The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Repetitive Transcranial Magnetic Stimulation for Tinnitus: A Pilot Study

Jason A. Smith, MD; Mark Mennemeier, PhD; Twyla Bartel, DO; Kenneth C. Chelette, MS; Timothy Kimbrell, MD; William Triggs, MD; John L. Dornhoffer, MD

Objectives/Hypothesis: **Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to alleviate tinnitus perception, presumably by inhibiting cortical activity associated with tinnitus. We conducted a pilot study to assess effectiveness of neuronavigated rTMS and its effects on attentional deficits and cortical asymmetry in four patients with chronic tinnitus using objective and subjective measures and employing an optimization technique refined in our laboratory.** ***Study Design:*** **Randomized, placebo-controlled (sham stimulation) crossover study.** ***Methods:*** **Patients received 5 consecutive days of active, low-frequency rTMS or sham treatment (using a 45-degree coil-tilt method) before crossing over. Subjective tinnitus was assessed at baseline, after each treatment, and 4 weeks later. Positron emission tomography/computed tomography (PET/CT) scans were obtained at baseline and immediately after active treatment to examine change in cortical asymmetry. Attentional vigilance was assessed at baseline and after each treatment using a simple reaction time test.** ***Results:*** **All patients had a response to active (but not sham) rTMS, as indicated by their best tinnitus ratings; however, tinnitus returned in all patients by 4 weeks after active treatment. All patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved ($P < .05$) after active but not sham rTMS.** ***Conclusions:*** **rTMS is a promising treatment modality that can transiently diminish tinnitus in some individuals, but further trials are needed to determine the optimal techniques required to achieve a lasting response. It is unclear whether the improved reaction times were caused by tinnitus reduction or a general effect of rTMS. PET/CT scans immediately after treatment suggest that improvement may be related to reduction of cortical asymmetry associated with tinnitus.** ***Key Words:*** **rTMS, Transcranial magnetic stimulation, tinnitus, attention, vigilance, psychomotor vigilance task, positron emission tomography/computed tomography, imaging.**

Laryngoscope, **117:529–534, 2007**

INTRODUCTION

Tinnitus is the perception of sound in the absence of external stimulation. Evidence for the central components of tinnitus and possible cortical reorganization comes from clinical, imaging, and behavioral studies. A lack of therapeutic response to surgical procedures, such as eighth nerve sectioning,[1] suggests that central mechanisms promote tinnitus. Functional magnetic resonance imaging[2] and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET)[3] reveal asymmetric metabolic activity in the auditory cortex associated with unilateral and bilateral tinnitus.[3,4] Other PET studies in tinnitus patients suggest that cortical activation is primarily in the left hemisphere, unrelated to the laterality of the tinnitus.[3,5] Behavioral studies have shown attentional deficits in tinnitus patients.[6] Attentional functions, such as vigilance and reaction time, are mediated in part by thalamocortical processes that regulate arousal to optimize performance.[7] Studies of sustained attention in tinnitus patients in our laboratory have shown that tinnitus patients are less vigilant than age-matched controls.[6]

Based on the hypothesis that maladaptive cortical reorganization may promote tinnitus, several investigators have studied the effect of repetitive transcranial magnetic stimulation (rTMS) on tinnitus.[5,8,9] Repeated low-frequency stimulation of a single neuron produces long-lasting inhibition of cell–cell communications (long-term depression).[10] Accordingly, low-frequency rTMS applied over the motor cortex produces an inhibitory effect.[11] Several studies have

From the Department of Otolaryngology–Head and Neck Surgery (J.A.S., J.L.D.), University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.; the Department of Neurobiology and Developmental Sciences (M.M., K.C.C., J.L.D.), University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.; the Department of Radiology (T.B.), Division of Nuclear Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.; the Department of Psychiatry (T.K.), University of Arkansas for Medical Sciences and Mental Health Service, Central Arkansas Veterans Healthcare System (CAVHS), North Little Rock, Arkansas, U.S.A.; and the Department of Neurology (W.T.), University of Florida, Gainesville, Florida, U.S.A.

