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ORIGINAL PAPER

# Influence of repetitive transcranial magnetic stimulation on psychomotor symptoms in major depression

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**Abstract** Psychomotor symptoms related to an impairment of the nigrostriatal dopaminergic system are frequent in major depression (MD). Repetitive transcranial magnetic stimulation (rTMS) has been discussed as a new treatment option for MD. In neurobiological terms, an influence of high-frequency rTMS on dopaminergic neurotransmission has previously been shown by several studies in animals and humans. Therefore, an improvement of psychomotor symptoms by rTMS could be assumed. The aim of this pilot study was to investigate the effect of high-frequency rTMS on psychomotor retardation and agitation in depressive patients. We investigated the effect of left prefrontal 10 Hz rTMS on psychomotor retardation and agitation in 30 patients with MD. Patients were randomly assigned to real or sham rTMS in addition to a newly initiated standardized antidepressant medication. We found a trend in the reduction of agitation ($t_{28} = 1.76$, $p = 0.09$, two-tailed), but not in the reduction of retardation. Furthermore, no general additional antidepressant effect of rTMS was observed. Although there was no statistical significant influence of high-frequency rTMS on psychomotor symptoms in depressive patients, the results showed a trend in the reduction of psychomotor agitation in MD. This effect should be systematically investigated as the primary end point in further studies with larger sample sizes.

**Keywords** Repetitive transcranial magnetic stimulation · Major depression · Psychomotor agitation · Retardation

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## Introduction

Psychomotor symptoms are very frequent in patients with major depression (MD), and have been found to correlate with anhedonia [13]. Compared to patients without psychomotor signs, patients with such signs (agitation and retardation) tended to be more severely ill and have a more complicated course of the depressive disorder [2]. From a pathophysiological perspective, an association with dopamine neurotransmission was shown. In [$^{11}$C]raclopride PET investigations, Meyer et al. [14] found an elevated putamen D(2)-binding potential in psychomotor retarded depressed patients. Furthermore, functional neuroimaging findings also imply an involvement of dopamine-related neuroanatomical substrates of the striatum, and the ventrolateral prefrontal and orbitofrontal cortex in anhedonic symptoms [23]. In addition, transcranial brain sonography

in depressive patients revealed that Parkinson's disease-like midbrain abnormalities point to an impairment of the nigrostriatal dopaminergic system [5, 24].

Prefrontal rTMS has been investigated as a possible new treatment option for MD, and it has been found to influence striatal dopaminergic activity. Animal studies have shown an elevation of extracellular dopamine in the striatum after frontal rTMS [9]. In depressed patients, an [123I] iodobenzamide (IBZM) SPECT study found that rTMS of the left dorsolateral prefrontal cortex (DLPFC) caused a reduction of specific striatal IBZM binding to dopamine D2 receptors [16]. These investigations suggest that prefrontal rTMS stimulates the release of endogenous dopamine and thereby exerts modulation of mesolimbic and mesostriatal dopaminergic pathways.

So far, literature suggests that rTMS might have a positive effect on clinical symptoms associated with striatal dysfunction in MD. Previously, we found a slight effect on psychomotor dysfunction after high-frequency rTMS on the left DLPFC in depressed patients. However, no differentiation was drawn between psychomotor agitation and retardation [6].

The aim of the current pilot study was to investigate the effect of high-frequency rTMS on psychomotor retardation and agitation in depressive patients. Data were collected as part of a recent randomized, double-blind, sham-controlled, multi-center trial investigating the antidepressant effects of augmentative rTMS [4]. Specifically, we hypothesized that rTMS would improve psychomotor agitation and retardation.

