1-Hz rTMS in the treatment of tinnitus: A sham-controlled, randomized multicenter trial

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**Abstract**

Background: Chronic tinnitus is a frequent, difficult to treat disease with high morbidity.

Objective: This multicenter randomized, sham-controlled trial investigated the efficacy and safety of 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied to the left temporal cortex in patients with chronic tinnitus.

Methods: Tinnitus patients were randomized to receive 10 sessions of either real or sham 1-Hz-rTMS (2000 stimuli, 110% motor threshold) to the left temporal cortex. The primary outcome was the change in the sum score of the tinnitus questionnaire (TQ) of Goebel and Hiller from baseline to end of treatment.

Results: A total of 163 patients were enrolled in the study (real rTMS: 75; sham rTMS: 78). At day 12, the baseline mean of 43.1 TQ points in 71 patients assigned to real rTMS changed by −0.5 points; it changed by 0.5 points from a baseline of 42.1 in 75 patients assigned to sham rTMS (adjusted mean difference −1.0; 95.19% confidence interval: −3.2 to 1.2; p = 0.36). All secondary outcome measures including measures of depression and quality of life showed no significant differences either (p > 0.11). The number of participants with side-effects or adverse events did not differ between groups.

Conclusion: Real 1-Hz-rTMS over the left temporal cortex was well tolerated but not superior compared with sham rTMS in improving tinnitus severity. These findings are in contrast to results from studies with smaller sample sizes and put the efficacy of this rTMS protocol for treatment of chronic tinnitus into question.

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Background

Subjective tinnitus is characterized by the perception of sound in the absence of a corresponding sound source [1]. Subjective tinnitus is a frequent disorder with prevalence rates of about 10% of the adult general population [2]. The majority of the affected people can habituate to the phantom sound, but approximately 10% of the tinnitus patients report severe tinnitus-related impairment of daily living [3] and seek medical help. Severe tinnitus is frequently associated with depressive symptoms, anxiety [4], and insomnia [5]; on the other hand there exist no evidence-based established treatments for curing tinnitus or for the reduction of its loudness [6].

Tinnitus mostly follows acute or chronic cochlear injury or diseases such as acoustic trauma, drug toxicity or presbyacusis. Findings from animal models [7] and functional human brain imaging [8] suggest that auditory deafferentation induces hypersynchrony and hyperactivity in the central auditory pathways, and also in connected non-auditory brain areas [9]. These alterations of brain activity are considered as the neuronal correlates of tinnitus [10].

Transcranial magnetic stimulation (TMS) is a non-invasive tool for inducing electric currents in the brain. Repetitive TMS (rTMS) has been demonstrated to induce a neuronal excitability shift of the stimulated cortical areas outlasting the actual stimulation period [11]. Based on the assumption that low-frequency rTMS may reduce tinnitus-related hyperexcitability in auditory brain areas [12] repeated 1-Hz-rTMS over the temporal or temporoparietal cortex has been investigated as a treatment for tinnitus with contradictory results [13]. The variability in the outcome may be related to relatively small sample sizes, to methodological heterogeneity and to high interindividual variability in the response to rTMS [14]. Based on the existing literature rTMS seems to be a safe intervention for treating tinnitus [13]. However, with respect to hearing function, the literature is inconclusive [15–17] and some patients complained of a worsening of hyperacusis and painful hypersensitivity to noise after rTMS application [18].

With the presented multi-center, randomized clinical trial we aimed to determine whether real 1-Hz-rTMS would be safe and superior to sham rTMS for the treatment of chronic subjective tinnitus.

Material and methods

This study was conducted at 7 centers (university ENT and psychiatry departments and 1 outpatient ENT clinic) in Germany from February 2008 (last patient in: May 2011) until October 2011 (last patient out). The study was approved by the ethic committee of the University of Regensburg (October 24th, 2006; No. 06/165) and was conducted in accordance with the Declaration of Helsinki and rules and regulations of good clinical practice (GCP). Clinical on site monitoring was performed by Multi-Service-Monitoring, Regensburg, Germany, and data management by the Center for Clinical Studies, University of Regensburg. The trial was funded by the German Research Foundation (DFG, HA 3547/4-1) and was registered at the Controlled Trials registry (ISRCTN89848288) on September 12th, 2007. In addition, the study protocol had been published [19].