This study was performed at the University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Editor's Note: This Manuscript was accepted for publication November 16, 2006.

This study was supported by the NIH National Center for Research Resources Centers of Biomedical Research Excellence (COBRE) Grant Number RR020146 and by a Tinnitus Research Consortium Grant-in-Aid.

Send correspondence to Dr. John L. Dornhoffer, Department of Otolaryngology–Head and Neck Surgery, University of Arkansas for Medical Sciences, 4301 W. Markham Slot #543, Little Rock, AR 72205. E-mail: dornhofferjohnl@uams.edu

DOI: 10.1097/MLG.0b013e31802f4154

shown that low-frequency rTMS applied over the auditory cortex can ameliorate tinnitus, at least temporarily.[5,8,9] This suggests that rTMS may inhibit abnormal cortical activity associated with tinnitus. We conducted a placebo-controlled (sham stimulation) crossover study with low-frequency (1 Hz) rTMS navigated over areas of cortical asymmetry within the temporal lobes of patients with chronic tinnitus using an optimization technique refined in our laboratory. Pre- and posttreatment PET/computed tomography (CT) scans were obtained to determine whether a change in tinnitus perception was associated with a change in cortical asymmetry. We also examined the effect of rTMS on reaction time to assess changes in attentional vigilance.

MATERIALS AND METHODS

Patient Population

Four male patients, 30 to 60 years of age, with chronic bilateral tinnitus (>6 mo duration) were enrolled in this randomized, controlled, crossover study. These were patients presenting to the senior author's clinic with a chief complaint of tinnitus for which they were seeking treatment and who met all the inclusion criteria. Each patient gave informed consent. The study was conducted with local institutional review board approval and oversight. An Investigational Device Exemption was not required because low-frequency rTMS is not deemed to present a significant risk to subjects.

Patients were excluded if they had a personal or family history of epilepsy, a significant head injury, stroke, aneurysm, previous cranial neurosurgery, pacemaker, or other metal implants. The use of medications that lower seizure threshold (tricyclic antidepressants or buproprion) or reduce cortical excitation (anticonvulsants, benzodiazepines, or other sedatives) was also exclusionary as was the presence of an acoustic neuroma, glomus tumor, brain tumor, profound hearing loss (HL) (>90 dB threshold at 4,000 Hz), or active Ménière's disease. Figure 1 shows the time course for interventions and baseline and follow-up measurements.

Neuroimaging

A baseline FDG-PET/CT scan was performed using a Biograph 6 PET/CT scanner (Siemens Medical Systems, Malvern, PA). The CT portion was a six-slice Siemens Sensation helical CT scanner, and the PET portion had "Hi-Rez" LSO (lutetium silicate oxime) 4 mm crystals arranged in a full-ring gantry with high-speed Pico Electronics. The baseline images were obtained 30 minute after the intravenous administration of 12 mCi (444 MBq) FDG.

Automated analysis of the PET brain studies was performed by the NeuroQ Display and Analysis Progam (version 2.0, Cardinal Health, Dublin, OH), which measures the magnitude and statistical significance with which activity in each region differs from mean activity values from a normal PET brain database of 50 patients. Any region with uptake beyond 1.65 standard deviations of the mean is identified by the program and color-coded and the statistical data provided. On the basis of previous reports of PET findings in tinnitus patients,[4,5] we focused on the asymmetric activity in the temporal lobe and surrounding primary auditory cortex. Quantitative and statistical comparisons were made with the normal brain scans and between the pre- and postscans for each patient. The registration algorithm for fitting the patient's brain scans to the normal template was a robust spatial transformation method.[12]

