Eur Arch Psychiatry Clin Neurosci (2003) 253 : 103 – 109 DOI 10.1007/s00406-003-0416-7

ORIGINAL PAPER

Jacqueline Höppner · Merten Schulz · Gisela Irmisch · Regina Mau · Detlef Schläfke · Jörg Richter

Antidepressant efficacy of two different rTMS procedures

High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation

Received: 10 October 2002 / Accepted: 18 March 2003

Abstract *Background* This placebo-controlled study was designed to investigate the influence of two different stimulation procedures of repetitive transcranial magnetic stimulation (rTMS) on depressive symptoms in patients with depressive disorders. Furthermore, effects on cognitive functions and psychomotor functioning were tested. *Methods* Thirty patients with depression (22 females and 8 males; mean age of 56.4 years) were included. They were treated with a stable dosage of antidepressant medication. They received either high frequency rTMS (20 Hz) over the left dorsolateral prefrontal cortex (LDLPFC), low frequency rTMS (1 Hz) over the right dorsolateral prefrontal cortex (RDLPFC) or sham stimulations (10 patients in each group) as add on treatment at 10 days within 2 weeks. Depressive symptoms were registered by means of observer ratings (Hamilton Depression Rating Scale – HDRS) and self reports (Beck Depression Inventory – BDI). Psychomotor retardation was investigated by the Motor Agitation and Retardation Scale and cognitive function by d2 test. *Results and conclusions* Differences between the rTMS procedures regarding depressive symptoms could not be found. Motor abnormalities, however, significantly improved exclusively after real stimulation procedures. Patients with less severe deficits in psychomotor speed and concentration responded more intensively than patients with severe deficits.

Key words repetitive transcranial magnetic stimulation (rTMS) · depression · motor retardation · concentration · psychomotor speed

D. Schläfke
Forensic Psychiatry Hospital
University Rostock, Germany

Dr. J. Höppner (✉) · M. Schulz · G. Irmisch · R. Mau · J. Richter
Department of Psychiatry and Psychotherapy
Centre of Nervous Disease
University of Rostock
Gehlsheimer Str. 20
18147 Rostock, Germany
Tel.: +49-381/494-9692
Fax: +49-381/494-9502
E-Mail: jacqueline.höppner@med.uni-rostock.de

Introduction

Since transcranial magnetic stimulation (TMS) was described by Barker et al. (1985) as a non-invasive tool for the investigation of the motor cortex, repetitive applications of this method (repetitive transcranial magnetic stimulation = rTMS) were used to study their influence on various brain functions. rTMS allows focal stimulation of cortical areas up to 2 cm under scalp and influences the cortical metabolism (George et al. 1996) as well as regional cerebral blood flow (rCBF) (Paus et al. 1998; Pecuch et al. 2000). Its effects were registered not only at the site of stimulation, but also in the network of interconnected areas, likely by mechanisms such as transsynaptic spread (Kimbrell et al. 1999).

An increased cortical excitability has been observed in humans after high-frequency (> 5 Hz) rTMS (Pascual-Leone et al. 1993) as indicated by an increase of the amplitude of motor evoked potentials (MEP) (Berardelli et al. 1998) and a decrease of motor threshold (Pascual-Leone et al. 1994). Stimulation with lower frequencies induces long-lasting inhibitory effects (Chen et al. 1997; Wassermann et al. 1996). It was assumed that rTMS could serve as a test for potential treatments in several neuropsychiatric disorders (Belmaker and Fleischmann 1995).

In psychiatric patients, a frontal hypometabolism was often described. For example dysfunctions of the left dorsolateral prefrontal cortex (LDLPFC), temporal, basal ganglia and anterior cingulate regions (decrease of rCBF and cerebral glucose metabolism) were found in depressed patients (Baxter et al. 1989; Bench et al. 1995; Paus et al. 1998; Pecuch et al. 2000). These areas have been the main target for rTMS as a therapeutic tool in depression. Some researchers (George et al. 1995; Kimbrell et al. 1999; Speer et al. 1998) observed a successful treatment of depression in combination with a reversal

of hypometabolism and hypoperfusion by means of high frequency rTMS. Kimbrell et al. (1999) reported a better antidepressant response to 20 Hz rTMS in association with the degree of baseline hypometabolism, whereas response to 1 Hz rTMS was associated with baseline hypermetabolism.

