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ORIGINAL PAPER

Transcranial magnetic stimulation for the treatment of depression: feasibility and results under naturalistic conditions: a retrospective analysis

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Abstract An increasing number of controlled studies strongly support an antidepressant effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex. However, these data come from highly selected study populations. Whether rTMS is a feasible therapeutic tool for the treatment of depression under naturalistic condition has not yet been addressed. Here, we report results from 232 depressive patients [aged 20–76 years, baseline Hamilton Depression Rating Score (HDRS-21) 24.0 ± 7.3] treated with rTMS add-on to continued psychopharmacological treatment in a naturalistic clinical setting. Two thousand stimuli of 20-Hz rTMS were applied daily over the left dorsolateral prefrontal cortex with an intensity of 110% of motor threshold. Treatment duration was individually planned and varied between 10 and 20 sessions. In average, patients received 13 ± 6.1 rTMS sessions. In 90% of the cases, treatment was terminated regularly. No severe side effects were observed. Only four patients stopped rTMS treatment because of side effects. Ratings with the HDRS-21 before and after treatment were available in 130 patients. The average improvement of the HDRS-21 in this subsample was 9.0 ± 9.2 points. Fifty-three patients had an improvement of 50% or more. These results document that rTMS is feasible, safe and well tolerated under naturalistic conditions.

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Introduction

Depression is a severe, common psychiatric illness with limited therapeutic options. Many patients with major depression do not improve appreciably despite antidepressant treatment [6, 22, 23]. Medication-resistant depression is associated with poor clinical and psychosocial outcome [22]. For the treatment of medication-resistant patients, several focal brain stimulation techniques are currently under investigation [27]. Among those, most evidence is available for repetitive transcranial magnetic stimulation (rTMS), first proposed more than 15 years ago [10, 25]. Most, but not all, controlled trials suggest beneficial effects of rTMS in the treatment of depression [14, 16, 24]. Several recent meta-analyses converge in the conclusion that high-frequency rTMS over the left dorsolateral prefrontal cortex exerts a significant antidepressive effect [11, 13, 19, 29]. However, patients included in these controlled treatment trials are highly selected and not representative for the general patient population. As an example, usually neither patients with suicidal tendencies nor with comorbidities are enrolled in clinical studies [3]. Furthermore, in general, only patients with a good compliance are included in controlled trials. Therefore, practical clinical studies under naturalistic conditions are needed before data from randomized controlled trials can be extended to real-world settings [30]. Here, we used broad inclusion and minimal basic exclusion criteria to investigate, whether rTMS is a feasible approach for the treatment of depression under naturalistic conditions. In particular, we were interested in

the compliance of an unselected patient population for rTMS treatment and in the occurrence of side effects and treatment results in such a population.

Patients and methods

Data of all patients who received rTMS for the treatment of depression between July 2004 and June 2009 in the Psychiatric Department of the University of Regensburg were retrospectively analyzed. The following information was routinely documented in these patients: age, gender, diagnosis of depressive episode, differentiation in unipolar and bipolar disorder, comorbidities according to an ICD 10 Diagnosis group, motor threshold, stimulation intensity, the amount of treatment sessions, information about regular termination of treatment, depressive symptoms as assessed with the Hamilton Depression Ration Scale (HDRS-21) [12] at the begin and the end of rTMS treatment and daily assessment of potential side effects. HDRS ratings were performed by experienced psychiatrists trained in the application of this scale. No standardized assessment of treatment resistance was performed before rTMS treatment. As surrogate markers for treatment resistance, the number of in-patient treatments in our hospital and the number of psychotropic drugs at the last discharge were registered. rTMS was applied on consecutive working days over the left dorsolateral prefrontal cortex usually starting on mondays. The center of the coil was positioned 6 cm anterior of the left-hand motor hot spot [15] with the handle of the coil pointing in posterolateral direction 45° away from the sagittal line. In each session, 2,000 stimuli were applied in 40 trains with an inter-train interval of 25 s at a frequency of 20 Hz with an intensity of 110% of the individual resting motor threshold. In all patients ($N = 29$; 13% of the total sample) with a motor threshold above 54% of the maximal stimulator output, treatment was performed with 60% of the maximal stimulator output, since stimulation at higher intensities is perceived painful by most patients. The stimulation intensity was also reduced, when patients claimed discomfort in order to prevent dropouts. Treatment duration was planned individually with a minimum of 10 sessions, but in most patients, therapy duration of 15 sessions was intended. Based on the individual response, treatment was extended up to 20 sessions in selected patients [7]. Treatment was performed with figure of 8 coils (MCF-B 65 and Cool-B65; Medtronic, Germany) connected to a Medtronic Mag Pro Option device (Medtronic, Germany). Based on the information from the manufacturer, both coils produce identical magnetic fields. All patients received rTMS as compassionate use treatment and gave written informed consent for rTMS treatment.

