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# Repetitive Transcranial Magnetic Stimulation in Bulimia Nervosa: Preliminary Results of a Single-Centre, Randomised, Double-Blind, Sham-Controlled Trial in Female Outpatients

M. Walpoth[a, b] C. Hoertnagl[a, b] B. Mangweth-Matzek[c] G. Kemmler[a]
J. Hinterhölzl[a] A. Conca[d] A. Hausmann[a, b]

[a]Department of General Psychiatry, [b]Laboratory for Magnetic Brain Stimulation, Department of General Psychiatry, and [c]Department of Psychosomatic Medicine, Innsbruck Medical University, Innsbruck, and [d]Department of General Psychiatry, Regional Hospital Rankweil, Rankweil, Austria

**Key Words**
Bulimia nervosa · Repetitive transcranial magnetic stimulation · Left dorsolateral prefrontal cortex · Depression · Biological treatment option

**Abstract**
***Background:*** Bulimia nervosa (BN) is often associated with depressive symptoms and treatment with antidepressants has shown positive effects. A shared deficient serotonergic transmission was postulated for both syndromes. The left dorsolateral prefrontal cortex was argued to regulate eating behaviour and to be dysfunctional in eating disorders. ***Methods:*** Fourteen women meeting DSM-IV criteria for BN were included in a randomised placebo-controlled double-blind trial. In order to exclude patients highly responsive to placebo, all patients were first submitted to a one-week sham treatment. Randomisation was followed by 3 weeks of active treatment or sham stimulation. As the main outcome criterion we defined the change in binges and purges. Secondary outcome variables were the decrease of the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI) and the Yale-Brown Obsessive Compulsive Scale (YBOCS) over time. ***Results:*** The average number of binges per day declined significantly between baseline and the end of treatment in the two groups. There was no significant difference between sham and active stimulation in terms of purge behaviour, BDI, HDRS and YBOCS over time. ***Conclusion:*** These preliminary results indicate that repetitive transcranial magnetic stimulation (rTMS) in the treatment of BN does not exert additional benefit over placebo. A larger number of patients might clarify a further role of rTMS in the treatment of BN.


## Introduction

According to Faravelli et al. [1], the lifetime prevalence of bulimia nervosa (BN) is 0.32%. Since the first description of bulimia as a clinical diagnosis by Russell in 1979 [2], little is known about the biological background of the disease. On the other hand, there is strong evidence for a sociocultural influence and psychological antecedents [3]. In addition, BN coaggregates with a high number of psychiatric comorbidities [4]. BN as well as depression seem to be based on alterations of serotonin activity [5, 6] and there is evidence that BN may respond to antidepressants [7]. Both diseases seem to share common steps in their aetiology as demonstrated by the affective spectrum disorder model, which includes depression, anxiety disorders, obsessive-compulsive disorder and others [8].

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Michaela Walpoth, MD
Department of General Psychiatry
Laboratory for Magnetic Brain Stimulation, Innsbruck Medical University
Anichstrasse 35, AT–6020 Innsbruck (Austria)
Tel. +43 512 504 23636, Fax +43 512 504 23628, E-Mail Michaela.Walpoth@i-med.ac.at

In addition, functional imaging techniques, such as SPECT and PET, indicate left frontal cerebral hypometabolism in both depressive as well as bulimic patients. These changes of activity in the frontal area might be critical for eating control [9, 10].

Repetitive transcranial magnetic stimulation (rTMS) is a therapeutic tool in psychiatry, exerting mild cognitive side-effects [11]. It is a non-invasive, neurophysiological method, able to depolarize cortical neurons with a short magnetic pulse.

High-frequency rTMS up-regulates metabolism locally as well as in remote, functionally linked areas [12]. Based on the evidence reviewed above, we hypothesised that rTMS modulates the feeding suppression area in the frontal lobe.

Since the response rate to existing treatment in bulimic patients is still moderate, we proposed to study the therapeutic effects of rTMS in outpatients with BN previously described in our case report [13].

**Table 1.** Patients' characteristics

| | Groups | |
|---|---|---|
| | rTMS (n = 7) | sham (n = 7) |
| *Sociodemographics* | | |
| Age[1], years | 27.4 ± 4.8 | 22.6 ± 2.6 |
| Education, years | 11.9 ± 1.8 | 11.6 ± 1.1 |
| *Baseline* | | |
| Duration of illness, years | 8.4 ± 3.2 | 8.0 ± 2.8 |
| Initial weight, kg | 55.0 ± 7.8 | 55.1 ± 6.2 |
| Initial BMI | 19.6 ± 2.4 | 19.7 ± 1.7 |
| Baseline number of daily vomiting | 2.57 ± 1.74 | 2.86 ± 2.39 |
| Baseline number of daily binges | 2.07 ± 0.98 | 2.92 ± 1.88 |
| Previous psychotherapy | 6 (86%) | 4 (57%) |

The patients met the criteria for major depressive episodes, but had an HDRS score <18 (exclusion criteria) in the last 4 months.
[1] $p = 0.053$ (Mann-Whitney U test).

