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

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Objective: To examine the effectiveness and safety of low-frequency repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal junction in a cohort of patients with bothersome tinnitus.

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

Setting: Outpatient academic medical center.

Participants: Fourteen adults aged 42 to 59 years with subjective, unilateral or bilateral, nonpulsatile tinnitus of 6 months’ duration or longer and a score of 38 or greater on the Tinnitus Handicap Inventory (THI).

Interventions: Low-frequency (1-Hz) 110% motor threshold rTMS or sham treatment to the left temporoparietal junction for 2 weeks.

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

Results: Active treatment was associated with a median (95% confidence interval) reduction in THI score of 5 (0-14) points, and sham treatment was associated with a median reduction in THI score of 6 (~2 to 12) points. The difference in THI scores between the change associated with active and sham rTMS ranged from a 34-point reduction in THI score after active treatment to a 22-point increase after sham treatment, with a median difference change of only 1 point (~6 to 4 points).

Conclusions: Daily low-frequency rTMS to the left temporoparietal junction area for 2 weeks is no more effective than placebo for patients with chronic bothersome tinnitus. Possible explanations for the negative findings are short duration of treatment, failure of rTMS stimulation over the temporoparietal area to affect the auditory cortex buried within the Sylvian fissure, or more widespread cortical network changes associated with severe bothersome tinnitus not amenable to localized rTMS effects.

Trial Registration: clinicaltrials.gov Identifier: NCT00567892

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The physiological processes responsible for subjective tinnitus remain unknown. The available evidence suggests that tinnitus is associated with disturbances in spontaneous neural activity in the auditory system. These abnormalities, as measured in animal models of tinnitus, include increased spontaneous activity (hyperactivity), changed timing of neural discharges (ie, the temporal firing properties of neurons), and increased bursting activity of neurons.

Multiple neuroimaging studies indicate that changes in auditory association areas and the primary auditory cortex are associated with tinnitus. Observations based on positron emission tomography (PET) indicate additional activation of the temporoparietal cortex located immediately posterior to auditory regions. However, it is difficult to evaluate the findings from these imaging studies because of methodological weaknesses, including the patients with tinnitus (hereinafter referred to as tinnitus patients) in each study not being matched against a nontinnitus control group with comparable hearing.

Melcher et al used sound-evoked activation of the auditory pathway of individuals with normal hearing and tinnitus lateralized to 1 ear and found abnormal functional magnetic resonance imaging (MRI) activation asymmetry in the inferior colliculi of tinnitus patients. In a subsequent report, Melcher et al selected tinnitus patients and controls matched for age, emotional state, and hearing loss and found abnormal gain within the auditory pathway. The studies by Melcher et al and Lanting et al suggest increased sound-evoked activation within the auditory midbrain of tinnitus patients.
Rauschecker et al\textsuperscript{21} proposed a model for tinnitus based on neuroimaging findings that focuses on the cortex, thalamus, and ventral striatum. In this model, the perception of tinnitus is viewed as an interaction among the limbic, auditory, and thalamic areas wherein feedback connections from limbic regions provide a noise cancellation mechanism. Llinas et al\textsuperscript{22} used magnetoencephalography in patients with tinnitus, neurogenic pain, Parkinson disease, or depression and controls; their findings described the presence of a thalamocortical dysrhythmia, whereby symptoms are a result of inhibitory asymmetry between high- and low-frequency thalamocortical modules at the cortical level. The identification of alterations in nonauditory cortical areas is consistent with the clinical observation that tinnitus does not habituate\textsuperscript{23} alters attention and memory,\textsuperscript{24-26} and can affect emotions.\textsuperscript{27-31}

