

Original Investigation

Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus

A Randomized Clinical Trial

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IMPORTANCE Chronic tinnitus negatively affects the quality of life for millions of people. This clinical trial assesses a potential treatment for tinnitus.

OBJECTIVES To determine if repetitive transcranial magnetic stimulation (rTMS) can reduce the perception or severity of tinnitus and to test the hypothesis that rTMS will result in a statistically significantly greater percentage of responders to treatment in an active rTMS group compared with a placebo rTMS group.

DESIGN, SETTING, AND PARTICIPANTS A randomized, participant and clinician or observer-blinded, placebo-controlled clinical trial of rTMS involving individuals who experience chronic tinnitus. Follow-up assessments were conducted at 1, 2, 4, 13, and 26 weeks after the last treatment session. The trial was conducted between April 2011 and December 2014 at Portland Veterans Affairs Medical Center among 348 individuals with chronic tinnitus who were initially screened for participation. Of those, 92 provided informed consent and underwent more detailed assessments. Seventy individuals met criteria for inclusion and were randomized to receive active or placebo rTMS. Sixty-four participants (51 men and 13 women, with a mean [SD] age of 60.6 [8.9] years) were included in the data analyses. No participants withdrew because of adverse effects of rTMS.

INTERVENTIONS Participants received 2000 pulses per session of active or placebo rTMS at a rate of 1-Hz rTMS daily on 10 consecutive workdays.

MAIN OUTCOMES AND MEASURES The Tinnitus Functional Index (TFI) was the main study outcome. Our hypothesis was tested by comparing baseline and posttreatment TFIs for each participant and group.

RESULTS Overall, 18 of 32 participants (56%) in the active rTMS group and 7 of 32 participants (22%) in the placebo rTMS group were responders to rTMS treatment. The difference in the percentage of responders to treatment in each group was statistically significant ($\chi^2 = 7.94, P < .005$).

CONCLUSIONS AND RELEVANCE Application of 1-Hz rTMS daily for 10 consecutive workdays resulted in a statistically significantly greater percentage of responders to treatment in the active rTMS group compared with the placebo rTMS group. Improvements in tinnitus severity experienced by responders were sustained during the 26-week follow-up period. Before this procedure can be implemented clinically, larger studies should be conducted to refine treatment protocols.

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Tinnitus (the perception of ringing or other phantom sounds in the ears or head) is perceived by 10% to 15% of the adult population.¹ Of those individuals who experience chronic tinnitus, approximately 20% consider it to be a “clinically significant” problem.² Because chronic tinnitus is a condition that negatively affects the quality of life for millions of people worldwide,^{3–11} a safe and effective treatment for tinnitus has been sought for decades.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive intervention that involves delivering electromagnetic pulses through a coil to the patient’s scalp. Ultimately, some of this energy is transmitted through the skull and affects the activity of underlying neural tissue (Theodoroff and Folmer¹² provide a history and overview of TMS). Low-frequency repetitive TMS (rTMS) (eg, 1 Hz) is known to reduce neural activity in directly stimulated brain regions^{13,14} and in structurally connected remote brain regions.¹⁵ For these reasons, low-frequency rTMS has been proposed as an innovative treatment strategy for pathologic conditions associated with increased cortical activity, including tinnitus.¹⁶

Mechanisms of Tinnitus

Several functional imaging studies^{17–20} have shown that individuals who experience tinnitus have increased activity in the auditory cortex compared with control subjects, even in the absence of external auditory stimuli. Other studies^{21–23} demonstrated that nonauditory brain regions might also contribute to the perception or severity of tinnitus. Because the neural mechanisms of tinnitus make the condition a good candidate for suppression by rTMS, this procedure has been investigated as a potential treatment for chronic tinnitus by several different groups of researchers around the world (Theodoroff and Folmer¹² provide a review).

Although rTMS has the potential to be an effective treatment method for tinnitus and recent evidence demonstrated improved effectiveness of the protocols,¹² several procedural issues and concerns remain. These include small sample sizes, lack of adequate placebo controls, inadequate blinding of study participants and research personnel, variability because of diverse outcome measures, and laterality of coil placement relative to patients’ perception of tinnitus (left side, right side, in the middle, or at the back of the head).