Prior to the retrospective analysis of the anonymized data, the local ethical committee has been consulted. No ethical concerns against the statistical analyses were expressed. It was also mentioned that a retrospective analysis of anonymized data would be in accordance with the declaration of Helsinki. In most cases, rTMS was performed add-on to psychopharmacologic treatment. Pharmacologic treatment was not further regulated, except that doses of benzodiazepines equivalent to more than 1 mg lorazepam/day were not allowed, since this medication was shown to inhibit rTMS effects [8]. Further exclusion criteria for rTMS treatment were implanted electronic devices such as cardiac pace makers, a history of epileptic seizures, metal implants in or next to the brain and severe unstable neurologic or internal diseases.

Data analysis was mainly performed in a descriptive way. Data is given as mean ± standard deviation. Comparisons between groups were performed as unpaired *t*-tests, comparison within groups as paired *t*-tests. For the group of patients for which HDRS scores before and after rTMS were available, a multiple regression analysis with treatment response as a dependent variable and age, gender, baseline score and treatment duration as independent variables was performed. Statistical analyses were performed with SPSS 16.0 for windows.

Results

Two hundred and thirty-two patients (99 men; 133 women) received rTMS for the treatment of a depressive episode in the observation period (Table 1). The age of the patients ranged from 20 to 76 years (mean 49.7 ± 24.4 years). The reason to administer rTMS treatment was not systematically documented in all patients. Based on the available data, the indication for rTMS treatment was in most cases treatment resistance to antidepressants. Due to lack of detailed information, the extent of treatment resistance (e.g., number of failed pharmacologic treatments) could not be exactly determined. Two patients had received electroconvulsive therapy in the past. Other indications included incomplete improvement with standard therapies, intolerance to antidepressants, refusal of pharmacologic treatment by the patient and breast feeding of patients with postpartal depression. Thirty patients suffered from bipolar depression and 202 from unipolar depression. Bipolar patients had in average more in-patient treatments (6.8 vs. 3.8) and received more psychotropic drugs (3.3 vs. 2.7).

Hundred and forty-four patients were in-patients and 86 out-patients, and two started as in-patients and completed treatment as out-patients. Baseline Hamilton Depression Rating Score (HDRS) were available for 161 patients ranging between 10 and 43 (mean 24.0 ± 7.3), with no

Table 1 Clinical and demographic characteristics of the patient population

N	232
Age (years)	49.7 ± 24.4
Sex	99 male; 133 female
ICD 10 diagnosis	Bipolar depression (F 31.*):30 (21 in-patients) unipolar depression (F32.*, F33.*) 202 (111 in-patients)
Comorbidities ICD 10	F1* 21; F2*:16; F4*:51; F6*:22; other F diagnosis: 8
Setting	144 in-, 86 out-patients, 2 switching
Resting motor threshold (% max. stimulation output)	44.1 ± 9.8; (12% of the patients >54%)
HDRS pre-treatment	24.0 ± 7.3
Completers	$N = 209$ (90%) with 13.8 ± 5.7 sessions
Dropouts	$N = 23$ (10%) with 6.3 ± 4.9 sessions

significant difference between in- and out-patients (in-patients 23.7 ± 7.3, out-patients 23.7 ± 6.9; $P > 0.05$). Some of the treated patients had relative low HDRS baseline scores. The indication for rTMS treatment in these patients was mainly incomplete remission of depressive symptoms under pharmacologic treatment. Depressive symptoms in these patients were frequently characterized by anhedonia or loss of energy, resulting in significantly reduced quality of life without revealing high HDRS scores.