To further quantify the asymmetry and to account for factors such as blood glucose, at the time of imaging, an asymmetry index was calculated using the following equation[13]:

$$[(A - B) \times 100]/[(A + B)/2],$$

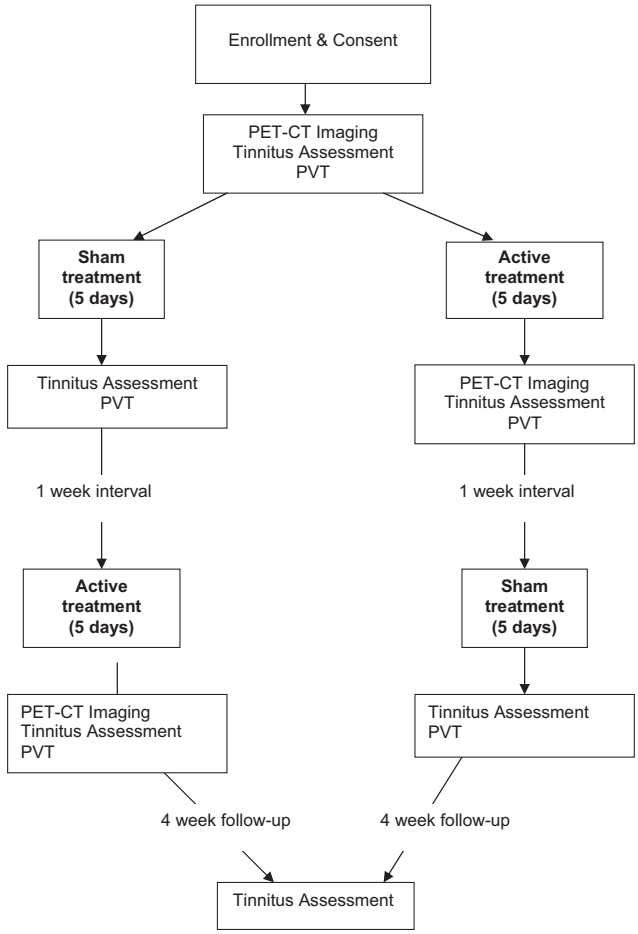


Fig. 1. Study flow chart.

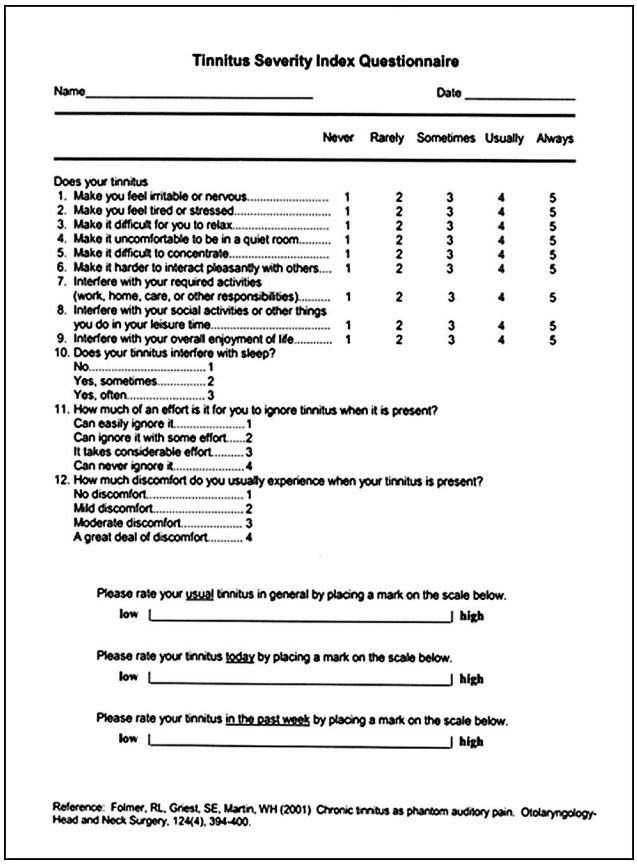
where A is the greatest counts per pixel for the area(s) with highest cortical uptake in the primary auditory cortex, and B is the respective contralateral uptake. The asymmetry index was used quantitatively for comparison with posttreatment imaging.

A repeat PET/CT scan was performed after the active treatment week, although patients were not informed when the repeat scan was to be given (i.e., after active or sham treatment). The first patient treated received the repeat scan after 3 days because of scheduling issues.