Unfortunately, most of the studies in depressive patients varied concerning stimulation parameters, concomitant medication and patient sample characteristics. Stimulation frequency is one of the most discussed parameters, which frequently varied between different studies. Pascual-Leone et al. (1996) first described the antidepressant effect of high frequency rTMS (10 Hz). A similar rTMS protocol were successfully used by Figiel et al. (1998) especially in younger patients (< 65 years), by Grunhaus et al. (2000) in patients with major depression without psychotic symptoms, by Eschweiler et al. (2000) in accordance with hemodynamic responses and by Avery et al. (1999). In contrast, Padberg et al. (1999) and Loo et al. (1999) have not found a significant reduction of depression after 10 Hz rTMS in comparison to sham stimulation.

Based on the findings of available data of 20 Hz rTMS studies, similar different results were found. George et al. (1996), Berman et al. (2000) and Triggs et al. (1999) reported a significant improvement of mood in patients with depressive disorders. In contrast, Garcia-Toro et al. (2001) found that real 20 Hz rTMS in combination with antidepressant medication resulted in a similar antidepressant effect as sham rTMS. Furthermore, Mosiman et al. (2000) could not show any significant mood changes in healthy male subjects.

The only few existing reports about 1 Hz rTMS over the right dorsolateral prefrontal cortex (RDLPFC) demonstrated an improvement of depression (Feinsod et al. 1998; Klein et al. 1999).

Comparisons of different stimulation frequencies were performed by Speer et al. (2000), Kimbrell et al. (1999) and Padberg et al. (1999). Speer et al. (2000) found that 20 Hz rTMS over the LDLPFC was associated only with an increase of blood flow measured by positron emission tomography (PET). In contrast, 1 Hz rTMS was associated with a decrease in regional cerebral blood flow (rCBF). When assessing clinical depressive symptoms Padberg et al. (1999) found only a clinically marginal improvement after slow (0.3 Hz) rTMS, but not after high frequency rTMS or sham stimulation.

In some of these studies, patients were mainly stimulated without medication, as far as this was possible (Berman et al. 2000; Figiel et al. 1998; Kimbrell et al. 1999; Pascual-Leone et al. 1996; Triggs et al. 1999). rTMS was used as an add-on treatment in de novo or medication resistant patients in other investigations (Avery et al. 1999; Garcia-Toro et al. 2001; George et al. 1997; Grunhaus et al. 2000; Klein et al. 1999; Loo et al. 1999; Padberg et al. 1999).

We found only a few reports about investigations of the influence of rTMS on cognitive performances. None of the patients in the study by Little et al. (2000) showed a deterioration of cognitive test batteries. An improvement in a list-recall test from pre- to post-rTMS was observed after either 1 Hz or 20 Hz rTMS. Trends for improvement of neuropsychological performance (Controlled Oral World Association Test, Rey Auditory – Verbal Learning Test and more), probably due to training effects, were reported by Loo et al. (2001).

The aim of our study was to compare clinical effects of two different stimulation procedures with sham stimulation as add-on treatments in patients with depressive disorders. Are there differences in changes of severity of depression, in concentration abilities and in psychomotor retardation between groups of patients treated with various procedures of rTMS?

Methods

Subjects

Thirty depressive, right-handed in-patients (22 females, 8 males) with a mean age of 56.4 ± 11.1 years have been included in this investigation. Diagnoses were made by means of the Structured Clinical Interview for DSM IV (American Psychiatric Association 1994; First et al. 1995). Patients with other relevant medical illness were excluded. Every patient received an antidepressant medication in a constant dosage over two weeks before and during the stimulation period. After comprehensive information about the study, the subjects signed a written informed consent concerning their participation in the study. The patients were unfamiliar with TMS procedures. The subjects were randomly (lottery method) allocated to receive either high-frequency rTMS over LDLPFC, low-frequency rTMS over RDLPFC or sham stimulation on 10 out of 12 days (2 weeks with five sessions each week). Ten patients were included in each group (Table 1).

rTMS

A repetitive transcranial magnetic stimulator "Maglite r 25" (medtronics), connected to a flat figure-eight-shaped coil, was used for the application of rTMS. Before rTMS was applied over prefrontal areas, the optimal stimulation location for producing motor evoked potentials (MEPs) in the right or in the left first dorsal interosseus (FDI) muscle was chosen. The stimulation threshold (ST) for the contralateral FDI muscle was determined at rest. It was defined as the lowest stimulation intensity which produced a MEP response of at least 50 μV amplitude measured peak to peak in 5 of 10 stimuli. RTMS was applied 5 cm anterior to the determined region of optimal stimulation location. We applied high-frequency rTMS with parameters essentially according to George et al. (1997) with some modifications. Twenty 20 Hz trains of 2 s duration with an inter-train-interval of 60 s were applied over the left dorsolateral prefrontal cortex (LDLPFC). Subsequently, the subjects received stimulation at 90 % of ST. For the low-frequency rTMS we used the parameters described by Klein et al. (1999). Two 1 Hz trains of 60 s duration with an inter-train-interval of 3 minutes were applied over the RDLPFC. The stimulation was performed with 110 % of ST. In contrast to the study by Klein et al. (1999), the coil was not a round but also a figure-eight-shaped coil. The sham stimulation consisted of the same conditions as the 20 Hz rTMS, except that the coil was placed with an angle of 90° in relation to the head. The outer edge of the coil remained in contact with the scalp, only.