Repetitive transcranial magnetic stimulation (rTMS) is a novel diagnostic and therapeutic tool for a variety of psychological and neurological conditions. Repetitive TMS temporarily produces disruptions in a circumspect area of the brain that interrupts normal functioning and has acute and chronic effects. Depending on the stimulus settings, rTMS can alter different excitatory and inhibitory circuits in the brain.\textsuperscript{32} The temporary effects can be followed by more enduring changes in neuronal excitability with low-frequency (1-Hz) stimulation inhibiting responses in a persistent fashion.\textsuperscript{33} Although the mechanisms by which rTMS reduces cortical excitability remain unclear, involvement of $\gamma$-aminobutyric acid (GABA) secretion and transmission seems plausible given the possible involvement of GABA-secreting and -transmitting interneurons in intracortical inhibition.\textsuperscript{34}

Several studies\textsuperscript{35-44} have evaluated the effect of rTMS on tinnitus. Findings from slightly more than 200 patients suggested that low-frequency (1-Hz) rTMS applied to the scalp overlying the lateral temporal cortex in the region of the primary and secondary auditory cortices reduces tinnitus severity. In their recent review of clinical results of rTMS for tinnitus, Londero and colleagues concluded that “TMS appears to be a very promising tool for the diagnosis and the treatment of tinnitus patients.”\textsuperscript{45-46} Despite the promise offered by these findings, many of the studies had various methodological weaknesses, most prominently failure to include adequate controls and valid sham treatment.

The goal of this study was to examine the effectiveness and safety of applying low-frequency rTMS in a cohort of patients with bothersome tinnitus. The target site was the temporoparietal junction (TPJ) (secondary and integrative auditory areas). We selected the TPJ because prior anatomical and PET imaging studies\textsuperscript{12} suggested TPJ involvement in tinnitus and success with rTMS applied to this area.\textsuperscript{35} We used a valid sham magnet and a crossover double-blind design treatment protocol, and we matched for hearing loss by having each patient serve as his or her own control.

METHODS

DESIGN

This was a crossover, double-blind, randomized clinical trial conducted at the outpatient facilities of a large academic medical center. Eligible patients were adults aged 18 to 60 years with subjective, unilateral or bilateral, nonpulsatile tinnitus with a duration of 6 months or longer, a score of 38 or greater on the Tinnitus Handicap Inventory (THI),\textsuperscript{46} and a score of less than 14 on the Beck Depression Inventory, Second Edition (BDI-II).\textsuperscript{47} Patients who remained eligible at the end of the screening period were randomized to receive as first treatment active or sham rTMS. The project biostatistician (E.L.S.) was responsible for generating the randomization code. Block randomization was used with blocks of 4, 6, and 8 patients; for any block, half the patients were randomly assigned to active treatment before placebo and the other half to placebo before active treatment. The research nurse coordinator (J.N.) enrolled the patients. Patients were randomized to receive active rTMS for 2 weeks and then switch to sham rTMS for 2 weeks or to start with sham rTMS for 2 weeks and then switch to active rTMS for 2 weeks. The washout period between the 2 interventions was a minimum of 2 weeks. Before starting the next intervention after the washout period, the participant’s tinnitus severity was reassessed. To ensure no carryover effect, the washout period was extended for patients whose tinnitus severity, as defined by the THI, was more than 20 points different from their baseline THI score.

MEASUREMENTS

All patients completed the following Oregon Hearing Research Center forms at enrollment: Tinnitus Description and History, Medical and Health Information, and Hearing History and Occupational Exposure (available at http://www.tinnitusarchive.org/forms). Patients also completed the 18-item Brief Symptom Inventory,\textsuperscript{48} BDI-II,\textsuperscript{49} and Mini-Mental State Examination (30-item version).\textsuperscript{49} Neurocognitive assessment included the California Verbal Learning Test,\textsuperscript{50} Controlled Oral Word Association Test,\textsuperscript{51} Semantic Association Test,\textsuperscript{52} Trailmaking Tests A and B,\textsuperscript{53} Grooved Pegboard Test,\textsuperscript{54} and Digit Symbol Substitution Task.\textsuperscript{55} All patients underwent audiometric and neurocognitive assessment, PET, and MRI on completion of each intervention arm. The hearing level was tested at the 500-, 1000-, 2000-, and 3000-Hz frequencies.