## Methods

*Study Design*

Female subjects had to meet the following inclusion criteria: current BN for at least 6 months and age between 18 and 35 years. Exclusion criteria were severe depressive symptoms [Hamilton Depression Rating Scale (HDRS) score >18], body mass index <17.5, contraindications to rTMS (epilepsy, craniocerebral injury, serious medical problems or suicidal ideation), psychotherapy and psychopharmacological medication during the last 3 months, and gravidity, which was ruled out by a pregnancy test. Fourteen women were recruited to this randomised, placebo-controlled double-blind study, which was approved by the local ethics committee.

After a week of placebo wash-out, subjects were randomised into two groups for 3 weeks of either active or placebo (sham) stimulation. Exclusion criteria after the first week of placebo wash-out were a 50% reduction in binging and purging as well as in the HDRS score. In order to have accurate information, subjects were asked to assess their binges and purges. The primary outcome criterion was defined as a 50% reduction in binging and purging. Purge behaviour was recorded in subgroups, such as vomiting, abuse of laxatives and diuretics, omitting meals, excessive sports or other compensation mechanisms.

*Treatment Setting*

Stimulation was performed by trained psychiatrists with a figure-of-eight air-cooled coil (focal coil) attached to a rapid Magstim Stimulator (Magstim Company Ltd., Whitland, UK) placed over the left dorsolateral prefrontal cortex [14]. Stimulation was delivered for 3 weeks (3 × 5 days) with an intensity of 120% motor threshold using 20 Hz, in one session a day. Ten trains of 10 s, with a train interval of 60 s, were performed per session. Patients got an amount of 2,000 stimuli per session summing up to a total of 30,000 in the actively treated group. Sham treatment was delivered just like active treatment differing in the use of a specially designed sham coil which was covered with a magnetic-field-absorbing μ-metal plate.

*Outcome Measures*

At baseline (t0), after 1 week of placebo wash-out (t1) and after finishing the 3-week rTMS or sham stimulation (t2), the binge/purge status was assessed by a blinded psychiatrist. Changes in depressive symptomatology were assessed by the HDRS [15] and the Beck Depression Inventory (BDI) [16]. Compulsive symptoms were measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) [17]. The Structured Clinical Interview for DSM-IV (SCID) [18] was used to assess lifetime psychopathology other than BN. After finishing the study, the enrolled women were offered a supportive pharmacological therapy and/or psychotherapy.

*Statistics*

The two treatment groups were compared with respect to sociodemographic and clinical patient characteristics by means of the Mann-Whitney U test and Fisher's exact test, depending on the variable type (ordinal/continuous, binary). The time course of the individual outcome measures (e.g. BDI, HDRS, YBOCS, number of binges) was evaluated by repeated-measures analysis of variance (between-subject factor 'treatment group', within-subject factor 'time'). Differential treatment effects were analysed on the basis of the group-by-time interaction. Post hoc comparisons for individual time points were performed if the main effect of the factor 'time' showed at least trend level significance ($p < 0.1$). Dependent variables with a clearly non-Gaussian distribution were transformed to approximate normality prior to analysis. As the two treatment groups differed slightly in their age distribution, age was added as a covariate throughout the analysis. Missing values were replaced using the 'last observation carried forward' method. Because of the small number of patients completing the study, the post-treatment phase was not analysed.

**Table 2.** Depression (BDI), obsessive-compulsive symptoms (YBOCS), number of binges and vomiting in the course of time

| Variable | Descriptive statistics for the individual treatment groups (mean ± SD) | | Between-group comparisons | | Within-subject comparisons for the total sample (mean ± SD)[3] |
|---|---|---|---|---|---|
| | rTMS (n = 7) | sham (n = 7) | age-adjusted difference[1] | p value[2] | |
| Total BDI score | | | | | |
| t0 Baseline | 21.6 ± 10.6 | 23.7 ± 11.0 | –1.6 (7.5) | n.s. | 22.6 ± 10.4 |
| t1 After placebo wash-out | 13.9 ± 12.9 | 17.3 ± 14.6 | –2.7 (9.8) | n.s. | 15.6 ± 13.4[b] |
| t2 End of treatment | 15.3 ± 10.5 | 13.0 ± 12.0 | +0.3 (8.0) | n.s. | 14.1 ± 10.9[b] |
| Change score (t2 – t1) | +1.4 ± 5.4 | –4.3 ± 5.1 | +3.0 (3.5) | 0.415, n.s. | |
| Total YBOCS score | | | | | |
| t0 Baseline | 25.6 ± 9.3 | 23.1 ± 9.7 | +2.4 (5.1) | n.s. | 24.4 ± 9.2 |
| t1 After placebo wash-out | 23.4 ± 7.6 | 21.6 ± 9.6 | +1.9 (4.6) | n.s. | 22.5 ± 8.4 |
| t2 End of treatment | 17.3 ± 8.3 | 17.0 ± 11.4 | +0.3 (5.3) | n.s. | 17.1 ± 9.6[b, c] |
| Change score (t2 – t1) | –6.1 ± 9.9 | –4.6 ± 6.9 | –1.6 (4.5) | 0.735, n.s. | |
| Binges per day | | | | | |
| t0 Baseline | 2.1 ± 1.1 | 2.9 (2.4[4]) ± 1.9 | –0.8 (0.8) | n.s. | 2.5 ± 1.5 |
| t1 After placebo wash-out | 1.6 ± 1.1 | 2.9 (2.5[4]) ± 2.3 | –1.3 (1.0) | n.s. | 2.3 ± 1.9 |
| t2 End of treatment | 1.5 ± 1.2 | 2.1 ± 1.4 | –0.6 (0.8) | n.s. | 1.8 ± 1.3[a] |
| Change score (t2 – t1) | –0.1 ± 0.5 | –0.8 (–0.4[4]) ± 1.3 | +0.7 (0.5) | 0.211, n.s. | |
| Vomiting, times per day | | | | | |
| t0 Baseline | 2.6 (2.2[4]) ± 1.7 | 2.9 (2.2[4]) ± 2.4 | –0.1 (0.8) | n.s. | 2.7 (2.2[4]) ± 2.0 |
| t1 After placebo wash-out | 2.0 ± 1.5 | 4.0 (2.6[4]) ± 3.8 | –1.2 (1.0) | n.s. | 3.0 (2.3[4]) ± 3.0 |
| t2 End of treatment | 1.5 ± 1.1 | 2.8 (2.0[4]) ± 2.1 | –0.9 (0.7) | n.s. | 2.1 (1.7[4]) ± 1.8[c] |
| Change score (t2 – t1) | –0.5 ± 1.2 | –1.2 (–0.7[4]) ± 1.8 | +0.3 (0.5) | 0.590, n.s. | |