Clinical ratings

Severity of depression was assessed by means of Hamilton Depression Rating Scale (HDRS) (21-item version) (Hamilton 1961). Fur-

Table 1 Characteristics of the patients

No.	Age	Sex	Stim	DSM-IV Diagnosis	Time since 1st episode	Number of episodes	Duration of current episode	Medication	Dosage	Response according to BDI
1	69	f	1	296.33	32 years	8	1 month	Trimipramine	150 mg	no
2	56	f	2	296.53	30 years	7	2 months	Amitriptyline	150 mg	yes
3	67	m	3	296.33	6 years	2	3 months	Doxepin	125 mg	no
4	34	f	2	296.33	6 years	12	3 months	Venlafaxine	300 mg	no
5	37	f	2	296.33	15 years	6	2 weeks	Doxepin	150 mg	no
6	57	f	1	296.33	12 years	5	2 months	Venlafaxine	300 mg	no
7	55	f	1	296.33	28 years	11	4 months	Trimipramine	350 mg	no
8	60	f	3	296.33	7 years	6	6 months	Venlafaxine	300 mg	no
9	72	f	1	296.23	6 months	1	6 months	Amitriptyline	150 mg	no
10	67	f	1	296.33	3 years	3	4 months	Citalopram	40 mg	yes
11	61	f	2	296.33	14 years	6	2 weeks	Mirtazapine	60 mg	no
12	58	f	1	296.33	31 years	12	2 months	Reboxetine	8 mg	yes
13	49	f	2	296.22	3 months	1	3 months	Citalopram	20 mg	no
14	58	m	2	296.33	13 years	4	2 months	Trimipramine	200 mg	no
15	49	f	2	296.33	7 years	6	6 months	Venlafaxine	300 mg	no
16	43	m	2	296.23	1 month	1	1 month	Nefazodone	400 mg	no
17	57	f	1	296.33	13 years	3	1 month	Mirtazapine	30 mg	no
18	61	f	3	296.33	33 years	6	1 month	Mianserin	120 mg	yes
19	74	f	3	296.22	1 year	1	1 year	Venlafaxine	150 mg	yes
20	70	f	2	296.33	18 years	4	1 month	Venlafaxine	100 mg	no
21	64	m	1	296.33	10 years	4	6 weeks	Maprotiline	150 mg	no
22	56	m	1	296.33	9 years	4	3 months	Trimipramine	225 mg	no
23	58	f	3	296.33	7 years	5	2 months	Citalopram	40 mg	no
24	43	m	3	296.53	23 years	20	6 months	Venlafaxine	150 mg	no
25	52	f	3	296.33	9 years	3	4 months	Mirtazapine	60 mg	no
26	61	f	1	296.33	16 years	5	2 months	Mirtazapine	60 mg	no
27	63	f	3	296.33	3 years	8	10 months	Clomipramine	300 mg	no
28	30	m	3	296.33	2 years	4	2 months	Trimipramine	250 mg	no
29	63	f	2	296.33	9 years	4	1 month	Trimipramine	300 mg	no
30	48	m	1	296.33	2 years	2	7 months	Trimipramine	250 mg	no

f female; *m* male; *stim* stimulation procedure of rTMS: 1 = 20 Hz rTMS over LDLPFC, 2 = 1 Hz rTMS over RDLPFC, 3 = sham-stimulation