rTMS PROCEDURE

A therapy system investigational device (Neuronetics Model 2100; Neuronetics, Inc, Malvern, Pennsylvania) and a commercially available patient chair (Ghaniemi GmbH, Moers, Germany) were used in this study. Three separate magnetic coils (2 active and 1 sham) similar in weight, external appearance, and acoustic properties when actively pulsed were used. One active coil was identified for investigational purposes and used as the coil to determine motor thresholds. The sham coil (Neuronetics Model 2100 CRS; Neuronetics, Inc) is created when an active coil is modified by internally interposing an aluminum plate between the magnet pole faces and the external surface that touches the patient’s head. The aluminum acts to redirect the magnetic flux away from the patient and back into the coil assembly. In addition, the sham coil is driven at a fixed level of 45% of the stimulator output, which acoustically matches the sound created when driving an active coil at an average treatment setting. The resulting magnetic field in the center of the stimulation volume (ie, 2 cm from the scalp surface into the cortex) is reduced to less than 10% of that produced by an active coil driven at 100% stimulator output, which is well below levels required for cortical neuron stimulation. The sham coil is designed to be identical in appearance and external design to the active treatment coil, with the only distinguishing visible characteristic a label identifying it as an A-, B-, or C-type coil. The resulting sound and percussive effect are virtually indistinguishable to the patient or operator.
The patient chair can be adjusted to allow for various patient positions, from sitting to lying supine. The chair has a removable head support system that allows for additional patient comfort. The custom boom-arm system attaches to a wheeled cart, on top of which sits the power-delivery console. The arm and its coil-holding attachment are custom designed to allow positioning of the coil over the temporoparietal cortex region. Without the arm, the rTMS machine is limited in motion and does not allow enough axial rotation to enable treatment to be administered to the temporoparietal cortex region of the brain. The system was designed especially for this clinical trial. The motor threshold was determined by stimulating the motor cortex with a dedicated motor threshold magnet to elicit a reproducible response (half of the time or more) in the right abductor pollicis brevis (thumb abductor).

The stimulation site was over the left TPJ regardless of the side of tinnitus laterality or the baseline PET results. The magnet placement for the first 5 patients was determined using surface electroencephalographic coordinates, a location midway between C3 and T5 based on the international 10-20 system of electroencephalographic electrode placement. For the remaining 9 patients, the TPJ was identified by one of us (M.M.) using imaging software (Analyze; Biomedical Imaging Resource, Mayo Clinic, Rochester, Minnesota) from the structural MRI (Figure 1). The coordinates of the TPJ were then determined by the software program using a standard coordinate system. A surface image of the face was created using the volume render feature of the software. The location of the stimulation site in relation to the surface of the scalp was then determined by the software. The angle measure feature was used to describe the angle created by the junction of a line from the surface landmark for the stimulation site to the center of the external auditory canal and a second line from the lateral canthus of the left eye to the center of the external auditory canal. The length (in millimeters) of these lines was determined by a trained neuroimaging research coordinator and used to calculate the height and the length of the placement template. The placement of the magnet was at the top corner of the template representing the stimulation site.

Patients received 5 stimulus (active or sham rTMS) sessions per week (1 per day) for 2 weeks. The stimulation settings were 1 Hz at 110% of motor threshold for a total of 42.5 minutes (330 s/train for the first 5 trains, with the last train of 350 seconds and with 90 seconds between trains). The volume of stimulated cortex is determined by coil position and drive level. When the coil is placed firmly against the scalp at a drive level of 120% of the average motor threshold, the cross-sectional area of the stimulation volume at a depth of 2 cm from the scalp surface into the cortex is approximately $3 \times 6 \text{ cm}^2$.

