Low-Frequency Repetitive Transcranial Magnetic Stimulation to the Temporoparietal Junction for Tinnitus

Four-Week Stimulation Trial

Jay F. Piccirillo, MD; Dorina Kallogjeri, MD, MPH; Joyce Nicklaus, RN, BSN, CRNC; Andre Wineland, MD; Edward L. Spitznagel Jr, PhD; Andrei G. Vlassenko, MD, PhD; Tammie Benzinger, MD, PhD; Jose Mathews, MD, PHD; Keith S. Garcia, MD, PhD

Importance: This research examines the impact of 4 weeks of repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal junction and compares the results of this longer duration of treatment with a similar stimulus protocol of only 2 weeks’ duration.

Objective: To examine the effectiveness and safety of 4 weeks of low-frequency rTMS to the left temporoparietal junction in a cohort of patients with bothersome tinnitus.

Design: Crossover, double-blind, randomized controlled trial.

Setting: Outpatient academic medical center.

Participants: The study population comprised 14 adults aged between 22 and 59 years with subjective, unilateral or bilateral, nonpulsatile tinnitus of 6 months’ duration or greater and a score of 34 or greater on the Tinnitus Handicap Inventory (THI).

Interventions: Low-frequency (1 Hz) 110% motor threshold rTMS or sham to the left temporoparietal junction for 4 weeks.

Main Outcome and Measure: The difference of the change in the THI score between active rTMS and sham rTMS.

Results: Active treatment was associated with a median reduction in THI score of 10 (range, −20 to +4) points, and sham treatment was associated with a median reduction of 6 (range, −24 to +12) points. The median difference in THI score between the change associated with active and sham rTMS was 4 (95% CI, −9 to 10; and range, −32 to +14) points.

Conclusions and Relevance: Daily low-frequency active rTMS to the left temporoparietal junction area for 4 weeks was no more effective than sham for patients with chronic bothersome tinnitus. Possible explanations for this negative study include the failure of rTMS to stimulate deeper parts of auditory cortex within the sylvian fissure and more widespread cortical network changes not amenable to localized rTMS effects.

Trial Registration: clinicaltrials.gov Identifier: NCT00567892


THE TECHNIQUE OF INDUCING small cortical currents using a pulsed electromagnetic field is called transcranial magnetic stimulation (TMS).1,2 Repetitive TMS (rTMS) refers to regularly repeated TMS delivered to a single scalp site.3,4 The resultant magnetic field passes through the skull and induces a small secondary current in the cortex with resultant inhibition or excitation depending on the frequency of stimulation.5,6 This electrical activity is insufficient to generate seizure activity unless the subject has a history of seizures or other functional or structural abnormalities of the brain. Depending on the stimulus parameters, rTMS can be used to enhance or suppress cortical activity.7-11 Several authors8,12-18 reported reduction in tinnitus with rTMS.

In previous research,19 we examined low-frequency (1 Hz) 110% motor threshold rTMS or sham to the left temporoparietal junction for 2 weeks. The enrolled adult subjects experienced subjective, unilateral or bilateral, nonpulsatile tinnitus of 6 months’ duration or greater and had a score of 38 or greater on the Tinnitus Handicap Inventory (THI). Daily low-frequency rTMS to the left temporoparietal junction area for 2 weeks was observed to be no more effective than sham. We hypothesize that the negative findings could be due to the short duration of treatment, insufficient stimulation strength, failure of rTMS stimulation over
the temporoparietal area to affect auditory cortex buried deep within the sylvian fissure, or more widespread cortical network changes not amenable to localized rTMS effects.

The goals of this study were to investigate the therapeutic impact of 4 weeks (twice as long as our previous study\(^9\)) of low-frequency (1 Hz) rTMS therapy and to assess factors related to outcome for patients with subjective idiopathic troublesome tinnitus. As in the previous study,\(^9\) the present study used a double-blind, crossover randomized trial design of active vs sham rTMS. In addition, we sought to identify predictors and correlates of response to rTMS therapy for patients with moderate to severe tinnitus.