thermore, we asked the patients to rate themselves their severity of depression by Beck's Depression Inventory (BDI) (Beck et al. 1961). Alterations of motor phenomena have been investigated by means of the Motor Agitation and Retardation Scale (MARS) (Sobin et al. 1998). This scale was developed to provide a comprehensive and non-redundant measure of the motor abnormalities associated with agitation and retardation among depressives. It provides a reliable and valid scale for the clinical assessment of 19 abnormal motor behaviors such as motility, locomotion, gesture, mimic, speech characteristics and tremor. These clinical ratings were used at the beginning of rTMS and on follow-ups on day five, at the end of treatment as well as two, four and eight weeks after the last rTMS treatment. The d2-test (Brickenkamp 2002; Düker and Lienert 1959) was performed in order to assess psycho-motor speed and concentration. It is the most widely used test for measuring this type of psychological performance in German-speaking countries. Particular letters have to be crossed out within 14 lines of 47 letters during 20 seconds for each line. The following figures were measured: a) the total number of processed letters as expression of uncorrected speed performance (GZ); b) the total number of processed letters minus the total number of mistakes as an expression of a concentration attention strain (GZ-F); c) the concentration performance – the total number of letters which were correctly crossed through in the sense of a concentration attention strain corrected with precision (KL). This test was performed at the beginning and at the end of rTMS treatment-period and on follow-up two, four and eight weeks after the end of treatment period. The rater was a psychiatrist, who was blind to the stimulation procedure.

Clinical response was defined as ≥ 50 % improvement of baseline scores (HDRS, BDI) between pre- and post-treatment assessments.

Data analysis

For statistical analysis, multiple analyses of variance with stimulation group and responding status as dependent variables and the rating scores as independent variables, t-tests, and non-parametric correlation coefficients (Spearman Rho) have been calculated by the SPSS program. MANOVA and multiple regression analyses were applied to search for predictive variables from baseline related with severity of depression at the last assessment.

Results

Twenty-nine out of the 30 patients who initially had been included in the study completed the treatment phase. One female patient from the 20 Hz rTMS group

refused to continue after 6 days, because of insufficient effectiveness and headache. The other 29 patients did not report about side effects.

Treatment response according to BDI

Two of the nine patients who were treated by 20 Hz rTMS over the LDLPFC were classified as responders based on their self-reported severity of depression (BDI). The reduction of the score between pre- and post-treatment assessments was 82 % and 59 %, respectively. Only one patient of the 1 Hz rTMS group (RDLPFC) responded (with 78 % reduction). Two patients of the sham-stimulation group responded, one of them showed a score reduction of 54 %, the other one of 71 %.

Significant reductions of the baseline compared with the post-treatment BDI-score were found in all of the three stimulation-groups. Within the two real stimulation groups, a reduction of the BDI-scores could already be observed after five days (20 Hz group: day five: $t = 3.38$; $p = 0.008$; end of treatment: $t = 3.22$; $p = 0.011$; 1 Hz group: day five: $t = 2.41$; $p = 0.039$; end of treatment: $t = 2.59$; $p = 0.029$), whereas the improvement was obvious only at the end of treatment ($t = 3.67$; $p = 0.005$) within the sham-stimulated group (Fig. 1).

Treatment response according to HDRS

The number of responding patients was higher compared with those who were classified as responders concerning the self-rating of the severity of depression. Five patients of the 20 Hz rTMS group were responders compared with three patients of the 1 Hz rTMS group and five patients of those who have been sham-stimulated. The averaged reduction of baseline score was 61.8 %.

Only one of the patients was classified as responder according to both BDI- and HDRS-score criteria.

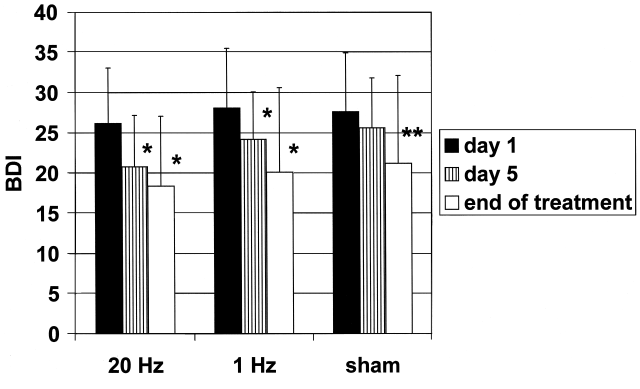

Fig. 1 Comparison of pre- to post-treatment BDI scores. Within the two real stimulation groups, a reduction of the BDI scores could already be observed after five days (20 Hz: day five: $t = 3.38$; $p = 0.008$; end of treatment: $t = 3.22$; $p = 0.011$; 1 Hz: day five: $t = 2.41$; $p = 0.039$; end of treatment: $t = 2.59$; $p = 0.029$), whereas the improvement was obvious only at the end of treatment ($t = 3.67$; $p = 0.005$) within the sham-stimulated group. * $p \leq 0.05$; ** $p \leq 0.005$

The HDRS scores were significantly reduced among the 20 Hz rTMS group and sham-stimulation group (20 Hz group: day 5: $t = 2.58$, $p = 0.030$; end of treatment: $t = 3.02$; $p = 0.015$; sham-stimulation group: day 5: $t = 2.91$, $p = 0.017$; end of treatment: $t = 4.78$; $p \leq 0.001$), whereas the improvement was not statistically significant in the 1 Hz rTMS group ($t = 1.48$; $p = 0.18$) (Fig. 2).