All patients and research personnel were blinded to magnet status (active vs sham). To assess the success of blinding, patients were asked after completion of each intervention arm to guess which magnet, active or sham, they believe they had just received.

Figure 1. Sagittal magnetic resonance imaging views with a marker overlying the left temporoparietal junction.
Descriptive statistics were used to describe the study population. Standard error of the mean was used to ensure data accuracy (SPSS, Inc, Chicago, Illinois). Standardized scores on the Brief Symptom Inventory and BDI-II were used to assess efficacy in the intervention and control arms. A Wilcoxon signed-rank test with a Bonferroni correction was used to determine statistical significance. The null hypothesis was that active tMS is no more effective than sham tMS in the treatment of tinnitus. The primary efficacy measure was defined as the change in THI score after active tMS and Sham tMS: 

\[ \Delta THI_{active} = THI_{active\ before} - THI_{active\ after} \]

as the change in THI score after active tMS, 

\[ \Delta THI_{sham} = THI_{sham\ before} - THI_{sham\ after} \]

as the change in THI score after sham tMS, and 

\[ \Delta (\Delta THI) = \Delta THI_{active} - \Delta THI_{sham} \]

as the primary efficacy variable.

To assess whether the observed difference in the change in THI score was statistically significant, we used a Wilcoxon signed rank test with a P value adjusted for the number of comparisons. Statistical significance was defined as P ≤ 0.05. Clinical significance was defined as a change in the THI score of 20 points or greater.

The secondary efficacy measures included the Patient Global Impression of Change assessment performed at the end of each intervention arm. In addition, patients were asked whether they would continue treatment and whether they would recommend this treatment to a friend. Finally, the changes in the 18-item Brief Symptom Inventory and BDI-II scores after each intervention arm were assessed.

The data were captured on paper-based forms and transferred to a specially created data set using double data entry to ensure data accuracy (SPSS, Inc, Chicago, Illinois). Standard descriptive statistics were used to describe the study population and outcomes of interest. Where appropriate, 95% confidence intervals (CIs) were calculated.

All sample size and power computations were based on a crossover design and 2-sided tests at the significance level of \( \alpha = 0.05 \). Anticipated characteristics of this population and study design, including standard deviation in the change in THI score, were estimated from data of 115 patients enrolled in the randomized placebo-controlled clinical trial of gabapentin conducted previously at Washington University. Because we desired to reject the null hypothesis and to obtain convincing confidence bounds for the size of the true effect, we computed an expected confidence interval length based on a proposed sample size of 50. The confidence interval, based on a sample size of 50, is expected to be of the form \( \Delta (\Delta THI) \pm 4.8 \). Even allowing for natural variation in the point estimate of the effect, this interval will be well bounded away from the null value of 0.

**RESULTS**

**PATIENT CHARACTERISTICS**

Potential patients were identified through the Washington University School of Medicine Research Participant Registry in response to an online Web site (https://tinnitus.wustl.edu). Of the 285 people interested in participating in the study, 22 passed the initial telephone screening process and consented to participate. The flow of patients through the study is shown in Figure 2. Of the 22 patients who underwent screening, 14 of them passed the screening process and were enrolled and randomized from August 1, 2008, through July 30, 2009. All 14 patients completed both arms of treatment and the 4-week follow-up assessment. Only 1 participant missed 1 day of treatment owing to an unrelated household accident. No participant was unavailable for follow-up or refused to answer questions. Of the 8 who failed screening, 5 had scores on the BDI-II of 14 or greater, which is suggestive of depression. A motor threshold could not be elicited for 1 patient, 1 patient became claustrophobic in the MRI device, and 1 patient changed his mind midpoint in screening and chose not to continue with the screening process.