Tinnitus Assessment

Tinnitus severity, as perceived by each subject, was measured on enrollment using the Tinnitus Severity Index Questionnaire (TSIQ) with visual analogue scales (Fig. 2).[14] Questions on the TSIQ allow the calculation of a tinnitus-related disability score, whereas visual analogue scales allow participants to indicate the severity of their tinnitus at three time points based on a 100-point measure. The tinnitus assessment was administered at baseline, at the completion of active treatment, at the completion of sham treatment, and 4 weeks after completion of the trial.

To determine whether there was any ear-specific response to rTMS and to ascertain how tinnitus was affected during the course of the trial, subjects rated their tinnitus in each ear at baseline, at the completion of the active treatment, and at the completion of the sham treatment using a scale of 0 to 100, with higher numbers representing worse tinnitus. Subjects were also asked to give the optimum score they achieved for their tinnitus in each ear during the course of the trial ("best tinnitus") and to



Tinnitus Severity Index Questionnaire

Name_____ Date _____

	Never	Rarely	Sometimes	Usually	Always
Does your tinnitus					
1. Make you feel irritable or nervous	1	2	3	4	5
2. Make you feel tired or stressed	1	2	3	4	5
3. Make it difficult for you to relax	1	2	3	4	5
4. Make it uncomfortable to be in a quiet room	1	2	3	4	5
5. Make it difficult to concentrate	1	2	3	4	5
6. Make it harder to interact pleasantly with others	1	2	3	4	5
7. Interfere with your required activities (work, home, care, or other responsibilities)	1	2	3	4	5
8. Interfere with your social activities or other things you do in your leisure time	1	2	3	4	5
9. Interfere with your overall enjoyment of life	1	2	3	4	5

10. Does your tinnitus interfere with sleep?
No.....1
Yes, sometimes.....2
Yes, often.....3

11. How much of an effort is it for you to ignore tinnitus when it is present?
Can easily ignore it.....1
Can ignore it with some effort.....2
It takes considerable effort.....3
Can never ignore it.....4

12. How much discomfort do you usually experience when your tinnitus is present?
No discomfort.....1
Mild discomfort.....2
Moderate discomfort.....3
A great deal of discomfort.....4

Please rate your usual tinnitus in general by placing a mark on the scale below.
low [_____] high

Please rate your tinnitus today by placing a mark on the scale below.
low [_____] high

Please rate your tinnitus in the past week by placing a mark on the scale below.
low [_____] high

Reference: Folmer, RL, Griest, SE, Martin, WH (2001) Chronic tinnitus as phantom auditory pain. Otolaryngology-Head and Neck Surgery, 124(4), 394-400.

Fig. 2. Questionnaire used for subjective tinnitus assessment. Questions 1 to 12 pertain to impact of tinnitus on quality of life and allow calculation of a tinnitus-related disability score, with a higher number reflecting a greater debility. Three analogue scales are each 10 cm in length and are similar to visual analogue scales used for pain assessment.

record the point during the 2 weeks of treatment at which this occurred.

Psychomotor Vigilance Testing

Psychomotor vigilance testing (PVT) is a test of simple reaction time that measures the amount of time it takes participants to respond to a visual stimulus. Subjects were given a visual cue consisting of blinking numbers to which they responded as quickly as possible by pushing a remote button with their dominant thumb or forefinger. Reaction time was measured in milliseconds, and the lapse between stimuli varied from 2 to 10 seconds. The entire trial lasted 10 minutes. Parameters measured and reported with the PVT include 1) mean reaction time for all responses, 2) optimum response time (average of the fastest 10% reaction times), 3) slowest 10% reaction times, 4) frequency of lapses (response time >400 ms), 5) frequency of false responses (response in the absence of a stimulus), and 6) fatigability function (extent to which the subject maintained performance throughout the trial). The PVT was performed at baseline, after sham treatment, and after active treatment.