A total of 163 patients gave informed consent for study participation. The inclusion criteria were as follows: patients (both sexes, age 18–70 years) with chronic tinnitus defined as a screening sum score in the tinnitus handicap inventory (THI; [20]) of at least 38 points. Hearing levels had to be normal (age-adjusted, not more than 5 dB below the 10% percentile according to DIN EN ISO 7029) in all standard frequencies. In addition, conductive hearing loss was not allowed to be more severe than 15 dB. Patients had to be naïve to rTMS to ensure blinding of the study. Exclusion criteria were objective tinnitus, simultaneous tinnitus-specific treatments, clinically relevant psychiatric comorbidity, especially diagnoses according to F1 to F3 main categories in the International Classification of diseases (ICD-10), simultaneous treatment with psychotropic agents (e.g. benzodiazepines, anticonvulsants, neuroleptics, antidepressants. Irregular intake of hypnotics was permitted), severe instalble somatic comorbidity, contraindications for rTMS, pregnancy and participation in a clinical trial within the last 30 days prior to study enrolment.

Study design and intervention, randomization and masking

After informed consent, patients were enrolled in this multi-center, randomized, sham-controlled trial. During the baseline visit (taking place 11 to 9 days before first treatment, see Fig. 1) a broad spectrum of psychometric as well as tinnitus specific scales (including the Tinnitus Questionnaire (TQ; [21]) and the THI) were applied complemented by neuropsychological measurements and a neuro-psychiatric examination (see Table 1 in the supplement material). In the week before first treatment, tinnitus severity was again measured twice with the TQ and the THI in order to obtain a stable average baseline measure of tinnitus severity. Eligible patients were randomized and entered a two-week, rater- and patient-blinded, parallel-group rTMS-intervention (real vs. sham rTMS treatment) followed by 24 weeks follow-up period (Fig. 1). Randomization was based on computer-generated random lists prepared by the Clinical Trials Unit (Medical Center — University of Freiburg). It was stratified by center, with randomly varying block sizes of 2 or 6 patients and a 1:1 treatment ratio. Randomization was performed centrally at the trial coordination center via fax to designated non-blinded technical study staff at the participating sites conducting rTMS treatment. Throughout the study, patients and raters remained blinded to the treatment assignment. These arrangements aimed to minimize selection and assessment biases. Patients randomized to real rTMS received two times 5 sessions (one session daily in two weeks) of 1-Hz-rTMS (2000 stimuli per session) applied to the left primary auditory cortex with a stimulation intensity of 110% related to the individual resting motor threshold. The left primary auditory cortex had been identified as a potential target region for 1-Hz-rTMS-treatment of tinnitus in pilot studies (see Ref. [12]). The position of the stimulation coil was defined using an algorithm based on the international standardized 10–20-EEG-system [22]. Patients in the sham group received the same treatment but the stimulation coil was tilted away from the skull by 45° with one wing touching the skull (to ensure skin sensations induced by the magnetic impulse without inducing
relevant biological activity). All study centers used TMS stimulators from Medtronic Co. (Denmark; MagPro X-100 or MagPro R30) with passively-cooled MCF-B65 figure-of-eight coils.

Baseline assessment and efficacy measures

The primary objective of this trial was to evaluate the efficacy of a two-week 1-Hz rTMS treatment in patients with chronic tinnitus. The primary outcome measure was the change of tinnitus severity assessed by means of the change of the TQ sum score (range: 0–84) between baseline score (averaged over three measurements) vs. day 12 (end of stimulation period). Secondary outcome measures were changes of the TQ sum score, the THI and the Tinnitus Severity Scale (TSS; six numeric rating scales; range 0–5 (scale 1) and 0–10 (scales 2–6) [23] during the treatment and the follow-up period (screening versus baseline and days 5, 12, 18, 67, and 181). Further outcome measures were changes of overall illness severity (Clinical Global Impression Scale, CGI [24]), changes in depressive symptoms (Becks-Depression-Inventory, BDI-II [25]), changes in quality of life (SF-12 questionnaire [26]) and changes in psychoacoustic measures of tinnitus (tinnitus-minimal-masking-level and tinnitus loudness).