The 14 enrolled patients are described in Table 1. The patients (median [SD] age, 52 [5.1] years; 4 women) had tinnitus for at least 6 months (median [SD], 7.0 [5.1] years; range, 0.5-17.9 years) with an average loudness of 7.5 (1.2) on a visual analog scale ranging from 1 to 10. Tinnitus interfered with sleep for 13 of 14 patients. Tinnitus was bilateral in 9 and unilateral in 5 patients (right-sided in 3 and left-sided in 2). None had hyperacusis. Mean (SD) pure-tone thresholds (PTTs) and speech reception thresholds (SRTs) were binaurally similar (right-sided PTT: 23.5 [22] dB [range, 0-70 dB]; left-sided PTT: 17.9 [14.9] dB [range, 0-75 dB]; right-sided SRT: 18.2 [19.9] dB [range, 0-80 dB]; left-sided SRT: 12.4 [8.5] dB [range, 0-25 dB]). The audiometric examination of the 14 patients showed normal hearing in 4 (29%) and hearing loss in 10 (71%). The hearing loss was slight in 5 patients (36%), moderate in 3 (21%), and severe in 2 (14%). Patients were excluded who had clinical depression (a score of ≥14 on the BDI-II) or other psychiatric or neurological disorders.
The primary efficacy variable was the THI score, which measures the impact of tinnitus on various aspects of a patient's life. THI scores before active treatment were equal to the baseline THI score for the patients who were randomized to receive active treatment first and were equal to the THI score after the washout period when the sham treatment was the second arm of treatment.

The distribution of change in THI scores after active and sham treatment is shown in Figure 3. The active treatment reduced the THI score with a median (95% CI) reduction of 6 (−2 to 12) points. The change in THI score after sham treatment had a median (95% CI) reduction of 4 (−14 to 10) points. The primary efficacy variable ranged from a 34-point reduction (median (95% CI) of 5 (0-14) points. The change in THI score after sham treatment (ΔTHIsham) had a median (95% CI) reduction in THI score of 6 (−2 to 12) points.

Secondary efficacy variables included the overall response to treatment assessed at the end of each treatment arm. A poor response to active treatment was reported by 12 patients (86%) compared with 11 (79%) at the end of sham treatment (Figure 4). The number of patients who reported fair outcomes was the same (2 patients [14%]) after active and sham treatments. A good response was reported by only 1 patient (7%) after sham treatment.

The distribution of scores on the various self-assessment instruments is shown in Table 2. The median (95% CI) baseline THI score was 51 (40-70). The median (95% CI) THI score after active and sham treatments were 43 (28-66) and 47 (30-62), respectively. The median (95% CI) THI score at 4-week follow-up was 45 (34-66).
The patients’ median (95% CI) Body Symptom Index score was 3.0 (2-5) at baseline, 1.5 (0-4) after active treatment, and 1.5 (0-5) after sham treatment. The median (95% CI) BDI-II score at baseline was 5 (1-8) and dropped to 1.5 (1-5) after active treatment and 2.0 (0-5) after sham treatment. None of these differences were statistically significant.

At baseline, after each intervention, and at 4-week follow-up, all patients were asked the following question: “All persons have their own unique problems and attach different importance to these problems. Please indicate the overall amount of disturbance or ‘bother’ that you experience in your life as a result of your tinnitus.”

As is shown in Figure 5, the number of patients reporting to be extremely bothered varied from 2 (14%) at baseline to a maximum of 3 (21%) after the active treatment arm, to only 1 (7%) after sham treatment and 4-week follow-up assessment. Seven patients (50%) reported being bothered a lot at baseline, 6 (43%) after active treatment, and 7 (50%) after sham treatment. When asked if they would recommend this treatment to a friend, 4 (29%) responded definitely yes; 6 (43%), maybe yes; 3 (21%), unsure; and only 1 (7%), maybe no.