Treatment With rTMS

Each subject received 5 consecutive days of active or sham treatment, followed by a week of no treatment; subjects then crossed over to the other treatment arm. rTMS was targeted to the hemisphere and area in or around the primary auditory cortex showing greatest activity on PET/CT. This area was marked on a CT scan and coregistered to the PET image. A Brainsight Frameless Stereotaxy (Rouge Research, Montreal, Canada) system was used to calibrate the three-dimensional CT image with anatomic landmarks on the subject's head (e.g., the incisure, nasal tip, and nasofrontal angle). The TMS coil could then be navigated over a region of interest in the subject's brain corresponding precisely with the area marked on the CT scan. Magnetic stimulation, applied using a MagStim SuperRapid 200 Series Stimulator (Dyfed, UK) with an air-cooled figure-of-eight coil, consisted of 1,800 pulses (1 pulse every second for 30 min) at 1 Hz frequency and 110% of the subject's motor threshold (MT). MT was determined in an ascending/descending manner by delivering single pulses over the motor cortex and stopping at the lowest intensity required to yield thenar muscle twitches in three of six trials.

Active treatment used optimization of rTMS in the following manner. Single pulses of magnetic stimulation were delivered at MT intensity over and immediately surrounding the marked location on the CT scan. Subjects were asked whether the pulse had any noticeable effect on their tinnitus perception. If so, that location was deemed an optimal point and targeted for active rTMS. An optimal point was found in all four subjects.

The coil was placed over the same location during sham stimulation but at a 45° angle to the scalp. This replicated the clicking sound of active stimulation and provided some limited temporalis muscle twitching while markedly attenuating any magnetic stimulation of the underlying cortex. TMS parameters were otherwise the same for active and sham stimulation.

Subjects 1 and 4 were chosen at random to receive active treatment first. Subjects 2 and 3 received sham treatment first.

RESULTS

Neuroimaging

PET asymmetries before treatment lateralized to the right temporal lobe (Brodmann's area 41 and 42) in subjects 1, 3, and 4 and to the left in subject 2. These findings are given in Table I. Representative PET images (from subject 4) are shown in Figure 3. Table II gives the asymmetry index for each subject before and after active rTMS. As shown, all subjects demonstrated a reduction in their asymmetry index. Subjects 2 and 4 nearly completely resolved the pretreatment asymmetry.

Tinnitus Assessment

TSIQ scores (Table III) show subjects 1, 2, and 3 had a modest response to active treatment. With our small

TABLE I.
Pretreatment Positron Emission Tomography/Computed Tomography (PET/CT) Findings.

Subject	PET/CT Localization
1	Increased uptake of FDG in right superior temporal gyrus near sylvian fissure
2	Increased uptake of FDG in left sylvian fissure (area 1) and left temporal lobe (area 2)
3	Increased uptake of FDG in right superior and middle temporal gyri (area 1) and right sylvian fissure (area 2)
4	Increased uptake of FDG in right middle and superior temporal gyrus

FDG = F-18-fluorodeoxyglucose.

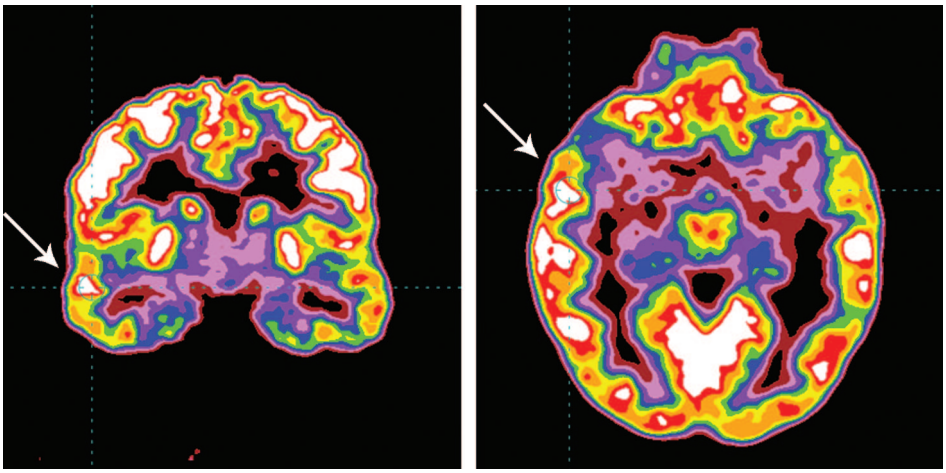


Fig. 3. Pretreatment positron emission tomography scan for subject 4. Scan demonstrates focus of increased activity in right temporal lobe (white arrow), as indicated by increased uptake of F-18-fluorodeoxyglucose in right middle and superior temporal gyrus.

patient population, this difference did not reach statistical significance ($P > .05$).

