supporting the lack of detrimental cognitive impact of the intervention. Our data on the within-group improvement of TMT A and B scores parallel previous data by Moser et al.,[17] who reported a significant time-by-treatment interaction in the TMT B in comparison with sham, and also parallel data of Hoeppner et al.,[32] who reported a significant improvement of motor retardation after active treatment over the left DLPFC (20 Hz) or the right DLPFC (1 Hz).

Furthermore, patients in the active rTMS treatment groups showed a more favorable time course for encoding in the verbal memory test compared with the sham-stimulated patients (Table 3). Given that controlling for depressive symptomatology did not lead to changes in our results, one might consider this finding to be independent of the alleviation of depressive symptoms.

The finding of no deleterious effects on cognition in the *unilateral* left DLPFC–stimulated sample (group A1) are consistent with the findings of other studies that also reported a lack of deleterious neurocognitive impact of rTMS over the left DLPFC in depressive patients.[3,10,12–14,17,19,33] In addition, we were able to show that a *bilateral* stimulation as used in the present study (group A2) does not exert additional cognitive side effects in comparison with unilateral stimulation (group A1) or sham stimulation (group C). A comparable outcome was seen in a bilateral rTMS trial by Cohen et al.[18] using a similar paradigm as that of group A2 but employing a noncontrolled study design on a small number of patients (N = 10) and limiting neuropsychological assessment to a brief global screening of cognitive functions, namely the Mini-Mental State Examination. Our study used an extensive neuropsychological test battery, enrolled a larger cohort of patients, and applied a higher number of stimuli to the left DLPFC (20,000 vs. 6000) (hf-rTMS) and to the right DLPFC (32,000 vs. 1200) (lf-rTMS), thus providing novel safety data on bilateral rTMS.

Our data are also in line with Loo et al.,[19] who did not find noxious rTMS effects on cognition in their simultaneous bilateral stimulation trial with 9 actively treated and 10 sham-stimulated participants. In addition to sample size, differences from our study design include the stimulation frequency (15 Hz bilateral vs. 20 Hz unilateral left and 1 Hz unilateral right), duration of stimulation (3 weeks vs. 2 weeks), and application mode (simultaneous bilateral stimulation vs. subsequent bilateral stimulation). The small sample of recruited patients in the active treatment group (N = 9) and the sham group (N = 10) in the study by Loo et al.[19] might have been a limitation to their findings. The choice of these parameters was aimed at increasing the antidepressant efficacy of rTMS. However, our trial failed to show a significant advantage of these rTMS parameters over sham stimulation in an add-on design. Testing of such bilateral rTMS parameters as mono-

therapy in comparison with antidepressant drug treatment might be desirable. Our findings support the safety of such an approach.

In regard to the question of an add-on treatment potentially having more adverse effects than a single treatment alone, we found that, although not more effective in terms of antidepressant outcome, add-on rTMS (A1 + A2) had no more cognitive side effects than administration of an antidepressant with sham stimulation (C). To the best of our knowledge, our chosen aggressive stimulation parameters have never been used in an antidepressant trial. Although out of range of the usual parameters,[21] they seem to be safe not only in terms of a lack of seizures, but also in terms of a lack of cognitive deterioration in the aftermath of stimulation. Low incidence of headache was seen throughout the studied patients. This translates to an incidence of headache of less than 5%, including the subject in group C receiving sham stimulation. This incidence is actually lower than the incidence reported in current safety assessments of rTMS.[21,34] As 1 patient in group A2 exerted symptoms of mania, it might be that the bilateral stimulation paradigm has inherent potential of inducing such symptoms. Alternatively, the add-on setting or the combination of both factors is to blame for this adverse event.

Several limitations to our data need to be addressed. First, despite the fact that the assessed number of actively treated patients (Table 3) is the largest ever reported, we cannot rule out that a larger sample may reveal differing effects in neuropsychological functioning after rTMS stimulation. The fact that we were not able to show a group difference in antidepressant outcome might be due to the difficult task of showing differences between 2 antidepressive biological intervention strategies. However, our results suggest that rTMS is more likely to increase than decrease neuropsychological functioning.

A second aspect addresses the add-on treatment with antidepressants, which in the present study was done on a naturalistic basis. More than half of patients in all groups received citalopram: 60% in the active groups and 54% in the sham group. Future studies using a controlled uniform medication treatment are needed to exclude the possibility that antidepressants might have had highly discrepant effects on cognitive measures and/or depressive symptoms.

Reports of adverse events like headache were based on spontaneous patient reports and were not assessed systematically, which might explain the small number of adverse events in our study in comparison with existing literature.

In unipolar depression, cognitive deficits are well established and encompass a wide range of deficits. Attention, short-term memory, psychomotor speed,[35] and executive functions[36] are the domains most affected. There is a growing body of evidence that bipolar patients in contrast to patients suffering from unipolar depression exert a different profile of cognitive deficits,[37,38] even outlasting the acute phase of the disease.[39] In addition, chronically ill patients with bipolar disorder exhibit more severe cognitive impairments than those patients with a more remitting course of their illness.[40] Although we preferentially enrolled patients with unipolar depression (84.2%), our data might have been confounded by a differing cognitive output in both unipolar or bipolar depression.