The clinical trial described herein addressed some of these issues by including a state-of-the-art placebo and control condition, participant and clinician blinding, improved participant evaluation methods, and outcome measures that include long-term follow-up. The hypotheses for this study were the following: (1) application of rTMS daily for 10 consecutive workdays will result in a statistically significantly greater percentage of responders to treatment in an active rTMS group compared with a placebo rTMS group, (2) the effectiveness of rTMS will be significantly greater when stimulation is delivered to the side of the participants’ head ipsilateral to the side where their perception of tinnitus is loudest compared with stimulation delivered to the side of the head contralateral to maximal tinnitus perception, and (3) improvements in tinnitus severity experienced by re-

sponders will be sustained during the follow-up period, and nonresponders will not experience significant changes in tinnitus severity during the follow-up period.

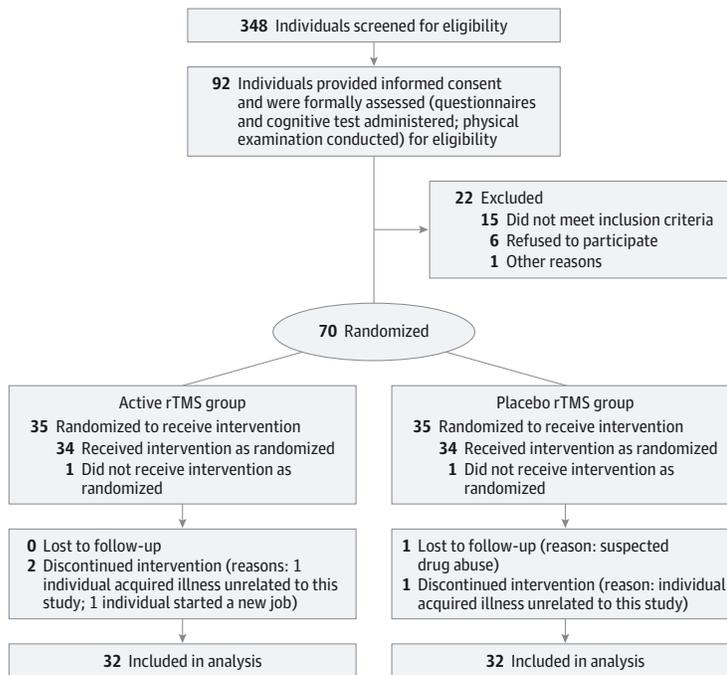
Methods

All procedures for recruitment, informed consent, and conduct of the study adhered to the requirements of the Institutional Review Board at Portland Veterans Affairs Medical Center, where the study was conducted between April 2011 and December 2014. This study was a prospective, randomized, participant and clinician or observer-blinded, placebo-controlled, parallel-group clinical trial of rTMS involving individuals who experience chronic tinnitus. The study protocol can be found in the trial protocol in [Supplement 1](#). Sixty-four eligible participants (51 men and 13 women, with a mean [SD] age of 60.6 [8.9] years) were randomized to receive active rTMS treatment or placebo rTMS treatment to the left or right temporal region of their head. Participants received 2000 pulses per session of active or placebo rTMS at a rate of 1-Hz rTMS daily on 10 consecutive workdays. Outcomes were measured before the start of treatment and immediately after the last (10th) TMS session. Follow-up evaluations were conducted at 1, 2, 4, 13, and 26 weeks after the last treatment session.

At the initial appointment, a research team member (S.M.T., L.C., or J.V.) obtained written informed consent from participants and administered the Mini-Mental State Examination.²⁴ A Mini-Mental State Examination score of at least 24 was required for participation in the study to identify and exclude individuals with dementia or other forms of cognitive impairment. A research team member also administered baseline assessments, including the following: Tinnitus History Questionnaire, Hearing History Questionnaire, Medical History Questionnaire, visual numerical scale (VNS) for self-rated tinnitus loudness (range, 0–10), Tinnitus Functional Index (TFI),²⁵ Tinnitus Handicap Inventory (THI),²⁶ Beck Depression Inventory II,²⁷ and State-Trait Anxiety Inventory.²⁸ The primary outcome measure was the TFI, and all other measures were secondary outcomes.