**METHODS**

**DESIGN**

This was the second of 2 studies using a crossover, double-blind, randomized clinical trial design of low-frequency rTMS to the left temporoparietal junction. The first study\(^9\) involved stimulation for 2 weeks. Subjects were identified through the Washington University School of Medicine Research Participant Registry or responded to an online website (http://tinnitus.wustl.edu). Eligible subjects were adults between the ages of 18 and 60 years with subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or greater and a THI score of 30 or greater.\(^8\) Additional eligibility criteria, inclusion criteria, randomization procedure, and battery of assessment tools were described previously.\(^9\) The full trial protocol can be accessed at http://otooutcomes.wustl.edu/Pages/index.aspx. The only difference between the 2 studies was the length of intervention in each study arm and the reduction of the minimum THI score required at enrollment from 38 to 30. The minimal THI score was lowered in an attempt to ease recruitment and increase the generalizability of results.

Subjects were enrolled by the clinical research nurse coordinator (J.N.), and interventions were assigned in a randomized double-blind fashion by one of the study biostatisticians (E.L.S.) to receive either (1) active rTMS for 4 weeks and then crossover to sham rTMS for 4 weeks or (2) sham rTMS and then crossover to active rTMS. The randomization sequence was generated as a block randomization using SAS software (SAS Institute Inc) and was concealed to the subjects and to all other study team members. The washout period between the 2 interventions was a minimum of 2 weeks and maximum of 6 weeks, depending on the subject’s response to the first treatment arm. To ensure no carryover effect, the subject’s postwashout THI score had to return within 20 points of baseline score, otherwise the washout period was extended.

Each participant underwent 3 fluorodeoxyglucose F 18 (FDG) scans: 1 baseline scan before entering the study and 2 scans after the active and sham treatments. There were 9 age- and sex-matched, healthy, right-handed, neurologically normal adults recruited from the Washington University community, who were used as normal controls for positron emission tomography (PET) imaging. Each individual in the control group underwent a single baseline FDG PET scan at the resting state with the eyes closed.

All participants were studied on the Siemens ECAT Exact HR+ scanner (Siemens/CTI), with 63 slices encompassing an axial field of view of 15.5 cm.\(^{21}\) Transaxial and axial spatial resolution at slice center are 4.4 mm and 4.2 mm, respectively, in 2-dimensional (2-D) mode. Attenuation data were obtained using \(^{68}\)Ga rotating rod sources to enable quantitative reconstruction of subsequent emission scans. Emission data were obtained in 2-D mode (septa extended). All PET data were reconstructed using a ramp filter (approximately 6 mm full width at half-maximum) and then blurred to 12-mm full width. Subject head movement during scanning was restricted by a thermoplastic mask. All PET images were acquired in the eyes-closed waking state. No specific instructions were given in regarding cognitive activity during scanning other to remain awake.

A transmission scan was obtained at the beginning of each PET session. Before and at the midpoint of the FDG scan, a blood sample was drawn for measurement of glucose (to ensure values are in the normal range). Each FDG study consisted of a 60-minute dynamic scan (rebinned to 12 × 5-minute frames) initiated with an approximate 20-second bolus intravenous injection of 5 mCi of FDG. Dynamic data analysis was limited to the frames between 40 to 60 minutes after FDG injection. These 4 individual 5-minute frames were aligned using rigid body linear affine transformation to correct for any head motion during the scanning and then summed to create a single 20-minute image representing relative cerebral metabolic rate for glucose (CMRGluc). In each individual, the regional CMRGluc image was scaled to a whole-brain mean of 1 (local to global ratio).

Magnetization prepared rapid acquisition gradient echo (MPRAGE) magnetic resonance images were processed using FreeSurfer 5.0\(^{22}\) to segment the brain and obtain regions of interest (ROIs) for PET processing. Visual inspection of the automated segmentation results was performed for quality control for all data sets. Correction was done when necessary according to the FreeSurfer manual. Relative CMRGluc images were resampled to MRI space, and FreeSurfer ROIs were applied. Regional CMRGluc was evaluated in 34 cortical gray matter and 7 subcortical ROIs in each cerebral hemisphere.