Safety measures

All patients underwent physical examination including measurement of vital signs (heart rate, blood pressure and body weight) and neuropsychological testing (test for attentional performance, TAP, version 1.7 [27] at baseline and visit 11 (day 12)). Otolologic examinations including audiological assessment were performed at baseline and visit 12 (day 17–19). For global assessment of hearing function the hearing loss at all tested frequencies of the standard audiogram (125 Hz–8 kHz) was determined as area under the curve (AUC) [28] for each ear separately. Adverse events were monitored throughout the treatment period (visits 2–11).

Sample size and statistical analyses

Power calculations were done for the primary endpoint. Based upon clinical experience, a difference of 5 points in the TQ sum score was considered as clinically relevant, and 0.486 was a conservative estimate of the corresponding effect size [29]. To achieve a power (1-β) of 0.80 to detect a difference with a two-sided unpaired t-test at a level of α = 0.05 assuming such an effect, 68 patients per arm (real vs. sham) were needed. Assuming that less than 5% of patients would fail to provide post-baseline data, it was decided that 150 should be randomized (see Ref. [19]).

The effect of rTMS treatment on TQ change was estimated on an intention-to-treat basis (ITT) including all patients with post-baseline data (carrying forward day 5 measurements if day 12 was missing), in an analysis of covariance including randomized treatment and average baseline score as fixed factors and center as a random factor. The two-sided significance level at final analysis was set to 0.0481 to maintain an overall level of 0.05, accounting for one interim analysis. Sensitivity analyses were to follow if more than 5% of patients would fail to provide post-baseline data. Exploratory secondary analyses of TQ change over time were performed in longitudinal linear mixed models based on a prespecified model-building strategy. For the other secondary objectives with respect to rating scales (THI, SF-12, BDI-II, TSS and CGI) a similar strategy was employed. Details were fixed in a statistical analysis plan before the blind was broken. Analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), graphics were produced with R version 3.2.4 [30].

A pre-planned interim analysis based on 76 patients was prepared by the blinded trial statistician and carried out by a second statistician (α’ = 0.0052 at interim; see Ref. [19]). Results were presented to a Data Safety Monitor Board (DSMB) in strict confidentiality. The DSMB recommended continuing the trial without modification.

Results

Study population

A total of 163 patients gave written informed consent for study participation. Of these, 11 patients were not randomized (screening
The primary outcome was based on the FAS and defined as a change in tinnitus severity measured by the change of the total score of the TQ (range 0–84; baseline vs. day 12). At day 12, there was no statistically significant difference between both study arms (Fig. 2; because of missing data for day 12, day 5 measurements were carried forward in 5 patients (1 real; 4 sham)). In the primary analysis adjusted for baseline TQ-scores and center effects, changes in the real rTMS group and the sham rTMS group differed only slightly (real rTMS: 4.7 [2.8 to 6.6]; sham rTMS: 3.2 [-3.2 to 11.8]; p = 0.36). However, in both groups there were no significant changes of tinnitus severity (mean TQ total score at baseline, real rTMS: 43.1 vs. sham rTMS: 42.1; TQ total score at day 12, real rTMS: 42.7, change [95% CI] −0.5 [-1.8 to 0.9] vs. sham rTMS: 42.6, change 0.5 [-1.2 to 2.3]).

Secondary outcome measures

In addition, no statistically significant differences were found in any of the secondary outcome parameters (Table 2). There were no differences in tinnitus severity changes between groups throughout the whole follow-up period (Fig. 3) independently of the used rating scale (interaction group x time for the TQ: p = 0.53; for the THI: p = 0.55; for the six TSS-scales: p > 0.11). In accordance, there was no difference in the overall illness severity changes as assessed by the CGI (p = 0.12). The minimal masking level, which was used for the assessment of tinnitus loudness, increased slightly in the sham group, while in the real rTMS group the minimal masking level showed a slight non-significant decrease (screening vs. week 3: left ear: real rTMS: −2.4 [-6.2 to 1.5] dB (N = 49), sham rTMS: 2.0 [-4.5 to 8.5] dB (N = 42); right ear: real rTMS: −2.2 ± 15.9 dB (N = 45), sham rTMS: 0.5 ± 12.5 (N = 36)). None of these differences reached statistical significance.