## Materials and methods

### Patients and study design

Inclusion criteria were: age 18–75 years, a moderate or severe major depressive episode according to ICD-10 and DSM-IV (SCID), and a score of 18 points or more in at least two of the three depression rating scales, Beck Depression Inventory (BDI), 21-item Hamilton Depression Rating Scale (HDRS) and Montgomery–Åsberg Depression Rating Scale (MADRS). A total of 30 patients (18 females, mean age: 52.3 ± 11.9 years) were investigated at two participating centers of the multi-center study (Psychiatric Departments of the Universities of Rostock and Munich). Details regarding the inclusion and exclusion criteria have been described previously in detail [4]. The patients were randomly assigned to either a real stimulation or a sham stimulation group. All patients gave written informed consent to participate in the study (approved by the local ethics committee and performed in accordance with the Declaration of Helsinki). Patients and raters were masked to the treatment conditions.

To integrate rTMS in a naturalistic routine clinical setting, and for ethical and safety reasons, rTMS was applied parallel to a standardized antidepressant medication. The stimulation sessions were started together with venlafaxine or mirtazapine treatment, both selected because of their combined serotonergic and noradrenergic profile to rule out neurotransmitter-specific confounding effects. The mean dosage of the antidepressant medication of the patients in the real and sham rTMS group is shown in Table 1a. No other antidepressants or concomitant neuroleptic medication was allowed. A maximum of 1.5 mg/day lorazepam was permitted as an exceptional crisis medication (mean dosage of each group during the whole study phase is given in Table 1a). Anticonvulsants were not allowed.

Psychomotor impairments were assessed with the Motor Agitation and Retardation Scale (MARS) [20], enabling a differentiation between retardation and agitation. Retardation symptoms rated as items of the MARS are very similar to Parkinson symptoms, including motor slowness, reduced voice volume, abnormal gait, lack of facial expressivity, delayed onset of speech and monotone speech. Agitation symptoms included items such as increased axial truncal movements, abnormal hand, foot and lower leg movements, tension of the mouth and increased blinking. To rate depressive symptoms, the BDI, the HDRS (21-item version) and the MADRS were used. All ratings were obtained prior to and after the end of the stimulation series.

### Transcranial magnetic stimulation

rTMS was initiated together with a standardized antidepressant medication [4]. In brief, the real rTMS was applied above the left DLPFC, targeted by guiding the coil to the position F3 according to the International 10–20 system for electroencephalography electrode placement with 110% of individual resting motor threshold (RMT). The sham stimulation was applied 5 cm lateral to F3 above the left temporal muscle. To further reduce the possible effectiveness, the coil was angled at 45°, touching the skull not with the center but with the rim opposite the handle, and the stimulation intensity was reduced to 90% RMT. This kind of sham stimulation had disturbing effects due to local sensations above the temporal muscle, which were similar to the disturbance caused by the real stimulation [17]. Stimulation was performed with a frequency of 10 Hz, 100 trains of 2 s, inter-train intervals of 8 s and 2,000 stimuli per day on 15 consecutive working days.