**MEASUREMENTS**

Subjects completed the 18-item Body Symptom Index–18 (BSI-18)\(^{23}\) and Beck Depression Index–II (BDI-II)\(^{24}\) at baseline and after each intervention arm at the Clinical Outcomes Research Office at Washington University School of Medicine. Subjects also completed audiometric and neuropsychometric assessment, FDG-PET, and resting-state functional MRI scans at baseline and on completion of each intervention arm. As in the 2-week treatment study, the Neuronetics Model 2100 Therapy System investigational device (Neuronetics Inc) and sham magnet (Model 2100 CRS) was used. The stimulation site was over the left temporoparietal junction, and the full description of the process for the identification of the temporoparietal junction was already described.\(^9\) The motor threshold was determined by stimulating the left motor cortex with a dedicated motor threshold magnet to elicit a reproducible response (one-half of the time or more) in the right abductor brevis pollicis (thumb abductor).

**rTMS PROCEDURE**

Subjects received 5 stimuli (active rTMS or sham) sessions per week (1 per day) for 4 consecutive weeks. The magnet was placed over the left temporoparietal area for all subjects regardless of side of tinnitus laterality. The stimulation settings were 1 Hz at 110% of motor threshold for a total of 42.5 minutes (330 seconds per train for the first 5 trains and 350 seconds for the last train, with 90 seconds off between trains). The sham magnet is actively driven by the console power system and is identical in physical appearance to the active treatment magnet. The sham coil contains a shielding mechanism, which diverts the mag-
netic field away from the patient. The sham coil looks, acts, and sounds like the active coil and is placed against the patient’s scalp in an identical fashion as the active magnet. Because this was a double-blind study, neither the subjects nor the medical personnel in direct communication with the subjects knew which magnet was active or sham. On completion of each arm, subjects were asked to guess what intervention, active or sham, they believed they had just received to assess the success of the blinding. The study statistician and the medical monitor held the sealed envelopes assigned rank test was used to test whether the median primary efficacy parameter $\Delta THI$ was significantly different from 0. When appropriate, 95% confidence intervals were calculated around important point estimates. All sample size and power computations were based on a crossover design, intention-to-treat analysis, and 2-sided tests at the $\alpha = .05$ level of significance. Anticipated characteristics of this study design were estimated from the first study.19 The power computation using the error covariance structure estimated from the previous study indicated that the sample size of 14 will provide 80% power to detect a differential improvement of at least 15 points (ie, a 20-point change in THI score after active treatment and a 5-point change in THI score after sham) over the course of the study. Standard descriptive statistics were also used to describe regional CMRGlut. Because assumptions of parametric statistics were not met, nonparametric tests were used for further PET analyses. Wilcoxon test was used to compare CMRGlut of patients with tinnitus with age- and sex-matched normal controls. Friedman analysis of variance (ANOVA) was used to test for differences in CMRGlut of patients with tinnitus at baseline and after active and sham treatments. Bonferroni correction and Q-Q plot approach were used to adjust the $\alpha$ level for multiple comparisons and to observe whether the obtained test statistic values were due to chance alone. Finally, to assess the impact of duration of stimulation, the results from the 4-week stimulation were compared with the results from the 2-week treatment stimulation. A mixed-model repeated measures ANOVA approach was used to compare the effect of active magnet vs sham magnet after controlling for duration of stimulation and other important clinical factors. Finally, we explored the effect of time on the change in THI score by comparing the baseline THI score with the posttreatment arm 1 THI score, regardless of whether arm 1 was active or sham, and the posttreatment arm 2 THI score, regardless of the arm 2 intervention. This exploration tested the null hypothesis that change in THI score is not related to treatment duration. A mixed-model ANOVA was used to test the within-subject differences through 3 time points (baseline, posttreatment arm 1, and posttreatment arm 2) after controlling for between-subjects differences. Statistical analysis was performed using the IBM-SPSS statistical package (SPSS Inc).