Half of the participants were randomized to the active rTMS group, and the other half of the participants were randomized to the placebo rTMS group. All participants were treated daily with active or placebo rTMS over a period of 2 weeks. Repetitive TMS was administered according to safety guidelines established by Wassermann²⁹ and by Rossi et al.³⁰ Transcranial magnetic stimulators (Magstim Rapid2; Magstim Company Ltd) and active and placebo TMS coils (Magstim Air Film; Magstim Company Ltd) were used in this study. The placebo coil was identical in appearance to the active coil and produced sounds and scalp sensations that were similar to those produced by the active coil. The manufacturer (Magstim Company Ltd) asserts that the placebo coil contains a metal plate that blocks much of the magnetic field it generates from affecting neural activity. Participants were randomized to 1 of 2 parallel groups with the following stimulation parameters: 1-Hz rTMS, stimulation intensity of 110% or lower related to the individual resting motor threshold, with the figure-of-eight coil positioned over the auditory cortex (the TMS target location

Figure 1. Consolidated Standards of Reporting Trials Participant Flow Diagram



Shown are the numbers of participants screened for eligibility, excluded, and included in the data analyses for this study. rTMS indicates repetitive transcranial magnetic stimulation.

Table 1. Characteristics of Study Participants

Characteristic	Active rTMS Group (n = 32)	Placebo rTMS Group (n = 32)	P Value for Between-Group Comparison
Men, No.	25	26	.89
Age, mean (SD), y	58.3 (9.5)	62.8 (8.3)	.06
Duration of tinnitus, No.			
1-2 y	4	2	.41
3-5 y	6	3	.32
6-10 y	5	3	.48
11-20 y	9	4	.17
>20 y	8	20	.02
Baseline Tinnitus Functional Index, mean (SD)	44.8 (19.4)	40.6 (22.2)	.42
Baseline visual numerical scale tinnitus loudness, mean (SD)	7.0 (1.4)	7.4 (1.2)	.22
Baseline Tinnitus Handicap Inventory score, mean (SD)	32.1 (21.2)	29.0 (20.1)	.55
Baseline Beck Depression Inventory II score, mean (SD)	6.8 (8.2)	5.4 (6.8)	.46
Baseline State Anxiety Inventory score, mean (SD)	31.8 (9.7)	29.1 (8.1)	.23
Tinnitus loudness match on the loudest side for a 1-kHz pure tone, mean (SD), dB sensation level	23.7 (12.9)	23.4 (13.5)	.93
Minimal masking level, mean (SD), dB sensation level	41.1 (19.8)	33.8 (16.8)	.12
Resting motor threshold, mean (SD), %	59.6 (4.6)	61.7 (5.1)	.09
TMS intensity, mean (SD), %	56.9 (3.9)	60.8 (7.7)	.002

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

specified by Langguth et al³¹). For additional details about the study procedures, see the eMethods in Supplement 2.

of randomized participants in each tinnitus laterality group were 30% (21 of 70) right-side dominant, 34% (24 of 70) left-side dominant, and 36% (25 of 70) central.

Results

The Consolidated Standards of Reporting Trials participant flow diagram for this study is shown in Figure 1. The proportions

Participant Characteristics

Table 1 lists characteristics of 32 participants who received active 1-Hz rTMS and 32 participants who received placebo 1-Hz rTMS. Comparing baseline characteristics of the active

Table 2. Change in Tinnitus Functional Index (TFI) From Baseline for Both Study Groups

Time	Change at Time After the Last Treatment Session, Mean (SD)						P Value for Between-Group Comparison
	Placebo rTMS Group ^a	P Value	Effect Size	Active rTMS Group ^b	P Value	Effect Size	
Immediately after	-1.8 (10.5)	0.34	0.17	-5.2 (11.8)	0.02	0.44	0.23
1 wk	-2.8 (13.4)	0.25	0.21	-9.8 (11.9)	<.001	0.82	0.03
2 wk	-4.3 (11.0)	0.04	0.39	-10.8 (12.5)	<.001	0.86	0.03
4 wk	-4.8 (12.0)	0.03	0.40	-8.5 (12.4)	<.001	0.68	0.24
13 wk	-5.0 (12.7)	0.04	0.39	-10.6 (16.3)	<.001	0.65	0.11
26 wk	-2.9 (15.8)	0.31	0.18	-13.8 (15.2)	<.001	0.92	0.007

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

^a The mean (SD) baseline TFI was 40.6 (22.2).

^b The mean (SD) baseline TFI was 44.8 (19.4).

and placebo groups, the only statistically significant differences were duration of tinnitus and TMS intensity.