**Table 1** Baseline characteristics and analysis of efficacy of the real and sham intervention groups

| | Stimulation | | *p* two-tailed |
|---|---|---|---|
| | Real ($n = 15$) | Sham ($n = 15$) | |
| **a. Demographic and clinical characteristics** | | | |
| Female/male | 13/2 | 5/10 | <0.01 |
| Age, years | 55.2 (11.2) | 49.3 (12.2) | ns |
| Age of onset, years | 42.4 (16.8) | 41.8 (15.3) | ns |
| Duration of current episode, weeks | 8.7 (5.1) | 12.5 (9.6) | ns |
| Number of episodes | 5.0 | 3.7 | ns |
| Venlafaxine/mirtazapine | 9/6 | 5/10 | ns |
| Venlafaxine, dosage (mg) | 142 (70) | 105 (41) | ns |
| Mirtazapine, dosage (mg) | 28 (6) | 28 (5) | ns |
| Lorazepam; mean dosage of all study days, mg | 5.8 (1.4) | 6.3 (1.6) | ns |
| **b. Depression** | | | |
| Treatment response rate (%) | 5 (33.3) | 4 (26.7) | ns |
| BDI | | | |
| Pre-treatment, mean (SD) | 25.1 (6.8) | 23.6 (8.8) | ns |
| Post-treatment, mean (SD) | 10.8 (6.2) | 14.1 (7.3) | ns |
| Absolute change (pre–post), mean (SD) | 14.3 (9.4) | 9.5 (9.8) | ns |
| Relative change in percent, mean (SD) | 53.9 (26.2) | 32.8 (48.1) | ns |
| HDRS | | | |
| Pre-treatment, mean (SD) | 22.9 (5.0) | 22.8 (3.0) | ns |
| Post-treatment, mean (SD) | 12.4 (5.6) | 13.4 (6.8) | ns |
| Absolute change (pre–post), mean (SD) | 10.5 (4.2) | 9.4 (5.6) | ns |
| Relative change in percent, mean (SD) | 47.2 (21.3) | 42.5 (28.0) | ns |
| MADRS | | | |
| Pre-treatment, mean (SD) | 27.0 (6.4) | 25.9 (3.9) | ns |
| Post-treatment, mean (SD) | 14.6 (6.7) | 14.8 (7.6) | ns |
| Absolute change (pre–post), mean (SD) | 12.3 (6.0) | 11.0 (7.9) | ns |
| Relative change in percent, mean (SD) | 46.3 (21.2) | 41.9 (28.9) | ns |
| **c. Psychomotor functioning** | | | |
| MARS sum | | | |
| Pre-treatment, mean (SD) | 32.5 (6.2) | 29.0 (5.3) | ns |
| Post-treatment, mean (SD) | 26.5 (5.5) | 24.9 (5.3) | ns |
| Absolute change (pre–post), mean (SD) | 6.1 (4.8) | 4.1 (4.7) | ns |
| Relative change in percent, mean (SD) | 17.7 (13.3) | 13.3 (15.2) | ns |
| Agitation | | | |
| Pre-treatment, mean (SD) | 15.6 (4.2) | 12.7 (2.8) | 0.037 |
| Post-treatment, mean (SD) | 12.5 (2.9) | 11.4 (2.5) | ns |
| Absolute change (pre–post), mean (SD) | 3.1 (3.2) | 1.3 (2.4) | 0.090 |
| Relative change in percent, mean (SD) | 16.9 (17.3) | 8.6 (16.1) | ns |
| Retardation | | | |
| Pre-treatment, mean (SD) | 16.9 (3.6) | 16.3 (4.3) | ns |
| Post-treatment, mean (SD) | 13.9 (3.3) | 13.4 (3.2) | ns |
| Absolute change (pre–post), mean (SD) | 3.0 (2.8) | 2.9 (3.8) | ns |
| Relative change in percent, mean (SD) | 16.8 (14.4) | 14.4 (20.3) | ns |

*BDI* Beck Depression Inventory, *HDRS* Hamilton Depression Ratings scale, *MADRS* Montgomery–Åsberg Depression Rating Scale, *MARS* Motor Agitation and Retardation scale, *MARS sum* MARS sum score, *Agitation* agitation subscore, *Retardation* retardation subscore

### Statistics

Group differences in gender and medication were tested using the $\chi^2$ test. Primary outcome was the symptom score change as assessed at the end of the rTMS phase (day 15) with the MARS. Secondary outcomes included changes on the BDI, the 21-item HDRS and the MADRS.

As Kolmogorov–Smirnov tests confirmed the normal distribution of the data, group differences were tested using Student's $t$ tests (two tailed) for independent samples. Further, the course of the scores within the groups was tested by comparing pre- and post-scores for real and sham stimulation. The significance level was set at $p < 0.05$. Considering the ordinal scale level of the rating scores, also a Mann–Whitney $U$ exact test was performed for trends or significant results. Additionally, the influence of medication on the course of psychomotor symptoms was calculated using Student's $t$ test for independent samples.