**RESULTS**

A total of 225 patients were assessed for eligibility in the study (Figure 1). Of these, 34 patients consented and
were screened. Twenty patients passed the screening process and were enrolled and randomized between December 14, 2009, and February 23, 2011. Fourteen patients did not pass screening (Figure 1). At least 19 of the 20 subjects received at least 1 day of treatment, and 14 subjects completed the study according to the protocol. One subject withdrew from the study between consent and the first day of treatment. Five subjects withdrew from the study after starting treatment for the following reasons: scheduling issues (n = 1), insomnia and personal issues at home (n = 1), failure to show up for treatment (n = 1), insomnia (n = 1), and principal investigator withdrawal because of other concerns with the subject’s ability to provide ongoing informed consent (n = 1). Of the 14 subjects enrolled, 13 completed both study arms. No participant was lost to follow-up or refused to answer questions. The one subject who did not complete the second arm had a 6-week washout THI score that was greater than 20 points from his baseline THI score after arm 1 (active rTMS). As per protocol, he was considered to have completed the study because he was ineligible to continue in arm 2. Interestingly, at 7 months after active intervention, his THI score was 40 points below baseline. His follow-up postintervention THI scores were between 40 and 50 points from baseline. The subject reported that he “just doesn’t notice it [tinnitus] anymore unless it is really quiet around him.” Before treatment he described his tinnitus as always being present, impossible to ignore, and very loud.

The 14 enrolled subjects were between the ages of 22 and 59 years, with a median age of 42 years (Table 1). The majority of the subjects were white (n = 11) and male (n = 9). The median (range) BSI-18 score at baseline was 2 (0 to 10), and for BDI-II score, 2.5 (0 to 12) (clinical depression: BDI-II score ≥14). The duration of tinnitus ranged from 6 months to 30 years, with a median of 8 years, and approximately 29% of the subjects enrolled had experienced tinnitus for 16 years or more. Two subjects had tinnitus for 30 years each, 1 subject had tinnitus for 20 years, and another subject had tinnitus for 16 years. The one subject who had a dramatic response to active rTMS in arm 1 had tinnitus for 3.5 years. The subjects rated their tinnitus loudness on a 10-cm visual analog scale, and the median score was 6.5 (range, 4 to 8). Tinnitus interfered with sleep for 10 of 14 subjects (71%). A majority of the patients reported that they had to use “considerable effort” to ignore their tinnitus (n = 6 [43%]) or “could never” ignore tinnitus (n = 3 [21%]). Although tinnitus caused at least “moderate discomfort” in 8 patients, only 5 (36%) reported that they had previously sought medical help. Audiometric assessment showed that 10 subjects had some type of hearing loss (9 sensorineural and 1 mixed types). The median (range) BSI-18 and BDI-II scores at baseline were 2 (0 to 10) and 2.5 (0 to 12), respectively.

At the study start, the median (range) baseline THI score was 52 (34 to 92). The median (range) for THI scores after active and sham interventions were 47 (18 to 82) and 44 (16 to 84), respectively. The median (range) THI score at 4-week follow-up was 41 (16 to 80). For the 13 subjects who completed both treatment arms, active treatment was associated with median reduction of 10 (range, −20 to 4) points in THI score, and sham was associated with a median reduction of 6 (range, −24 to 12) points. Primary efficacy parameter ∆(∆THI) = ∆THI_{active} − ∆THI_{sham} had a median reduction of 4, and the range of response varied from a 32-point reduction for one subject to a 14-point increase for another (Figure 2). There were 3 subjects (23%) who achieved a 10-point or larger reduction. The presence of normal hearing was not associated with a significant response to rTMS treatment. There were no statistical or clinical significant changes

### Table 1. Description of Study Population at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, median (min-max), y</td>
<td>42 (22-59)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>BSI-18 and BDI-II scores at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>BDI-II score</td>
<td>2.5 (0 to 12)</td>
</tr>
<tr>
<td>BSI-18 score</td>
<td>2 (0 to 10)</td>
</tr>
<tr>
<td><strong>Type of hearing loss</strong></td>
<td></td>
</tr>
<tr>
<td>Normal hearing</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Mix</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Sensorineural</td>
<td>9 (64)</td>
</tr>
<tr>
<td><strong>Severity of hearing loss</strong></td>
<td></td>
</tr>
<tr>
<td>None (−10 to 15 dB)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Slight (16 to 25 dB)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Mild (26 to 40 dB)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Moderate (41 to 55 dB)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Moderate/severe (56 to 70 dB)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Severe (71 to 90 dB)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Configuration of audiogram</strong></td>
<td></td>
</tr>
<tr>
<td>Flat</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Down sloping</td>
<td>3 (22)</td>
</tr>
<tr>
<td>Gradually sloping</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Sharply sloping</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Precipitously sloping</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Trough</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Previous sought medical help, No. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (36)</td>
</tr>
<tr>
<td>No</td>
<td>9 (64)</td>
</tr>
</tbody>
</table>

Abbreviation: min-max, minimum-maximum.