With respect to changes in depressive symptoms assessed by the BDI-II neither at day 12 (mean [95% CI] difference in BDI-II for real vs. sham rTMS: −0.5 [-1.6 to 0.7]; p = 0.43) nor throughout the follow-up period (p = 0.78) any relevant or statistically significant change between both study arms could be observed. The same holds true for quality of life as assessed by the mental and physical subscales of the SF-12 (smallest p-value: p = 0.14).

Overall, there was a continuous tendency for slightly greater improvement in the real group compared to the sham rTMS group in all outcome measures. However, these differences were small and reached in none of the cases at any time point clinical relevance or statistical significance.

Predictor analysis revealed that none of the following parameters significantly modified the effect of real vs. sham rTMS with respect to TQ sum scores over time: tinnitus severity at baseline as measured by TQ and THI, age, gender, hearing level, tinnitus duration, tinnitus localization, comorbid depressive symptoms, or the SF-12 mental and physical subscales. Only tinnitus tone characteristics (tonal vs. non-tonal tinnitus) modified the effect of real vs. sham treatment (p = 0.017), with a significant benefit of real over sham rTMS in the subgroup with non-tonal tinnitus (N = 37; p = 0.012). However, as subgroup investigations are of highly exploratory nature, these results should be interpreted with caution.

Treatment Adherence and blinding

Adherence to study treatment was overall high in both study arms and drop-out rates were low. One patient in the real rTMS group (1.4%) and 4 (5.3%) patients in the sham rTMS group did not complete the whole treatment period and dropped out before day 12 (primary endpoint). Reasons for drop-out were patient wish (N = 2), adverse event (N = 2) and deterioration of tinnitus (N = 1). Drop-outs due to adverse events and deterioration of tinnitus were all in the sham rTMS group. Until the end of the study the drop-out rates increased slightly in both study arms (real rTMS group: N = 5 (7%); sham rTMS group: N = 9 (12%)). At the final visit, patients were asked which treatment they thought they had received. Most patients answered “sham rTMS” (61%; 84/138), with only a slightly increased rate in those who really received sham compared to real rTMS (rate ratio: 1.07; 95% CI 0.77 to 1.49; p = 0.68).

Safety and tolerability

To study safety of rTMS in the treatment of chronic tinnitus, a variety of safety parameters were recorded at different time points (see above). With respect to the otological examinations, there were no clinically relevant findings reported in any of the randomized patients. Since hearing loss is one of the major pathological mechanisms in chronic tinnitus, the hearing level was measured at screening and in week 3 to control for any deterioration in hearing level due to rTMS treatment. In the real rTMS group there was a change (mean, [95% CI]) of 3.8 [-0.1 to 7.7] in the left ear (area-under-the-curve; AUC), for the right ear of 4.4 [0.4 to 8.4]. In the sham group changes were 2.2 [-2.7 to 7.1] and 2.6 [-2.9 to 8.2], respectively. These deteriorations did not differ significantly between treatments (baseline-adjusted difference, real - sham rTMS, left ear: 1.0 [-4.7 to 6.9], p = 0.73; right ear: 0.7 [-5.7 to 7.02], p = 0.84). In addition to these tinnitus-relevant safety parameters, neuropsychological tests (test for attentional performance; TAP) were conducted at baseline and at the end of the treatment period (day 12). Non-inferiority of real rTMS compared to sham rTMS was pre-defined as an odds ratio below 1.2 (real vs. sham rTMS) for the risk to fall below the 20% -percentile. Except for the standard deviation for the tonic alertness (odds ratio = 1.57), all odds ratios were below 1.2 indicating non-inferiority of real rTMS compared to sham rTMS.