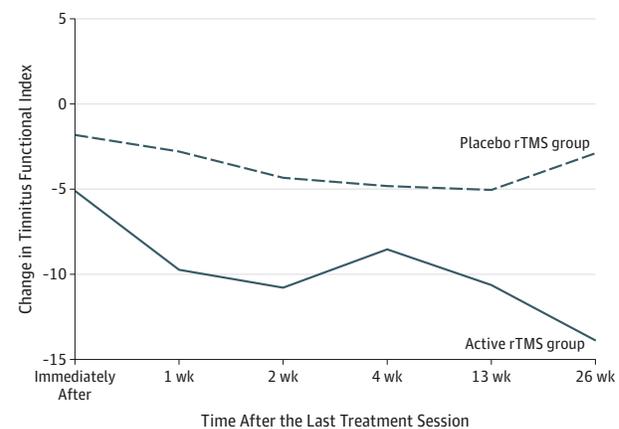
Primary Outcome Measure

Figure 2 and Table 2 summarize the change from baseline in the TFI for both study groups at all posttreatment assessment time points. The active rTMS group exhibited statistically significant reductions in TFIs at all posttreatment assessments, with the greatest improvement at 26 weeks after their last TMS session. The placebo rTMS group exhibited statistically significant reductions in TFIs at 2 weeks (4.3-point decrease), 4 weeks (4.8-point decrease), and 13 weeks (5.0-point decrease) after treatment. However, these improvements were not sustained by the placebo rTMS group at the 26-week assessment (2.9-point decrease). While the active rTMS group as a whole exhibited a 30.8% reduction in the TFI at the 26-week follow-up assessment compared with baseline, the placebo rTMS group as a whole exhibited only a 7.1% reduction in the TFI at the 26-week follow-up assessment compared with baseline.

Responders to rTMS were participants who improved more than 7 points on the total TFI from baseline to the end of their last TMS session. Using this criterion, 18 of 32 participants (56%) in the active rTMS group and 7 of 32 participants (22%) in the placebo rTMS group were responders to TMS treatment. The difference in the percentage of responders to treatment in each group was statistically significant ($\chi^2 = 7.94, P < .005$). Table 3 lists the percentage of responders in each treatment group at each post-rTMS assessment. The authors of the TFI (Meikle et al²⁵) proposed that clinically significant improvement in tinnitus severity would require a reduction in the TFI of 24% or more. In the present study, responders to TMS exhibited post-treatment reductions in TFIs of 24% or more immediately following the last (10th) rTMS session and at all follow-up assessments (eTables 1, 2, 3, and 4 in the eResults in Supplement 2).

The TFI effect sizes ranged from 1.2 to 1.9 for responders in the active rTMS group at different follow-up time points, indicating that rTMS facilitated clinically significant improvement in tinnitus severity that persisted for at least 6 months. Baseline TFIs ranged from 10 to 82 for the active rTMS group and from 6 to 92 for the placebo rTMS group. This wide range of baseline TFIs contributed to the variable responsiveness to

Figure 2. Change in Tinnitus Functional Index



Shown is the change from baseline for the repetitive transcranial magnetic stimulation (rTMS) groups at all posttreatment assessment time points among 64 participants (32 in the active rTMS group and 32 in the placebo rTMS group).

rTMS exhibited by participants in this study. The mean (SD) TFI at baseline for 25 responders (18 who received active rTMS and 7 who received placebo rTMS) was 52.4 (19.6), while the mean (SD) TFI at baseline for 39 nonresponders (14 who received active rTMS and 25 who received placebo rTMS) was 36.5 (19.8). All 11 participants in the active rTMS group who scored 50 or higher on baseline TFI assessment exhibited statistically significant improvement after rTMS treatment, but only 4 of 11 participants in the placebo rTMS group who scored 50 or higher on baseline TFI assessment exhibited statistically significant improvement after rTMS treatment.