<sup>a</sup>Loudness was rated on a 10-cm visual analog scale.
in BSI-18 or BDI-II score after active or sham treatment or at the 4-week follow-up.

There were 32 subjects with tinnitus who underwent FDG-PET at baseline, and 27 subjects met study inclusion criteria and successfully completed both arms of the study. When tested for multiple comparisons by Bonferroni correction or Q-Q plot approach, there was no evidence for significant differences in mean regional CMRGlu values for patients with tinnitus and normal controls beyond chance. The differences of CMRGlu values at baseline compared with CMRGlu values after active and sham treatments for 2 weeks and 4 weeks, respectively, as well as for all patients grouped together, were explored. Our analyses revealed that there were no statistically significant differences in CMRGlu values of PET imaging when comparing baseline, post–active treatment, and post–sham treatment assessments. In addition, there was no evidence of a significant influence of duration of treatment (4-week treatment vs 2-week treatment), type of treatment (active vs sham), or the order the treatment was received on CMRGlu values.

To assess the quality of the sham, all subjects provided their best guess as to which magnet treatment (active or sham) they believed they had just received. Of the 5 subjects who received sham as arm 1, 4 (80%) correctly guessed they had received sham. Of the 8 subjects who received sham as arm 2, 7 (88%) correctly guessed sham. Of the 9 subjects who received active rTMS as arm 1, only 3 (33%) correctly guessed active. Of the 5 subjects who received active rTMS as arm 2, 3 (60%) correctly guessed active. The subjects’ post–arm 1 and post–arm 2 guesses were correct no more than would be expected by chance alone (Fisher exact test, \( P = .22 \)).

To explore this issue of blinding in more detail, the “best guess” for subjects in the 2- and 4-week studies were combined to create a larger sample size for analysis. There were a total of 27 subjects who were treated with both active and sham magnets in the 2- and 4-week Collaborative Tinnitus Research at Washington University studies, and so there was a total of 54 “best guess” responses. Of the 54 “best guess” responses, only 21 (39%) were guesses of active treatment. From the 21 active treatment “best guess” responses, 12 (57%) were actually active treatment. Of the 33 sham treatment “best guess” responses, 18 (54%) were actually sham treatment. This “best guess” result was not different from what would be expected by chance alone, thus confirming the successful nature of the sham magnet (\( \chi^2 = 0.701; P = .40 \)).

The distribution of patient responses to the question “How bothered are you from your tinnitus?” is summarized in Table 2. The number of subjects reporting to be “extremely bothered” varied from 1 (7%) at baseline to 2 (14%) after active intervention, 1 (7%) after sham intervention, and 2 (14%) at the 4-week follow-up. “Bothered a lot” was reported by 9 subjects (64%) at baseline, 4 (29%) after active intervention, 7 (54%) after sham intervention, and 4 (29%) at the 4-week follow-up. None of these differences were significantly different.

The distribution of Patient’s Global Impression of Change after active and sham interventions is shown in Figure 3. Only 1 patient (7%) reported that his tinnitus was minimally worse after active intervention. The

![Figure 2](image-url)  
**Figure 2.** Changes in Tinnitus Handicap Inventory (THI) scores after active and sham treatments and difference between active and sham treatments. The solid bar indicates the median; shaded box boundaries are the 25th and the 75th percentiles; bars up and below the box extend to 1.5 box lengths. Horizontal dotted and dash lines represent statistical and clinical significant levels, respectively.