Adverse events (AEs) and serious adverse events (SAEs) were recorded during the treatment period (days 1–12). Analyses were performed according to received treatment in the safety population, i.e. in all patients receiving at least one real (N = 74) or sham rTMS treatment (N = 76). Overall, rTMS treatment was well tolerated. AEs were reported in 35.1% of the patients in the real rTMS group compared to 39.5% in the sham rTMS group (rate difference real - sham rTMS: −4.3%; 95% CI -19.3% to 10.9%). AEs with a potential causal relationship to the intervention were seen in 21.6% (real rTMS) vs. 27.6% (sham rTMS) of the patients. By trend, patients in the sham group reported more AEs (mean: 0.66 AEs per patient) than patients in the real rTMS group (0.51 AEs). Interestingly, more patients in the sham rTMS group complained about deterioration of their tinnitus compared to the real rTMS group (11.8% vs. 5.4%, respectively). In both groups, headache was the most frequently reported AE (10.8% in the real rTMS group vs. 14.5% in the sham rTMS group; see Table 3). The majority of AEs were of mild to
moderate severity. In both groups, one SAE was reported. In the real rTMS group, this was a tachyarrhythmia in context of a known cardiac insufficiency, in the sham group severe headache and deterioration of the tinnitus. The latter SAE was considered as potentially causally related to rTMS treatment. Taken together, the safety data demonstrate that rTMS is a safe and well-tolerated intervention in patients suffering from chronic subjective tinnitus. However, a slight trend towards worsening of hearing loss has been observed in both treatment groups without a significant difference between real and sham rTMS.

Discussion

The main result of the study is that real 1-Hz-rTMS applied to the left temporal cortex did not provide any therapeutic benefit as compared to sham treatment in patients with chronic tinnitus. There was no relevant or significant difference between the real- and sham-treated group in any of the outcome parameters, neither at the end of treatment, nor during the follow-up period.

1-Hz-rTMS over the temporal cortex has been investigated in several sham-controlled studies with small sample sizes before with heterogeneous results. Whereas most studies were positive [31–37], several recent trials failed to demonstrate a benefit of low-frequency rTMS for tinnitus treatment [38–41]. In line with these recent results, no beneficial clinical effect of rTMS could be detected in this first national multicenter trial with a large sample size. This result is even more disappointing since inclusion criteria of this trial were chosen according to early studies suggesting that shorter tinnitus duration and better hearing function would be positive predictors for treatment outcome [29,33,34].

The negative result cannot be attributed to limited power of the study. Since there was almost no difference between real and sham stimulation even a much larger sample would not have resulted in a relevant separation between real and sham treatment.

The encountered scenario, that promising results in pilot studies cannot be replicated in larger multicenter studies, resembles the situation in other applications of rTMS. A recent multicenter study investigating high frequency rTMS for the treatment of negative symptoms in schizophrenia [42] has failed in spite of positive pilot studies. One possible explanation is that multicenter studies can be confounded by heterogeneities in the study population in different centers and also by differences between centers in treatment application. However we tried to minimize these effects by investigator trainings and standard operating procedures to ensure e.g. correct positioning of the stimulation coil. Moreover we accounted for a potential center effect in the statistical analysis, but the data revealed no relevant center-effect.

A more probable explanation is that the negative result in this multicenter study is related to its more rigorous methodology as compared to earlier positive studies with smaller sample sizes. Our trial was designed according to good clinical practice and specific methods against potential bias were applied (i.e. randomization and blinding procedures, standard operation procedures). Furthermore, blinding quality was assessed at the end of the study, the trial was clinically monitored and the trial and the statistical analysis were performed according to an a priori defined study.