In 211 (90%) of the cases, treatment was completed regularly, and in 23 cases (10%), treatment was terminated earlier than planned. Most frequent reasons for stopping the treatment were ambivalence concerning the consent for treatment (6 patients), side effects (4 patients) or the subjective impression of missing effectiveness (3 patients). However, in some of the 23 cases, treatment was also stopped, because of discharge from hospital after unexpected rapid clinical improvement [20] or for reasons not related to the patient's psychiatric disease (e.g. an outpatient stopping treatment because the spouse, who drove him to treatment broke her leg). In average, the number of treatment sessions was 13 ± 6.1. There were no severe side effects, particularly no epileptic seizures [26], no rTMS-induced manic [5] or psychotic [32] episodes. In one patient, dramatic improvement of depressive symptoms under rTMS was repeatedly accompanied by relapses of a chronic rheumatoid arthritis [20]. Thirty-nine (16%) patients complained side effects, mostly mild and transient headache, unpleasant loudness of the stimulation procedure, discomfort and unpleasant sensations in the stimulated area, tooth pain, vegetative alterations or stiffness of facial muscles. But notably only four patients stopped treatment due to side effects (2 headache, 1 unpleasant sensations, 1 tooth pain).

Among the 161 patients with baseline HDRS scores, there were 130 for which also post-rTMS HDRS scores were available (56% of the whole sample). This relatively low proportion is mainly due to organizational reasons such as lack of availability of a trained rater at the first or the last treatment session. For dropouts and out-patients more frequently no ratings were available (pre- and post-treatment rating available in 13% of the dropouts and in 41% of out-patients). The magnitude of treatment effects can only be reported from the group where ratings before and after rTMS were available, and data should not be extrapolated to the total patient group. Among the 130 patients with HDRS scores before and after rTMS, there was an average reduction of the HDRS of 9.0 ± 9.2 points. Patients with unipolar and bipolar depression responded similarly (average reduction of the HDRS: unipolar: 9.2 ± 9.5; bipolar 7.5 ± 7.6; $P > 0.05$), and there was also no gender difference in the response to rTMS (average reduction of the HDRS: male: 7.7 ± 8.1; female 9.6 ± 9.2; $P > 0.05$). Neither the number of in-patient treatments (average reduction of the HDRS: ≤2 in-patient treatments: 8.2 ± 9.3; >2 in-patient treatments: 9.8 ± 9.1; $P > 0.05$) nor the number of psychotropic drugs (average reduction of the HDRS: ≤2:8.3 ± 9.0; >2:9.4 ± 9.4; $P > 0.05$) had a significant influence on treatment outcome.

Response, defined as a 50% reduction of the HDRS, occurred in 53 cases (HRDS score before rTMS 24.2 ± 7.9, HRDS score after rTMS 7.2 ± 4.4). Even under the conservative assumption that there were no responders in the group with the missing HDRS scores, at least 23% of the totally treated population fulfilled the response criterium. The multiple regression analysis did not reveal any significant influence of age, gender, baseline HDRS score and treatment duration on treatment response ($P > 0.05$ for all variables).

Discussion

The main goals of the current retrospective study were to determine whether rTMS is a feasible tool for the treatment of depression under real-world conditions and to which extent data obtained from highly selected populations in controlled studies can be extrapolated to an unselected

collective. Here, we report data from 232 patients receiving high-frequency rTMS over the left dorsolateral prefrontal cortex for the treatment of depression in the psychiatric department of the Bezirksklinikum Regensburg between July 2004 and June 2009. The hospital provides the psychiatric services for a catchment area of about 1 million inhabitants.