![Figure 3](image-url)  
**Figure 3.** Distribution of responses of patient global impression of change post active and post sham intervention.

| Table 2. Response to Treatment as a Function of Secondary Outcome Measures Represented by the Self-Reported bother Score |
|---|---|---|---|---|
| **Bother Score** | **Baseline** (n = 14) | **Post–Active Treatment** (n = 14) | **Post–Sham Treatment** (n = 13) | **4-Week Follow-up** (n = 13) |
| Not bothered | 0 | 0 | 0 | 0 |
| Bothered a little but not much | 1 (7) | 2 (14) | 3 (23) | 2 (15) |
| Bothered more than a little, but not a lot | 3 (22) | 6 (43) | 2 (15) | 5 (39) |
| Bothered a lot | 9 (64) | 4 (29) | 7 (54) | 4 (31) |
| Extremely bothered | 1 (7) | 2 (14) | 1 (8) | 2 (15) |
rest of the patients reported either no change to their tinnitus or at least minimal improvement. The majority of patients reported no change after either active (60%) or sham (50%) intervention.

There were no significant differences in subject response as defined by the primary efficacy measure between the 2- and 4-week treatment protocols (Figure 4). The mean reduction in THI score was 5 points after 2 weeks of active treatment and 10 points after 4 weeks of active treatment, for a difference of 5 points. The mean reduction in THI score after 2- and 4-weeks of sham treatment was 6 points, for a difference of zero. The difference of 5 points in THI score between 2 and 4 weeks of active and sham intervention was not significantly different from zero.

Because there was no statistically significant difference between active and sham treatments, we explored the effect of time on the change in THI scores. After controlling for whether the subject was enrolled in the first or second study, there was a statistically significant drop in THI score with time (between baseline and post–arm 1 treatment, post–arm 2 treatment, and 4-week follow-up), but these statistically significant differences did not reach the clinical significance level of 20 points. The time effect disappeared in the models with age and tinnitus duration as covariates. There was not a statistically significant difference between THI scores post–arm 1 and post–arm 2 treatments.

All subjects tolerated the rTMS interventions. There were no serious adverse effects (related or nonrelated) in the study and no unexpected related adverse events reported. The most common complaint was jaw twitch.

In the present study we found that low-frequency (1 Hz) rTMS treatment administered at 110% of motor threshold for 4 weeks to the left temporoparietal junction did not reduce tinnitus severity better than the sham. This negative finding is not different from our previous null finding among patients with tinnitus who received treatment for 2 weeks to the same location.19 Despite numerous neuroimaging studies in the published literature that describe tinnitus to be associated with hyperactivity of a variety of cortical regions,25-27 especially the auditory cortices and middle temporal regions, we were unable to detect hyperactivity at baseline nor changes after rTMS.

A recently completed Cochrane Review of rTMS for tinnitus identified 283 articles, of which 5, comprising 233 patients with tinnitus, met the inclusion criteria for the review.28 Of the 5 articles, 315,17,18 described trials using low-frequency (1 Hz) rTMS. The authors of the Cochrane Review stated that rTMS certainly seems to be a safe treatment in the short-term, although more knowledge about long-term safety is required. The authors acknowledged that the different durations of intervention and assessments of treatment response across the articles complicated the interpretation of results and ability to draw meaningful conclusions from the studies. However, the perception of tinnitus was not abolised for a single subject. In addition, there was no statistically significant difference in the number of subjects who reported a lesser response of “good improvement” between treatment and sham groups. The authors concluded that there is little high-quality evidence to support the use of low-frequency rTMS for the treatment of patients with tinnitus. They conclude by stating that more prospective, randomized, placebo-controlled, double-blind studies with large sample sizes are needed and that these studies should include uniform, validated, tinnitus-specific questionnaires and measurement scales.

Several other studies also failed to find a significant improvement in tinnitus after rTMS treatment. For instance, Plewnia et al29 used a placebo-controlled 3-arm study to examine the effects of 4 weeks of theta-burst or sham stimulation over the secondary auditory cortex or temporoparietal association cortex. The study included 48 subjects with chronic tinnitus of 5-year duration or less. None of the subjects reported a complete suppression of tinnitus. Tinnitus severity was slightly reduced from baseline in each group, including sham, but none of the differences between groups were statistically significant. The treatment was well tolerated with only minimal adverse effects of headache, worsening of tinnitus, increased sensitivity to noise, painful local sensation, and sleep disturbance.