[a] $p < 0.05$, significant improvement between baseline and actual measurement time; [b] $p < 0.01$, highly significant improvement between baseline and actual measurement time; [c] $p < 0.05$, significant improvement between the end of the wash-out period and the end of treatment.

[1] Estimate of the age-adjusted mean difference between the two groups (rTMS – sham). Figures in parentheses indicate standard errors.

[2] n.s. = Not significant (always $p > 0.2$). Exact p values only shown for analysis of treatment effects (i.e., comparison of rTMS and sham with respect to change score).

[3] As there were no significant group effects or group-by-time interactions, only the results for the total sample (n = 14) are shown, using repeated-measures ANOVA.

[4] If the mean is strongly affected by outliers, an estimate of the mean that is less sensitive to outliers (Huber's M-estimator) is provided in addition to the sample mean (in parentheses).

## Results

Forty-two women responded to our advertisement. Nine did not meet the criteria for BN. Only 16 from the remaining 33 potential candidates met our inclusion criteria. Of these 16 patients, 14 women completed the study protocol. Two patients, both in the sham group, terminated the study prematurely, 1 because of a 50% reduction in binging and purging and 1 because of worsened depressive symptoms during the placebo wash-out phase. No seizure-like phenomena were observed during stimulation in the study group.

Patients' characteristics are listed in table 1. At baseline, the two groups were comparable with respect to all sociodemographic and clinical parameters except age (patients of the active treatment group were slightly older than those of the placebo group, $p = 0.053$).

With regard to the SCID diagnosis, 36% of the subjects (5/14) reported current major depression, however not reaching the 18-point cut-off level for exclusion in the HDRS.

The time course of the patients' psychopathology and their binge and purge behaviour are shown in table 2. The two treatment groups did not differ significantly in any of the outcome measures investigated. In particular, the two groups did not show any remarkable differences with respect to changes in the outcome measures during the treatment period, i.e., between t1 and t2 (details in table 2).

In longitudinal analyses, changes of the outcome measures in the time course were investigated. These changes were similar in both treatment groups, as the group-by-time interaction never reached significance. Significant improvements from baseline (t0) to the end of treatment (t2) were observed for self-rated depression (BDI), obsessive-compulsive symptoms (YBOCS) and frequency of binging. Vomiting improved significantly between the end of the placebo wash-out (t1) and t2. No significant change in physician-rated depression (HDRS), abuse of laxatives and diuretics, skip of meal or sports was observed.

## Discussion

Our results are preliminary data from a study using rTMS in the treatment of BN. The main limitation is the small sample size. The presence of additional personality disorders interferes with a good clinical outcome in biological interventions for affective symptoms for example in bipolar patients [19]. Our results show considerable improvements of binging and purging as well as depressive and obsessive-compulsive symptoms. However, no significant difference between the active treatment and the placebo-stimulated groups could be detected. One explanation for this unspecific treatment effect might be due to regular contacts with a trained psychiatrist. In recently published studies investigating the treatment of bulimia or binge eating disorder with selective serotonin re-uptake inhibitors, patients also showed a high placebo response [7, 20, 21]. In one of these studies [21], the authors attributed this unspecific treatment effect to an increased awareness and the regular documentation of the binge behaviour. Similar considerations may also apply for our study.

A higher number of patients is needed to clarify the future of rTMS in the treatment of BN. Further research has to address optimisation of the stimulation paradigm used, based on functional imaging data and stimulation parameters.

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