Secondary Outcome Measures and Other Findings

Additional information and data are available in the eResults in Supplement 2. These data include the following: secondary outcome measures (eTables 5, 6, 7, 8, 9, and 10 in the eResults in Supplement 2), laterality of tinnitus perception vs laterality of rTMS for responders and nonresponders (eTable 11 in the eResults in Supplement 2), duration of tinnitus perception for responders and nonresponders, effectiveness of the TMS placebo coil (eTable 12 in the eResults in Supplement 2),

Table 3. Percentage of Responders to Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment (Based on Decrease of >7 Tinnitus Functional Index Points Compared With Baseline)

Time	Responders at Time After the Last Treatment Session		
	Placebo rTMS Group, %	Active rTMS Group, %	P Value for Between-Group Comparison
Immediately after	22	56	0.005
1 wk	31	50	0.13
2 wk	41	66	0.05
4 wk	41	59	0.13
13 wk	38	59	0.08
26 wk	38	66	0.02

other effects of TMS, clinical trial dropouts and missing data, and 10 individuals in the placebo rTMS group who returned to receive active rTMS.

Discussion

Results from this clinical trial indicate that rTMS might be an effective and viable treatment option for some patients who experience chronic tinnitus. Several other studies^{12,32,33} have also reached this conclusion, but some of these studies^{31,34-36} involved fewer participants and other studies³⁶⁻³⁹ did not include a placebo (control) condition. In the present study, hypothesis 1 was supported: application of rTMS daily for 10 consecutive workdays resulted in a statistically significantly greater percentage of responders to treatment in the active rTMS group (56% [18 of 32]) compared with the placebo rTMS group (22% [7 of 32]). However, hypothesis 2 was not supported by study data: the effectiveness of rTMS was not significantly greater when stimulation was delivered to the side of the participants' head ipsilateral to the side where their perception of tinnitus is loudest compared with stimulation delivered to the side of the head contralateral to maximal tinnitus perception. Data from additional participants will be necessary to definitively address the issue of the side of rTMS stimulation vs laterality of tinnitus perception. Finally, hypothesis 3 was supported in the present study: improvements in tinnitus severity experienced by responders were sustained during the follow-up period. The group of nonresponders experienced no significant changes in tinnitus severity during the follow-up period. Although the primary outcome measure of this clinical trial (the TFI) exhibited significant changes for many participants following TMS treatment, the VNS for tinnitus loudness and other secondary outcome measures were less responsive or sensitive to treatment-related change.

Factors That Contribute to the Effectiveness of 1-Hz rTMS for Tinnitus Treatment

The most obvious characteristic that contributed to study participants' being responders to rTMS was their TFI at baseline. The mean (SD) TFI at baseline for 25 responders (18 who received active rTMS and 7 who received placebo rTMS) was 52.4 (19.6), while the mean (SD) TFI at baseline for 39 nonre-

sponders (14 who received active rTMS and 26 who received placebo rTMS) was 36.5 (19.8). One could argue that individuals with higher TFIs are more susceptible to the placebo effects of a novel and somewhat exotic treatment such as TMS. However, individuals with high TFIs (and tinnitus severity) experience the greatest negative effect of tinnitus and therefore have the greatest need for clinical help and care. The fact that many participants in this study with high TFIs exhibited significant and sustained reductions in tinnitus severity after undergoing 10 sessions of TMS provides compelling evidence for the efficacy of this treatment. Given these findings, it is likely that baseline TFIs are among the factors that could be used to identify patients with tinnitus who are most likely to respond favorably to TMS treatment.

It was somewhat surprising that most of the other outcome measures in this study did not change significantly following rTMS treatment. For example, compared with the TFIs (which consist of ratings on 25 different scales ranging from 0 to 10), the VNS scores listed in eTable 5 in the eResults in Supplement 2 demonstrate the limitations of a single scale for detecting change following tinnitus treatment. Meikle et al stated: "Effect sizes for the TFI were generally larger than those obtained for the VAS [visual analog scale]."^{25(p153)} They continued: "The TFI should be useful in both clinical and research settings because of its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity."^{25(p153)} Results from our clinical trial support these assertions regarding the usefulness of the TFI for tinnitus assessment and the limited responsiveness of a single VNS or visual analog scale, such as our VNS for self-rated tinnitus loudness.

In their systematic review of tinnitus outcome measures, Kamalski et al⁴⁰ evaluated 6 different questionnaires (the THI, Tinnitus Questionnaire, Tinnitus Reaction Questionnaire, Tinnitus Severity Index, Tinnitus Handicap Questionnaire, and Tinnitus Severity Questionnaire) that have been used to assess health-related quality of life in published studies. The authors concluded that all these instruments "were validated only for discriminative use"^{40(p183)} and that none of them have been "validated for evaluative purposes, which is necessary to be useful in clinical trials."^{40(p183)} Therefore, these questionnaires may not adequately measure the effectiveness of intervention therapies for tinnitus.