Minami et al30 investigated the effects of a single session of low-frequency (1 Hz) rTMS to the left auditory cortex in 16 subjects with chronic tinnitus. The authors reported a significant reduction in visual analog scale scores for loudness and annoyance immediately after rTMS with gradual return over the next 7 days. Unfortunately, the failure to include a control group prohibits definitive conclusions about rTMS effectiveness from this study.

Transcranial direct current stimulation (tDCS) is another type of cortical stimulation31,32 and is distinct from rTMS. Transcranial DCS induces neuronal excitability changes in the cortex through the application of weak direct current stimulation through the intact skull. Depending on the polarity of the stimulation, tDCS can increase or decrease cortical excitability in the brain regions to which it is applied.33 Vanneste et al33 used an
open-label design to assess the effects of 20 minutes of bilateral tDCS on dorsolateral prefrontal cortex on 478 patients with tinnitus (anode right, cathode left [448 patients] and anode left, cathode right [30 patients]). They found that tDCS with right anode and left cathode reduced tinnitus perception in 30% of patients but that no tinnitus-suppressing effect was found for tDCS with left anode and right cathode. The authors concluded that the results of their study support the involvement of the prefrontal cortex in the pathophysiologic profile of tinnitus. In a follow-up article, Vanneste and De Ridder speculated that tDCS treatment response is achieved not only by directly affecting the underlying dorsolateral prefrontal cortex but also indirectly on functionally connected brain areas relevant for tinnitus distress and tinnitus intensity, such as the pregenual anterior cingulate cortex, parahippocampal area, and right primary auditory cortex areas.

There are several limitations to this study that should be considered when interpreting the results. First, the generalizability of the results is limited owing to the unique characteristics of our study population. These patients were moderately to severely bothered by their tinnitus and had no signs of active depression or anxiety. As a result, they may not necessarily reflect the typical patients who are bothered by their tinnitus. The unique nature of this study population is illustrated by the fact that fewer than 50% of the patients with tinnitus screened ultimately enrolled in the study. The duration of tinnitus was long for several subjects and, as reported by several groups, the degree of response to rTMS seems to be indirectly related to the duration of tinnitus. The one subject with the dramatic improvement after active rTMS had a tinnitus duration of 3.5 years. Therefore, a positive overall result in this study may have been achieved if the subjects were restricted to those with tinnitus of a shorter duration, for example, 1 year or less. It should be noted, however, that in the present study we did not see a differential response based on duration of tinnitus.

The 95% confidence intervals around the primary efficacy parameter [$\Delta (\Delta \text{THI})$] extended from $-9$ to $+10$ points. Therefore, the data are compatible with a true benefit of rTMS, as reflected by a decrease in THI score as great as 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.

It is unlikely that subjects were unblinded and therefore aware of which treatment they were receiving. The sham magnet looks and feels similar to the active treatment. The best guess of treatment was correct no greater than 9 points or harm of rTMS, as reflected by an increase in THI score of 10 points. Because a clinically significant change in THI score is 20 points or greater, neither of these conditions is likely to be clinically significant.
take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Piccirillo and Garcia. Acquisition of data: Piccirillo, Kallogjeri, Nicklaus, Wineland, Vlassenk, Benzing, Mathews, and Garcia. Analysis and interpretation of data: Piccirillo, Kallogjeri, Spitznagel, Vlassenk, and Benzing. Drafting of the manuscript: Piccirillo, Kallogjeri, Nicklaus, and Vlassenk. Critical revision of the manuscript for important intellectual content: Piccirillo, Kallogjeri, Nicklaus, Wineland, Spitznagel, Benzing, Mathews, and Garcia. Statistical analysis: Piccirillo, Kallogjeri, Spitznagel, and Vlassenk. Obtained funding: Piccirillo. Administrative, technical, and material support: Nicklaus, Wineland, Benzing, Mathews, and Garcia. Study supervision: Piccirillo, Nicklaus, Benzing, and Garcia.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by grant R01 DC009095 from the National Institutes of Deafness and Other Communication Disorders.

REFERENCES