Fig. 2. Primary endpoint.
Primary endpoint: change of the total score of the TQ between baseline and day 12 in the FAS-population. There was a slightly higher, statistically non-significant improvement in tinnitus severity in the real rTMS group compared to the sham group (−1.0; 95.19% confidence interval: −3.2; 1.2; p = 0.36).
Thus, we conjecture that the higher methodological quality of this trial may have minimized bias that could have contributed to positive results of earlier studies. Another possible explanation is the heterogeneity of tinnitus. There is consensus that there exist different forms of tinnitus that also differ in their pathophysiology and their response to specific treatments. A higher proportion of responders in studies with small sample sizes may have been responsible for positive results in these studies. In this study, an exploratory sub-group analysis revealed a significant superiority for real rTMS versus sham rTMS in patients with non-tonal tinnitus. It has been assumed that non-tonal tinnitus differs in its pathophysiology from tonal tinnitus by additional involvement of the extralemniscal system [43]. In early studies, in which the effects of single rTMS sessions on tinnitus reduction were investigated, differential responses of rTMS on tonal and non-tonal tinnitus have already been reported [44,45].

| Table 2  |
|----------|-----------------|-----------------|-----------------|-----------------|
| Outcome Parameter | Visit | Group | N | Mean (SD) | 95% CI lower | 95% CI upper |
| TQ mean baseline (V1) | sham rTMS | 75 | 42.1 (13.8) | 38.9 | 45.3 |
| | real rTMS | 71 | 43.1 (14.7) | 39.6 | 46.6 |
| | real rTMS | 71 | 42.7 (15.8) | 38.9 | 46.4 |
| Week 2 (V11) | sham rTMS | 75 | 42.6 (16.5) | 38.8 | 46.4 |
| | real rTMS | 71 | 42.7 (15.8) | 38.9 | 46.4 |
| Week 26 (final visit) | sham rTMS | 65 | 41.9 (19.4) | 37.1 | 46.7 |
| | real rTMS | 65 | 40.3 (19.8) | 35.4 | 45.2 |
| THI mean baseline (V1) | sham rTMS | 75 | 50.5 (17.8) | 46.4 | 54.6 |
| | real rTMS | 71 | 51.2 (20.5) | 46.4 | 56.0 |
| Week 2 (V11) | sham rTMS | 75 | 49.0 (20.2) | 44.4 | 53.7 |
| | real rTMS | 71 | 50.2 (21.3) | 45.2 | 55.3 |
| Week 26 (V14) | sham rTMS | 66 | 47.1 (22.5) | 41.6 | 52.7 |
| | real rTMS | 65 | 45.5 (25.5) | 39.1 | 51.8 |
| BDI Baseline (V1) | sham rTMS | 74 | 8.5 (5.9) | 7.1 | 9.9 |
| | real rTMS | 68 | 9.4 (7.2) | 7.6 | 11.1 |
| Week 2 (V11) | sham rTMS | 75 | 7.7 (5.9) | 6.3 | 9.1 |
| | real rTMS | 71 | 8.1 (6.6) | 6.6 | 9.7 |
| Week 26 (V14) | sham rTMS | 66 | 8.2 (6.8) | 6.5 | 9.9 |
| | real rTMS | 65 | 8.8 (9.1) | 6.6 | 11.1 |
| SF-12 (normed) Physical component Baseline (V1) | sham rTMS | 63 | 45.6 (8.1) | 43.5 | 47.6 |
| | real rTMS | 63 | 47.7 (8.2) | 45.6 | 49.8 |
| Week 2 (V11) | sham rTMS | 73 | 47.5 (8.3) | 45.5 | 49.4 |
| | real rTMS | 70 | 47.8 (7.3) | 46.0 | 49.5 |
| Week 26 (V14) | sham rTMS | 56 | 46.6 (8.8) | 44.3 | 49.0 |
| | real rTMS | 55 | 46.9 (9.6) | 44.3 | 49.4 |
| SF-12 (normed) Mental component Baseline (V1) | sham rTMS | 63 | 48.4 (9.8) | 45.9 | 50.9 |
| | real rTMS | 63 | 46.9 (10.5) | 44.3 | 49.6 |
| Week 2 (V11) | sham rTMS | 73 | 48.1 (10.6) | 45.6 | 50.6 |
| | real rTMS | 70 | 47.1 (10.0) | 44.7 | 49.5 |
| Week 26 (V14) | sham rTMS | 56 | 47.1 (11.9) | 43.9 | 50.3 |
| | real rTMS | 55 | 46.6 (10.8) | 43.7 | 49.5 |

Scores of primary and secondary outcome scales for both study arms at baseline and week 2 (visit 11) for TQ, THI, BDI and SF-12 and at screening and week 3 (visit 12) for tinnitus loudness.