In 2014, the American Academy of Otolaryngology published clinical practice guidelines for tinnitus.⁴¹ Statement 13 of the report recommended the following: "Clinicians should not recommend TMS for the treatment of patients with persistent, bothersome tinnitus."^{41(p530)} The report cited 2 articles by Piccirillo and colleagues^{42,43} and other studies as evidence against the efficacy of rTMS for the treatment of tinnitus. Unfortunately, these cited studies used the THI or Tinnitus Questionnaire as outcome measures, which as stated in the previous paragraph may not adequately or sufficiently assess the effectiveness of rTMS for tinnitus. Certainly, selection of the most appropriate outcome measure is key for any clinical trial.

Perhaps the decision by Piccirillo and colleagues^{42,43} to use the THI as the main outcome measure for their 2011 and 2013 studies of 1-Hz rTMS for tinnitus contributed to their findings

that active rTMS was not more effective than placebo rTMS. In addition to different outcome measures, several other factors might also help to explain the disparate results obtained in the present study compared with those reported by Piccirillo and colleagues, including scalp target for TMS, sample size, and their use of a crossover design. These issues have been discussed previously.⁴⁴ The intensity of rTMS also contributes to the effectiveness of this treatment. Piccirillo and colleagues applied rTMS at an intensity of 110% of each participant's resting motor threshold. However, because the present study used a different method to determine resting motor threshold, it is difficult to compare our values with those reported by them. Also, Piccirillo and colleagues used a Neuronetics TMS system, while the present study used a Magstim Company Ltd system. Therefore, it is not possible to compare the intensity of rTMS delivered during these studies. If the intensity of active rTMS in our study was significantly greater than that used by Piccirillo and colleagues, this difference could also contribute to the disparity in study results.

Limitations

Although results of the present study are encouraging, the sample size was small. We plan to continue and expand this clinical trial to address 6 questions.

First, will the magnitude of improvement in tinnitus severity (24% or more as measured by the TFI) exhibited by responders to active rTMS remain consistent when additional individuals participate in the clinical trial? Second, will improvement in tinnitus severity (as measured by the TFI) exhibited by responders to rTMS persist for 12 months or longer compared with 6 months in the present study? Third, what is the optimal side of rTMS stimulation (left or right) for individuals who perceive tinnitus primarily on the right side, left side, or equally on both sides or centralized? Fourth, are 5 rTMS sessions as effective as 10 rTMS sessions for reducing tinnitus severity (as measured by the TFI)?

Fifth, which characteristics of individuals or their tinnitus contribute to patients' responding or not responding favorably to rTMS treatment? For example, Kleinjung et al⁴⁵ reported that patients in their study who had experienced tinnitus longer than 10 years did not respond as favorably to 1-Hz rTMS as patients who had experienced tinnitus for shorter durations. In the present study, participants in the active rTMS group who had experienced tinnitus for at least 11 years exhibited greater reductions in tinnitus severity compared with participants who had experienced tinnitus for 1 to 10 years.

Sixth, if the intensity of placebo stimulation is reduced to 30% or 40%, will the percentage of responders in the placebo rTMS group (22% [7 of 32] in this study) decrease? Because 7 individuals in the placebo rTMS group exhibited significant improvement in TFIs, it is possible that the Magstim Company Ltd "sham" coil we used is not a completely inert placebo. In future clinical trials, we plan to reduce the stimulation intensity of the placebo coil (to 40%, as used by Mennemeier et al⁴⁶) to determine if this reduction results in a smaller percentage of responders for the placebo condition.

Conclusions

If rTMS continues to demonstrate efficacy as a treatment for tinnitus, future investigations should include multisite clinical trials. If these larger clinical trials replicate efficacy of rTMS that has been demonstrated in the present study, then steps should be taken to implement the procedure as a clinical treatment for chronic tinnitus.

We do not believe that rTMS should be viewed as a replacement for effective tinnitus management strategies that are available now.^{2,47-50} Instead, rTMS could augment existing tinnitus therapies and provide a viable option for patients who do not respond favorably to other treatments.

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Study concept and design: Folmer, Theodoroff, Shi, Griest.

Acquisition, analysis, or interpretation of data: All authors.

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Critical revision of the manuscript for important intellectual content: All authors.

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