Treatment response according to MARS

Patients of the sham-stimulated group showed on average no reduction of psychomotor retardation. Within the 20 Hz rTMS group, the improvement of MARS scores was already statistically significant after 5 days ($t = 3.33$; $p < 0.001$) with a further improvement at the end of rTMS-treatment ($t = 6.98$; $p < 0.001$). The MARS-scores of the patients of the 1 Hz rTMS group showed a reduction exclusively after 10 days ($t = 2.73$; $p = 0.023$) (Fig. 3).

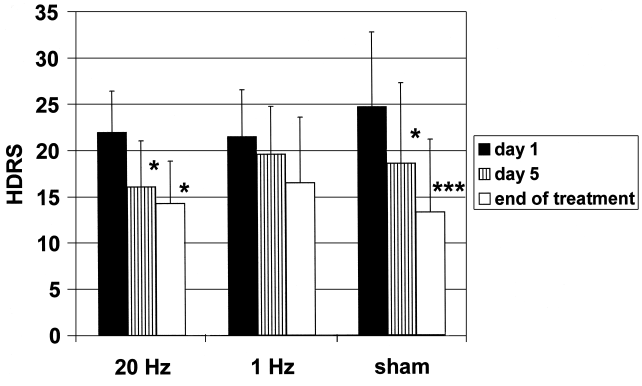

Fig. 2 Comparison of pre- to post-treatment HDRS scores. The HDRS scores were significantly reduced among the 20 Hz rTMS group and sham-stimulation group (20 Hz: day 5: $t = 2.58$, $p = 0.030$; end of treatment: $t = 3.02$; $p = 0.015$; sham-stimulation: day 5: $t = 2.91$, $p = 0.017$; end of treatment: $t = 4.78$; $p \leq 0.001$), whereas the improvement was not statistically significant in the 1 Hz rTMS group ($t = 1.48$; $p = 0.18$). * $p \leq 0.05$: *** $p \leq 0.001$

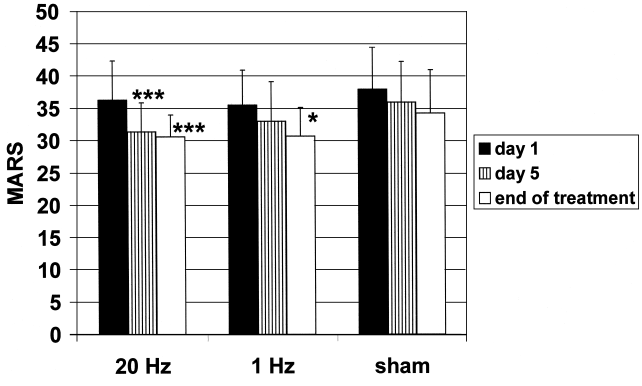

Fig. 3 Comparison of pre- to post-treatment MARS scores. Within the 20 Hz rTMS group, the improvement of psychomotor retardation was already statistically significant after 5 days of treatment with rTMS ($t = 3.33$; $p < 0.001$) with a further improvement at the end of rTMS treatment ($t = 6.98$; $p < 0.001$). The MARS scores of the patients of the 1 Hz rTMS group showed a reduction exclusively after 10 days ($t = 2.73$; $p = 0.023$). * $p \leq 0.05$; *** $p \leq 0.001$

Concentration

Concerning *concentration and psychomotor speed* (test d2), there was an increase for the patients in each stimulation group of the KL score (20 Hz: $t = -8.17$; $p < 0.001$; 1 Hz: $t = -4.04$; $p = 0.005$; sham-group: $t = -4.67$; $p = 0.002$) between baseline and the end of stimulation. Furthermore, significant differences were found for the GZ-F score within the 1 Hz group ($t = -5.95$; $p = 0.001$) and the sham-stimulated group ($t = -2.81$; $p = 0.023$).