## Results

The two patient groups did not differ in terms of age, clinical baseline characteristics, concomitant antidepressant medication, concomitant exceptional crisis medication of lorazepam or in the severity of depression (Table 1a, b). There were more women in the real, than in the sham stimulation group ($\chi^2 = 8.89$, $p = 0.01$; Table 1a). Female and male patients did not differ in clinical baseline characteristics, in depressive symptoms (BDI: $t = 0.44$, $p = 0.66$/HDRS: $t = -0.02$, $p = 0.99$/MADRS: $t = 0.39$, $p = 0.70$) or in psychomotor symptoms (agitation: $t = 1.70$, $p = 0.10$/retardation: $t = 1.58$, $p = 0.12$). Furthermore, men and women did not differ in these variables at the end of the study (BDI: $t = -0.60$, $p = 0.55$/HDRS: $t = -0.56$, $p = 0.58$/MADRS: $t = -0.21$, $p = 0.84$/agitation: $t = 1.81$, $p = 0.80$/retardation: $t = 1.07$, $p = 0.29$).

With regard to psychomotor functioning, we found a reduction of the agitation after real compared to sham stimulation, which only approached statistical significance ($t_{28} = 1.76$, $p = 0.09$, two tailed; one tailed, $p = 0.045$), although the real stimulation group showed higher pretreatment scores ($t_{28} = 2.19$, $p = 0.037$; Table 1c). When considering the course of scores within the groups, we found a significant difference between pre- and post-stimulation scores in the real stimulation group ($p = 0.002$), which was not the case in the sham group ($p = 0.061$). The Mann–Whitney $U$ exact test revealed a borderline trend to significant effect of pre- to post-agitation scores in the group comparison with a $p$ value of $p = 0.053$, one tailed. Analyzing effect sizes, we found a medium effect of rTMS on agitation compared to sham stimulation (absolute change; Cohen's $d = 0.66$). There were no group differences for the total and the retardation score of the MARS ($t_{28} = 0.109$, $p = 0.914$; Table 1c). Furthermore, there were no significant differences between patients who received venlafaxine ($n = 14$) and those who received mirtazapine ($n = 16$) on the absolute changes of psychomotor symptoms irrespective of the rTMS condition (MARS sum score: $t = -0.73$, $p = 0.47$/agitation score: $t = -0.08$, $p = 0.93$/retardation score: $t = -1.03$, $p = 0.31$).

Regarding the depression rating scales, there were no significant differences in clinical ratings of depression severity (Table 1b).

## Discussion

We investigated the effects of high-frequency rTMS on different psychomotor symptoms in MD using a double-blind placebo-controlled design. Whereas we did not observe an antidepressant effect of rTMS in the reported sample, as was also the case in the whole sample of the European Multicentre Trial [4], a trend toward the improvement of a certain domain of psychomotor functioning was found after real rTMS compared to the sham stimulation.

Although the exact biological basis for the observed trend toward the reduction in the agitation domain remains unclear, some possible pathways could be discussed. High-frequency rTMS stimulates the release of endogenous dopamine and thereby enhances mesolimbic and mesostriatal dopaminergic neurotransmission [9, 16, 21, 22]. One might expect that this direct dopaminergic modulation should in turn result in a reduction of retardation symptoms. However, our results did not show that. Therefore, it is possible that indirect pathways other than the direct modulation of dopaminergic dysfunction account for the present results. In addition, serotonin neurotransmission deficits are thought to be involved in agitation and hyperactivity [3]. Neurochemical investigations have shown an effect of rTMS on serotonergic neurotransmission: high-frequency frontal rTMS in rats resulted in an increase of extracellular 5-HT concentration in the prefrontal cortex [8]. Regarding the lack of an observable significant influence on depressive symptoms in our study, however, the serotonin effect also does not completely explain our results. Rubin et al. [18] have shown that agitation in depression correlates with increased hypothalamic–pituitary–adrenocortical (HPA) activity. Regarding the HPA system activity, rTMS has been reported to suppress post-dexamethasone cortisol levels in rTMS-responsive patients with MD [25]. Hence, modulation of HPA and serotonergic functioning by rTMS should be discussed as possible biological mechanisms for the influence on psychomotor agitation.