Fig. 3. Secondary endpoints.
Secondary endpoints: change of the tinnitus severity measured with the TQ during the whole observation period (baseline to week 26). There were neither significant differences between groups over time (p > 0.53) nor at any single time point (p > 0.14).
Table 3
Adverse events.

<table>
<thead>
<tr>
<th>Category</th>
<th>Received real rTMS (N = 74)</th>
<th>Received sham rTMS (N = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic (headache)</td>
<td>8 (10.8)</td>
<td>11 (14.5)</td>
</tr>
<tr>
<td>ENT</td>
<td>4 (5.4)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>(subjective deterioration of tinnitus)</td>
<td>3 (4.1)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td>Orthopedic (e.g., back pain, muscle hardening, etc.)</td>
<td>4 (5.4)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>(vegetative symptoms sleep disturbances, exhaustion, restlessness, etc.)</td>
<td>5 (6.8)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Internal (e.g., heart complaints, influenza infection, nausea, etc.)</td>
<td>3 (4.1)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Neurologic (vertigo)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Chirurgical (fracture, surgery)</td>
<td>1 (1.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Psychiatric (anxiety, panic attacks)</td>
<td>1 (1.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>ENT</td>
<td>2 (2.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>(hyperacusis)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Neurologic (paresthesia)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Neurologic (scalp discomfort under tms coil)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Psychiatric (concentration problems)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Psychiatric (depressive symptoms)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

Number (percent) of patients with at least one adverse event by received treatment in the safety set of patients who received at least one real or sham rTMS treatment. Adverse events were categorized to main medical disciplines during blind review clustering similar symptoms where applicable.

However, in contrast to our results these studies showed better tinnitus suppression after rTMS in patients with tonal tinnitus. Thus it remains unclear why patients with non-tonal tinnitus responded better to rTMS than those with tonal tinnitus. We are well aware that this finding has to be interpreted with caution, as it comes from a pre-planned but still exploratory additional analysis. Nevertheless further studies should consider the possible influence of type of tinnitus on rTMS response. With respect to other parameters, exploratory analyses of this study could not identify reliable predictors for positive outcome, which is in line with previous analyses of large samples [46,47]. Probably, imaging data may be better suited for identifying subgroups [48] and for predicting outcome [49,50].

A clear result of this trial is, that ten sessions of 1-Hz-rTMS over the temporal cortex as applied in our study, cannot be recommended as an efficient treatment for chronic tinnitus. However this does not exclude the efficacy of other rTMS protocols. First, one could assume that treatment duration may have been too short for achieving a clinical benefit [51]. In studies treating depression, real rTMS separates from sham treatment after 4 weeks of treatment, but not after 2 weeks [52,53]. Second, the coil positioning over the left temporal cortex may not have been optimal. Other studies found best results after stimulation of the temporoparietal cortex contralateral to the side of the tinnitus [54]. Third, a greater and more prolonged efficacy from high frequency (10/25 Hz) rTMS as compared to 1-Hz-rTMS has been demonstrated by one group [33,55]. More recent studies suggest better effects for rTMS therapy when frontal or prefrontal cortical areas are stimulated in addition to the temporal cortex [41,56–60]. These results are in line with imaging findings of increased functional connectivity between frontal and temporal cortical areas in tinnitus patients [61,62]. Further potentially more promising applications of rTMS include individualized stimulation protocols [63] or paired associative stimulation of an auditory stimulus with rTMS of the auditory cortex [64]. However, also these new approaches will require validation in clinical trials.

Conclusions

Taken together, this so far largest multicenter trial testing repetitive transcranial magnetic stimulation in the treatment of chronic tinnitus revealed that 1-Hz-rTMS over the left primary auditory cortex is not an efficient treatment protocol. Possibly, non-tonal tinnitus may show better response to this treatment protocol than other types of tinnitus. Furthermore, since modified treatment protocols have shown positive results in smaller pilot studies, proving these preliminary results in larger patient samples appears promising to find more efficient treatment options for tinnitus patients.

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Appendix A. Supplementary data

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References