Group differences based on HDRS response criteria

The results of MANOVA (PILLAI'S Trace) showed neither any significant main effects of response ($F(7/14) = 1.4$; $p = 0.284$ and 2.99; $p = 0.096$) or of the kind of stimulation ($F(14/30) = 0.92$; $p = 0.551$ and 0.72; $p = 0.499$) nor any significant interrelationships within the data of baseline assessment and day five ($F(14/30) = 0.70$; $p = 0.753$ and 0.98; $p = 0.916$). However, the post hoc test of the comparison between the various groups indicated differences between responders and non-responders at baseline concerning the total number of processed letters (GZ; $F(1) = 5.63$; $p = 0.028$) and the total number of processed letters minus the total number of failures (GZ-F; $F(1) = 5.86$; $p = 0.025$) implying higher scores of the non-responders each. At the end of treatment, the MANOVA showed a main effect of response ($F(7/13) = 4.65$; $p = 0.008$) which was expected because of the response criteria. This effect is due to significant differences for the HDRS scores ($F(1) = 21.61$; $p < 0.001$), the GZ score ($F(1) = 7.52$; $p = 0.013$) and GZ-F score ($F(1) = 6.95$; $p = 0.016$). Non-responders, on average, reported higher HDRS scores as well as higher GZ scores compared with the responders at the end of treatment. The variance of all clinical ratings of the baseline assessment are able to explain 30 % of the variance of the HDRS score at the last stimulation day (multiple regression; method: enter ($r^2 = 0.30$; $F(6/19) = 1.35$; $p = 0.284$).

Group differences based on BDI response criteria

The results of MANOVA (PILLAI'S Trace) pointed to the significant main effect of response ($F(7/14) = 3.45$; $p = 0.023$). There were no significant main effects of the kind of stimulation procedure ($F(14/30) = 0.88$; $p = 0.589$) and no significant interrelationships within the data of baseline assessment ($F(14/30) = 1.64$; $p = 0.126$). The post hoc test of the comparison between the various groups indicated differences between responders and non-responders at baseline concerning the total number of processed letters minus the total number of mistakes (GZ-F; $F(1) = 4.94$; $p = 0.038$) implying higher scores of the non-responders. At the end of stimulation, the MANOVA showed a significant main effect of response ($F(7/13) = 7.59$; $p = 0.001$) which was also expected because of the response criteria. This effect is mainly due to significant differences between the BDI scores ($F(1) = 10.65$; $p = 0.004$). Furthermore, we found a significant interaction between response and stimulation ($F(14/28) = 2.18$; $p = 0.038$) based on interactions concerning the GZ-F score ($F(2) = 4.71$; $p = 0.022$) and KL score ($F(2) = 5.79$; $p = 0.011$). The main effect of the stimulation procedure did not reach the 5 % level of significance ($F(14/28) = 1.99$; $p = 0.059$). Fifty-one per cent of the variance of the BDI scores at the end of treatment were explained by the variance of all clinical ratings from baseline assessment (multiple regression; method: enter ($r^2 = 0.51$; $F(6/19) = 3.33$; $p = 0.021$).

However, a slight tendency was found indicating a relationship between treatment-response according to BDI criteria and age of the patients. The responders were on average 63.2 ± 7.3 years of age, whereas the non-responders were 55.0 ± 11.3 years ($t = 1.54$; $p = 0.13$).

We could not find any difference in the baseline HDRS concerning the age of the patients and between responders and non-responders. Responders ($n = 13$) showed a baseline score of 23.1 ± 5.4 points compared with 22.4 ± 4.3 points of the non-responders ($n = 17$ – $t = 0.42$; $p = 0.67$). Responders were of age 58.7 ± 9.0 years and non-responders of 54.6 ± 12.4 years ($t = 0.99$; $p = 0.33$).

Discussion

We presented findings of a preliminary and explorative comparison study of two different stimulation procedures of rTMS (20 Hz rTMS over LDLPFC versus 1 Hz rTMS over RDLPFC) with sham stimulations. The interpretation of our results is mainly limited by the small sample size. However, we could not find any substantial differences in the severity of depression between the groups according to clinical ratings at baseline as well as at follow-ups of the stimulation. A decrease of depressive symptoms was found after all stimulation procedures. A moderate response rate after rTMS in each group was found independent of the stimulation procedure.

Our finding that patients of the real stimulated groups did not substantially differ from the sham stimulated patients might be explained by enhanced placebo effect of rTMS (Kaptchuk et al. 2000) due to its impressive name, its ability to cause involuntary movements as if by magic, its discomfort, and its bulky and sophisticated-looking equipment (Wassermann and Lisanby 2001, p. 1370).

We found a low agreement between self-rating scores and scores of the rating of others, i. e., only one patient could be classified as responder according to both BDI- and HDRS-score criteria.

The 20 Hz rTMS over LDLPFC seems to be more effective than the 1 Hz rTMS over RDLPFC or sham stimulation, because these patients already "responded" on day 5 (according to BDI).