Since the effect of rTMS on psychomotor agitation was moderate and only approached significance, methodological as well as biological reasons need to be mentioned. Especially, the different gender ratio (more female patients in the real compared to the sham rTMS group) should be discussed. Some studies on gender differences have reported that female patients showed significantly more symptoms of psychomotor retardation than male patients [10, 11], whereas other studies reported that men and women do not differ in their symptom profiles of MD [15]. Accordingly, significant differences between female and male patients in psychomotor agitation or retardation were not found in the present study, at baseline or at the end point. Pathophysiologically, psychomotor symptoms in depressive patients are associated with Parkinson's disease (PD)-like impairment of the nigrostriatal dopaminergic system [5, 24]. Similar to studies on depressive patients [10, 11], in patients with PD, clinical observations suggest gender differences of brain physiology. Furthermore, women and men with PD appear to differ in response to dopaminergic and deep brain stimulation [1]. These findings indicate possible differences in human brain function between the sexes with regard to neuroplasticity. Transcranial direct current stimulation (tDCS) studies specifically showed an enhancement of excitability-diminishing neuroplasticity in female subjects, which could be related to the effects of sex hormones [12]. Using paired-pulse TMS protocols, less intracortical inhibition and more facilitation were found when the estradiol level was high, while the reverse effect appeared during high progesterone level [19]. Gender differences could also be discussed in the response to rTMS. To our knowledge, there is only one study that investigated this question explicitly and found a comparable response of male and premenopausal female patients. Post-menopausal women responded less to rTMS [7], indicating a different response to excitability-changing brain stimulation methods. In the present study, we did not find differences between female and male patients in clinical outcome at the end of our study. However, due to the small group sizes, we did not differentiate between pre- and post-menopausal females and did not analyze the hormonal state of our female patients. Nevertheless, the gender effect is an interesting and important fact that could be addressed in future rTMS studies.

From a methodological viewpoint, the use of two different antidepressant medications in parallel to the onset of the rTMS session may be a confounding issue of the present study. This procedure was selected to integrate rTMS in a naturalistic clinical routine setting, and for ethical and safety reasons. It could be assumed that the differentially sedative side effects of the concomitant medication together with an apparent uneven distribution of mirtazapine (sedative) and venlafaxine treatment across the groups may have caused the group effect in the agitation scores. However, the distribution of the medication between both groups was not significantly different, possibly due to the small sample size. Furthermore, a lower number of patients in the active, compared to the sham, group received mirtazapine, which does not support this notion. In addition, there were no group differences in the mean dosage of the antidepressant medications. Furthermore, the explorative analysis of the medication effects on psychomotor symptoms irrespective of the rTMS condition supported the lacking influence of medication on psychomotor symptoms. Nevertheless, in further studies a homogeneous antidepressant medication should be applied.

To validate rTMS for therapeutic use, it is necessary to better understand the mechanisms involved, particularly the nature of the changes induced and the brain regions affected. Combined investigation of rTMS effects on clinical psychomotor dysfunctions and neurobiological mechanisms are promising approaches to further elucidate the role of rTMS in the modulation of neural transmission and its potential benefit in the treatment of various depressive symptoms, especially in the treatment of psychomotor dysfunctions. However, if the findings could be replicated, the present data suggest that high-frequency rTMS on left DLPFC might be an additional treatment, particularly for patients who exhibit enhanced agitation.

### Limitations

The present results are of a preliminary nature. The number of patients randomized in each rTMS-arm in this study was rather small. The baseline score of agitation was different between the sham and real rTMS-groups. Furthermore, the different gender distribution between real and sham stimulation has to be assessed critically. In addition, the heterogeneous distribution of the medication (venlafaxine, mirtazapine) has to be taken into account. Therefore, larger sample sizes with comparable baseline characteristics and consideration of gender and medication effects are needed for further studies.

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