CONCLUSIONS

Our results demonstrate that rTMS, conservatively spoken, had no negative impact on cognition in a 2-week trial. Actively treated groups even showed some improvement on several neuropsychological measures in the aftermath of the rTMS treatment. However, these improvements did not reach statistical significance in comparison with sham stimulation. Although the time × treatment data in memory could not withstand a Bonferroni correction, rTMS might have beneficial cognitive effects independent of its antidepressant efficacy.

The data extend prior findings as they indicate no detrimental effect on cognitive functioning in a stimulation paradigm using aggressive stimulation parameters outside current recommended guidelines and applied bilaterally to both frontal lobes.

Drug name: citalopram (Celexa and others).

REFERENCES

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex [letter]. Lancet 1985;1:1106–1107
2. Paus T, Jech R, Thompson CJ, et al. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 1997;7:3178–3184
3. Shajahan PM, Glabus MF, Steele JD, et al. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. Prog Neuropsychol Biol Psychiatry 2002;26:945–954
4. Pascual-Leone A, Rubio B, Pallardó F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;347:233–237
5. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry 2000; 48:962–970
6. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a metaanalysis. Int J Neuropsychopharmacol 2002;5:73–103
7. Martin JL, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression. Cochrane Database Syst Rev 2000; 2:CD003493
8. Lisanby SH. Focal brain stimulation with repetitive transcranial magnetic stimulation (rTMS): implications for the neural circuitry of depression. Psychol Med 2003;33:7–13
9. Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 2000;1:73–79
10. Triggs WJ, McCoy KJM, Greer R, et al. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition and corticomotor threshold. Biol Psychiatry 1999;45:1440–1446
11. Ereshefsky L, Dugan D. Review of the pharmacokinetics, pharmacogenetics, and drug interaction potential of antidepressants: focus on venlafaxine. Depress Anxiety 2000;12(suppl 1):30–44
12. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic

stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res 1999; 88:163–171
13. Little JT, Kimbrell TA, Wassermann EM, et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation: preliminary reports. Neuropsychiatry Neuropsychol Behav Neurol 2000;13:119–124
14. Loo C, Sachdev P, Elsayed H, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. Biol Psychiatry 2001;49:615–623
15. O'Connor M, Brenninkmeyer C, Morgan A, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. Cogn Behav Neurol 2003;16:118–127
16. Martis B, Alam D, Dowd SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin Neurophysiol 2003;114:1125–1132
17. Moser DJ, Jorge RE, Manes F, et al. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 2002;58:1288–1290
18. Cohen CI, Amassian V, Akande B, et al. The efficacy and safety of bilateral rTMS in medication-resistant depression [letter]. J Clin Psychiatry 2003;64:613–614
19. Loo C, Mitchell PB, Croker VM, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. Psychol Med 2003;33:33–40
20. Loo C, Taylor JL, Gandevia SC, et al. Transcranial magnetic stimulation (rTMS) in controlled treatment studies: are some "sham" forms active? Biol Psychiatry 2000;47:325–331
21. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation; June 5–7,1996. Electroencephalogr Clin Neurophysiol 1998;108:1–6
22. Hamilton N. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
23. Beck AT. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 1974;7:151–169
24. Illmberger J. Muenchner Verbaler Gedaechtnistest (MVG). German version of the California Verbal Learning Test (CVLT). MD: Universitaet Muenchen, Institut fuer Medizinische Psychologie; 1988
25. Delis DC, Kramer JH, Freeland J, et al. The California Verbal Learning Test. San Antonio, Tex: Psychological Corporation; 1987
26. Reitan RM. Validity of the Trailmaking Test as an indication of organic brain damage. Percept Mot Skill 1958;8:271–276
27. Baeumler G. Farbe-Wort-Interferenztest nach J.R. Stroop (FWIT). Goettingen, Germany: Hogrefe; 1985
28. Neisser U. Cognitive Psychology. New York, NY: Appleton-Century-Crofts; 1967
29. Shiffrin R, Schneider W. Controlled and automatic human information processing. Psychol Rev 1977;84:127–190
30. Spreen O, Benton A. Comprehensive Examination for Aphasia (NCCEA), revised edition. Victoria, British Columbia: Neurosensory Center, University of Victoria, Neuropsychology Laboratory; 1977
31. Hausmann A, Kemmler G, Walpoth M, et al. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add-on" trial. J Neurol Neurosurg Psychiatry 2004;75:320–322
32. Hoeppner J, Schulz M, Irmisch G, et al. Antidepressant efficacy of two different rTMS procedures. Eur Arch Psychiatry Clin Neurosci 2003;253: 103–109
33. Speer AM, Repella JD, Figueras S, et al. Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. J ECT 2001;17:259–263
34. Hallett M, Wassermann EM, Pascual-Leone A. Repetitive transcranial magnetic stimulation. In: Deuschl G, Eisen A, eds. Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology. 2nd ed. Ireland: Elsevier Science; 1999
35. Brown RG, Scott LC, Bench CJ, et al. Cognitive function in depression: relationship to the presence and severity of intellectual decline. Psychol Med 1994;24:829–847
36. Porter RJ, Gallagher P, Thompson JM, et al. Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 2003;182:214–220
37. Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 2000;48:674–684
38. Murphy FC, Sahakian BJ. Neuropsychology of bipolar disorder. Br J Psychiatry 2001;178:120–127
39. Zubieta JK, Huguelet P, Lajiness R, et al. Cognitive function in euthymic bipolar I disorder. Psychiatry Res 2001;102:9–20
40. McKay AP, Tarbuck AF, Shapleske J, et al. Neuropsychological function in manic-depressive psychosis: evidence for persistent deficits in patients with chronic severe illness. Br J Psychiatry 1995;167:51–57
41. Avery D, Claypoole K, Robinson L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. J Nerv Ment Dis 1999;187:114–117
42. Benton AL, Hamsher KD. Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates; 1989
43. Spreen O, Strauss E. A Compendium of Neuropsychological Tests. New York, NY: Oxford University Press; 1991
44. Levin HS, O'Donnell VM, Grossman RG. The Galveston Orientation and Amnesia Test: a practical scale to assess cognition after head injury. J Nerv Ment Dis 1979;167:675–685
45. Reitan RM, Davison LA. Clinical Neuropsychology: Current Status and Applications. New York, NY: Winston/Wiley; 1974
46. Rey A. L´Examen Clinique en Psychologie. Paris, France: Presses Universitaires de France; 1964
47. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York, NY: Psychological Corporation; 1981
48. Kathmann N, Soyka M, Gallinat J, et al. Effects of acamprosate on verbal learning in healthy young subjects. In: Soyka M, ed. Acamprosate in Relapse Prevention of Alcoholism. Berlin, Germany: Springer; 1996: 105–110
49. Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. Boston, Mass: Kaplan & Goodglass; 1978
50. Benedict R, Schretlen D, Groninger L, et al. Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 1998;12:43–55
51. Folstein MF, Folstein SE, Mc Hugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
52. Spielberger CD. The measurement of state and trait anxiety: conceptual and methodological issues. In: Levi L, ed. Emotions: The Parameters and Measurements. New York, NY: Raven Press; 1975:713–725
53. Buschke H. Selective reminding for analysis of memory and learning. J Verbal Learn Verbal Behav 1973;12:543–550
54. Davis HP, Bajszar GM, Squire LR. Colorado Neuropsychology Tests, Version 2.0. Colorado Springs, Colo: Neuropsychology Tests Co; 1994
55. Leonesio RJ, Nelson TO. Do different metamemory judgements tap the same underlying aspects of memory? J Exp Psychol 1990;16: 464–470
56. Barsalou LW, Scwell DR. Contrasting re-representation of scripts and categories. J Mem Lang 1985;24:646–665
57. Newcombe F. Missile Wounds of the Brain. London: Oxford University Press; 1969
58. Conners CK. Continuous Performance Test Computer Program 3.0. Toronto, Ontario, Canada: Multi-Health Systems Inc; 1994
59. Shipley WC. Shipley Institute of Living Scale. Los Angeles, Calif: Western Psychological Services Publishers and Distributors; 1991
60. Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. J Clin Exp Neuropsychol 1989;11:724–744
61. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Tucson, AZ: Neuropsychology Press; 1993
62. Cohen NJ, Squire LR. Preserved learning and retention patterns-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 1980;210:207–210
63. Abrams R. Electroconvulsive Therapy. 3rd ed. New York, NY: Oxford University Press; 1998
64. Lezak MD. Neuropsychological Assessment. New York, NY: Oxford University Press; 1995
65. MacKay C, Cox T, Burrows G, et al. An inventory for the measurement

of self-reported stress and arousal. Br J Soc Clin Psychol 1978;17:283–284
66. Robertson IH, Ward T, Ridgeway V, et al. The Test of Everyday Attention Manual. Edmunds, England: Thames Valley Test; 1994
67. Wechsler D. Wechsler Memory Scale-Revised. New York, NY: Psychological Corporation, Harcourt Brace Jovanovich; 1987
68. Parker G, Hadzi-Pavlovic D, Boyce P, et al. Classifying depression by mental state signs. Br J Psychiatry 1990;157:55–65
69. Trahan DE, Larrabee GJ, Quintana JW, et al. Development and clinical validation of an expanded paired associate test with delayed recall. Clin Neuropsychol 1989;3:169–183
70. Vanderplas JM, Garvin EA. The association value of random shapes. J Exp Psychol 1959;57:147–154
71. O'Connor MG, Sieggreen M, Bachna K, et al. Longterm retention for transient news events. J Int Neuropsychol Soc 2000;6:44–51
72. Sobin C, Mayer L, Endicott J. The Motor Agitation and Retardation Scale: a scale for the assessment of motor abnormalities in depressed patients. J Neuropsychiatry Clin Neurosci 1998;10:85–92
73. Brickencamp R. Test D2 (Aufmerksamkeits-Belastungs-Test). 8th ed. Goettingen, Germany: Hogrefe; 1994