Similar results emerged from the analysis of psychomotor retardation exclusively for really stimulated patients. This could be interpreted as an effect of rTMS on the dopamine release in the caudate nucleus, mesolimbic and mesostriatal system as previously described by Keck et al. (2002) and Strafella et al. (2001).

Psychomotor speed and concentration, measured by the d2 test, was improved in all groups. Differences between the groups according the response dependent on the kind of stimulation procedure could not be found.

The combination of all clinical baseline parameters (severity of depression, psychomotor retardation and psychomotor speed and concentration) were able to explain 30 % (HDRS) and 51 % (BDI) of the variance of depression at the end of treatment.

It is difficult to explain whether these results were different from those of other authors, who described substantial response after similar techniques and treatment characteristics of high frequency rTMS as well as low frequency rTMS. In contrast to the study by Klein et al. (1999), we used not a circular coil but a figure-eight-shaped coil. These two types differ regarding the stimulated area under the coil. The figure-eight-shaped coil produces a more focal area, while the circular coil produces a more diffuse stimulation of cortical area. This could be a possible reason for the higher response rate in this study. It could be postulated that a circular coil is generally more effective in the stimulation of either the left or the right hemisphere because of the non-specificity of the underlying area. Up to now, it is not clear which cortical area of frontal lobe has to be stimulated to get an antidepressant response.

Furthermore, open questions refer to the stimulation parameters and number of treatment sessions. We used the parameters like George et al. (1996) with some modifications in the high frequency stimulation group of the present study. Nevertheless, we found no significant improvement of depressive symptoms compared with a sham stimulation group, which is in agreement with Garcia-Toro et al. (Garcia-Toro et al. 2001).

Cognitive effects of rTMS have been rarely investigated. According to our knowledge, only a few studies exist which consider cognitive side effects of this method. The aim of these was to determine possible adverse cognitive side effects because high frequency rTMS was reported to induce specific neuropsychological deficits such as errors in a delayed response task (Pascual-Leone and Hallett 1994), recall deficits (Grafman et al. 1994) or speech arrests (Pascual-Leone et al. 1991). In contrast, Padberg et al. (1999) reported that verbal memory and reaction performances were not impaired after rTMS and that verbal memory performance was improved after fast (10 Hz) rTMS. Little et al. (2000) described an improvement on a list-recall test between pre- and post-assessments after 1 Hz and 20 Hz rTMS. Loo et al. (2001) used neuropsychological tests to examine frontal lobe functions. There was no significant mean deterioration in any of these tests after 10 Hz rTMS over LDLPFC. After 4 weeks of stimulation, there was no worsening and some non-significant improvement in neuropsychological test scores. An association between these scores and severity of depression measured by HDRS, however, was not found.

In our study, we found an improvement of psychomotor speed and concentration in all groups. Differences between responders and non-responders at baseline were demonstrated implying more severe retardation in non-responders. Furthermore, a significant interaction between response and stimulation procedures was observed. It could be concluded that patients with less severe deficits in psychomotor speed and concentration responded more intensively on rTMS than patients with severe deficits. The current working hypothesis is that high frequency rTMS enhances synaptic efficacy (Kimbrell et al. 1999) and increases rCBF (Paus et al. 1998). If rTMS improves synaptic efficacy and rCBF in LDLPFC in depressive patients, this could result in better cognitive frontal functions in these patients. Our results showed that rTMS is not able to improve severe retardation in psychomotor speed in contrast to only slight retardation.

In summary, the results of our preliminary data points to the necessity of further research to be able to answer the still open questions regarding stimulation procedures of rTMS, location of stimulation and of the number of treatment sessions. Furthermore, future interest should be focussed onto particular depressive symptoms which are influenced by rTMS.

References

1. Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, Wilson L, Roy-Byrne P (1999) Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. J Nerv Ment Dis 187:114–117
2. Barker AT, Freestone IL, Jalinous R, Merton PA, Morton HB (1985) Magnetic stimulation of human brain. J Physiol 369:3P
3. Baxter LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 46:243–250
4. Beck AT, Ward CH, Mendelson M (1961) An inventory for measuring depression. Arch Gen Psych 4:561–571
5. Belmaker RH, Fleischmann A (1995) Transcranial magnetic stimulation: a potential new frontier in psychiatry. Biol Psychiatry 38:419–421
6. Bench CJ, Frackowiak RS, Dolan RJ (1995) Change in regional cerebral blood flow on recovery from depression. Psychol Med 25:247–261
7. Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Curra N, Modugno N, Manfredi M (1998) Facilitation of muscle evoked responses after repetitive transcranial magnetic stimulation in man. Exp Brain Res 122:79–84
8. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, Charney DS, Boutros NN (2000) A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry 47:332–337
9. Brickenkamp R (2002) Test d2. Aufmerksamkeits-Belastungs-Test (d2). Göttingen: Hogrefe

10. Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M, Cohen LG (1997) Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. Electroencephal Clin Neurophysiol 105(6):415–421
11. Düker H, Lienert GA (1959) Der Konzentrations-Leistungs-Test. Göttingen
12. Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, Buchkremer G (2000) Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. Psychiatry Res 99:161–172
13. Feinsod M, Kreinin B, Chistyak A, Klein E (1998) Preliminary evidence for beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. Depression and Anxiety 7:65–68
14. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, Glover S (1998) The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 10:20–25
15. First MB, Spitzer RL, Williams JBW, Gibbon M (1995) Structured clinical interview for DSM IV (SCID). Washington DC: American Psychiatric Press
16. Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, Mico J, Ibarra O, Arnillas H, Capploch I, Masol A, Tormos JM (2001) Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. J Neurol Neurosurg Psychiatry 71: 546–548
17. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM (1997) Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 154: 1752–1756
18. George MS, Wassermann EM, Williams W, Steppel J, Pascual-Leone A, Basser P (1996) Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 8:172–180
19. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, Hallett M, Post RM (1995) Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6:1853–1856
20. Grafman J, Pascual-Leone A, Alway D, Nichelli P, Gomez-Tortosa E, Hallett M (1994) Induction of a recall deficit by rapid transcranial magnetic stimulation. Neuroreport 5:1157–1160
21. Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, Lefkifker E (2000) Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry 47:314–324
22. Hamilton M (1961) Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 4:561–571
23. Kaptchuk TJ, Goldman P, Stone DA, Stason WB (2000) Do medical devices have enhanced placebo effects? J Clin Epidemiol 53:786–792
24. Keck ME, Welt T, Muller MB, Erhardt A, Ohl F, Toschi N, Holsboer F, Sillaber I (2002) Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. Neuropharmacol 43:101–109
25. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM (1999) Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 46:1603–1613
26. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben-Shachar D, Feinsod M (1999) Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression. Arch Gen Psychiatry 56:315–320
27. Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, Danielson A, Repella J, Huggins T, George MS, Post RM (2000) Cognitive effects of 1- and 20 Hz repetitive transcranial magnetic stimulation in depression: preliminary report. Neuropsychiatry, Neuropsychol and Behav Neurol 13:119–124
28. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S (1999) Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry 156:946–948
29. Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, Parker G, Gandevia S (2001) 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 49: 615–623
30. Mosimann UP, Rihs TA, Engeler J, Fisch H, Schlaepfer TE (2000) Mood effects of repetitive transcranial magnetic stimulation of left prefrontal cortex in healthy volunteers. Psychiatry Res 94: 251–256
31. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, Hampel H, Möller HJ (1999) Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res 88:163–171
32. Pascual-Leone A, Gates JR, Dhuna A (1991) Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurol 41:697–702
33. Pascual-Leone A, Hallett M (1994) Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. Neuroreport 5: 2517–2520
34. Pascual-Leone A, Houser CM, Reese Kea (1993) Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electreoencephal Clin Neurophysiol 89(2):120–130
35. Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996) Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348:233–237
36. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117:847–858
37. Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1998) Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. J Neurophysiol 79:1102–1107
38. Pecuch PW, Evers S, Folkerts HW, Michael N, Arolt V (2000) The cerebral hemodynamics of repetitive transcranial magnetic stimulation. Eur Arch Psychiatry Clin Neurosci 250:320–324
39. Sobin C, Mayer L, Endicott J (1998) The motor agitation and retardation scale: a scale for the assessment of motor abnormalities in depressed patients. J Neuropsychiatry Clin Neurosci 10 (1):85–92
40. Speer A, Kimbrell T, Willis M, Benson BE, Dunn RT, Osuch EA, Wassermann EM, Post RM (1998) 20 Hz rTMS increases and 1 Hz rTMS decreases regional cerebral blood flow (RCBF) in depressed patients. Electroencephal Clin Neurophysiol 107:97P
41. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, Post RM (2000) Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 48:1133–1141
42. Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 21: RC157
43. Triggs WJ, McCoy KJM, Greer R, Rossi F, Bowers D, Kortenkamp S, Naudeau SE, Heilma KM, Goodman WK (1999) Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition and corticomotor threshold. Biol Psychiatry 45: 1440–1446
44. Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M (1996) Use and safety of a new repetitive transcranial magnetic stimulator. Electroenceph Clin Neurophysiol 101: 412–417
45. Wassermann EM, Lisanby SH (2001) Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 112:1367–1377