The main result is that the vast majority of our unselected sample completed the treatment regularly. The proportion of 90% completers reflects an extraordinary high acceptance and tolerability of rTMS, especially when accounting for the disease inherent high ambivalence of treatment-resistant depressive patients. The amount of side effects of rTMS treatment was low and thus in line with data from controlled studies [1, 17–19, 28]. No severe side effects were observed. It is noteworthy that no EEG exams were performed routinely before treatment, suggesting that the exclusion criteria of epileptic seizures in the medical history together with a treatment protocol according to published safety limits [31] is sufficient to prevent rTMS-induced epileptic seizures. Even if our sample size is among the largest reported for rTMS studies, it is by far not big enough to exclude the possibility of rare side effects. Therefore, multicentric collection of rTMS safety data in databases would be desirable.

It should be noted that from our data, no firm conclusions about the therapeutic efficacy of rTMS can be drawn. First, the data come from a retrospective analysis and not from a controlled study. Second, efficacy data (ratings before and after rTMS) were only available for 56% of the sample and may not be representative for the total sample (Table 2). Third, almost all patients received rTMS as an add-on treatment to standard treatment, which consisted of psychopharmacotherapy in most patients, but also in cognitive behavioral therapy, occupational therapy and in-patient treatment setting in many patients. Fourth, pharmacologic and non-pharmacologic treatment was not kept constant during rTMS treatment, and fifth, the duration of treatment was individualized. Noteworthy, outcome was not significantly better for in-patients when compared to out-patients who received naturally less intense standard treatment (Table 2). Also, no other clinical predictors for treatment outcome could be identified. There was no difference in the response between patients with bipolar and monopolar depression. Keeping in mind all the limitations of our retrospective analysis and also the small proportion of bipolar patients in our sample, this finding is of clinical relevance. First, we did not observe a switch into mania after high-frequency rTMS of the left DLPFC, and second, our results suggest an efficacy of rTMS in bipolar depression, an indication for which only very limited knowledge is available [4]. Neither age, nor gender, HDRS baseline score, number of in-patient treatments nor number of psychotropic drugs had an influence on treatment outcome. These findings, which are partly discrepant to findings from controlled studies [2, 9, 21], have to be interpreted very carefully, since many of the parameters have been assessed retrospectively. However, the observed average improvement of the HDRS of 38% (in the group with ratings before and after rTMS) and the responder rate of at least 23% are in a similar range like data from controlled studies [11, 19, 24, 29]. In spite of all mentioned limitations of the presented data, coming from a retrospective analysis of rTMS as add-on to a non-standardized psychiatric "treatment as usual", the observed improvement is of considerable clinical relevance for this collective of difficult to treat depressive patients.

In summary, the lack of severe side effects and a treatment adherence of 90% demonstrate the safety, feasibility and high acceptance of rTMS as an antidepressant treatment under real-world conditions. A relevant proportion of our unselected sample experienced a clinically significant improvement of depressive symptoms after relative short treatment duration. These results further indicate the potential of rTMS for the treatment of depression in an integrated therapy setting. Future studies will be necessary for evaluating the added value of new developments in transcranial magnetic stimulation, such as neuronavigated coil positioning or innovative stimulation protocols.

Table 2 HDRS scores before and after treatment

	Patients with pre- and post-treatment HDRS scores	Patients in the total sample	HDRS score pre-treatment	HDRS score post-treatment
All patients	130	232	24.1 ± 7.2	15.0 ± 9.0
Responders (≥50% reduction of HDRS score)	53	n.a.	24.2 ± 7.9	7.2 ± 4.4
Completers	127	209	24.1 ± 7.2	15.0 ± 9.1
Dropouts	3	23	20.7 ± 4.9	17.7 ± 8.1
In-patients	95	144	23.7 ± 7.3	14.2 ± 8.4
Out-patients	35	86	24.2 ± 7.4	15.4 ± 10.4

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Conflict of interest The authors declare that they have no conflict of interest in relation to the topic of this paper.

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