To assess the quality of the sham treatment, patients were asked at the end of arms 1 and 2 for their best guess of which treatment, active or sham, they believed they received. All but 1 of the patients (93%) guessed that they received sham treatment during arm 1. When the same question was asked at the end of study (end of arm 2), 3 of them changed their guess from sham treatment in the first arm to active treatment in the first arm and sham treatment in the second. When the patients’ guess at the end of study was compared with the actual treatment received, only 50% of the patients guessed the correct arm to which they had been randomized. This result was not different from what would be expected by chance alone, thus confirming the successful nature of the sham magnet.

There were no serious adverse events reported in this study (Table 3). The most common adverse events included jaw twitch (mild in 5 and moderate in 1) and neck or shoulder tightness or twitch (mild in 4 and severe in 1). The number of adverse events reported was greater during the active treatment (11 events) compared with sham treatment (8 events), but this difference was not statistically significant ($P = .42$).

The primary goal of this study was to examine the effectiveness and safety of applying low-frequency rTMS in a cohort of patients with bothersome tinnitus. The target site was the TPJ. In this study, we found that 2 weeks of low-frequency rTMS to the left temporoparietal cortex was no more effective than placebo for the treatment of chronic bothersome tinnitus. Because response to rTMS treatment was so poor, the trial biostatistician (E.L.S.) recommended early termination of the trial and that no additional patients be recruited. All patients tolerated active and sham rTMS without significant complaints, and there were no dropouts or withdrawals.
These results are at odds with prior reports in the published literature and may reflect differences in treatment site and duration of stimulation, efficacy of sham treatment, and patient selection. All prior studies reporting positive results in the treatment of tinnitus with rTMS and targeted auditory cortex lacked adequate controls or did not guard against placebo effects. Unlike these prior studies, we used a crossover double-blind protocol with active and sham treatments, which enabled within-patient controls. In particular, we used a sham magnet that looked, felt, and sounded like the active magnet. Posttreatment reports indicated no probable placebo effects because patients were unable to reliably discern any differences between active and sham treatments. In addition, the procedures used to align the magnet position for different patients and across sessions were not clearly described in prior studies, making reproduction of their results nearly impossible. The template used in the present study had great accuracy for magnet placement across patients and sessions. The template was created by an experienced radiology technician under the direction of one of the authors (M.M.). Given the size of the stimulation field, we are confident that the temporal-roparietal junction area was stimulated. However, lack of response to rTMS stimulation may be because the auditory cortex is buried deep within the Sylvian fissure and beyond the penetrating reach of the magnet.

It is possible that the duration of treatment used in this protocol was too short and that longer duration of treatment is needed. Previous clinical studies in depression suggest that longer stimulation is more effective than shorter duration. To address this issue, our current protocol extends treatment to 4 weeks of active and sham rTMS. Another possibility is that our patients were too severely bothered to obtain relief from rTMS alone. A THI score of 38 or greater represents the 75th percentile of bother. Furthermore, our results are not generalizable to most tinnitus patients because we had to screen 285 people to obtain 22 who were severely bothered (THI score ≥38) but not depressed (BDI-II <14). In addition, rTMS localized to a single site may not be effective for tinnitus because the neurocognitive symptoms reflect more widespread alterations in cortical networks. Consequently, treatments suited for localized brain areas might not effect a sufficient alteration in synaptic circuits involved in a broad-based network. Finally, because the THI has only 3 response categories (yes, no, and sometimes), real changes in tinnitus may not have been detected. Although we might have missed a true effect, we do not believe it was a likely explanation for our results because we also failed to detect a significant impact of treatment based on our secondary outcomes.

We believe that rTMS is a very promising tool for the treatment of tinnitus, but more basic, clinical, and translational research is needed to identify the correct treatment settings. Future studies may significantly benefit from bringing emerging imaging techniques and stimulation protocols together to determine the most optimal site for targeting rTMS stimulation. Finally, administration of neuropsychological assessments may be a profitable avenue of investigation into the attentional factors that may be interfering with severely bothered patients' ability to habituate to their tinnitus in the manner that other tinnitus patients achieve.

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