No differences were found in visual analogue scores when comparing "usual tinnitus" or "tinnitus in the past week" after active or sham treatments with those scores reported at baseline (Table IV). However, two of the subjects (1 and 4) showed improvement in their "tinnitus today" scores after active treatment. These were the patients who received active treatment first. There was an order effect found ($P = .05$) when comparing "tinnitus today" at baseline with that after active treatment for these two patients, but no order effect was found ($P > .05$) for those who received sham treatment first or for the group as a whole.

Ear-specific tinnitus ratings (Table V) indicate rTMS was able to elicit a positive effect on the tinnitus of all patients. Subjects 1 and 4 had complete resolution of their tinnitus at points during active treatment. Improvement in tinnitus perception persisted until the end of treatment in three subjects. Subject 1 showed improvement lasting until the end of active rTMS in both ears; subject 2 showed improvement lasting until the end of treatment in the ipsilateral ear; and subject 3 showed improvement in the contralateral ear. Posttreatment improvements did not reach statistical significance for either the contralateral or ipsilateral ear ($P > .05$), although a trend was approached when comparing the mean baseline score for the ear contralateral to the cortical stimulation (47.5) with the mean best rating for that ear (13.8; $t(1) = 2.2$; $P = .12$). The best tinnitus ratings occurred on 1 of the last 2 days of active treatment for all subjects.

TABLE II.
Asymmetry Index Before and After Treatment.*

Subject	Baseline	Post-rTMS
1	2.8	1.7
2		
Area 1†	3.5	0.3
Area 2	2.2	2.9
3		
Area 1†	8.6	7.5
Area 2	2.2	0.1
4	0.4	0.2

*Calculated using $[(A - B) \times 100]/[(A + B)/2]$, where A is greatest counts per pixel for area(s) with highest cortical uptake in primary auditory cortex, and B is respective contralateral uptake. A higher value represents a greater degree of asymmetry.

†Area treated with repetitive transcranial magnetic stimulation (rTMS).

Psychomotor Vigilance Testing

The mean reaction time at baseline (286 ± 19.27 SEM, ms) was significantly slower than the mean reaction time recorded after active rTMS (258.5 ± 16.96 ms), $P < .05$. In contrast, there was no difference in reaction times between baseline and sham treatment (290 ± 13.21 ms). The other PVT parameters were not significantly different pre- and postactive stimulation.

Safety Measures

No significant adverse events occurred during our trial. An audiogram obtained after rTMS was compared with the pretreatment audiogram and showed no change in hearing levels (Table VI).

DISCUSSION

Our results converge with previous reports suggesting that low-frequency rTMS can positively affect tinnitus perception in some patients, at least temporarily. DeRidder et al.[9] demonstrated a positive effect in approximately half of 114 patients with unilateral tinnitus treated with a single session of rTMS. In a placebo-controlled crossover trial, Kleinjung et al.[5] demonstrated that low-frequency

TABLE III.
Tinnitus Severity Index Questionnaire Disability Scores.*

Subject	Baseline	Post-rTMS	Post-sham	4 Weeks
1	29	26	29	27
2	21	17	22	21
3	38	33	34	34
4	26	29	25	23

*Higher score represents greater perceived tinnitus-related disability, with total score of 56 possible.

rTMS = repetitive transcranial magnetic stimulation.

TABLE IV.
Visual Analog Scores.*

	Usual Tinnitus				Tinnitus Today				Tinnitus Past Week			
Subject	Baseline	Post-rTMS	Post-sham	4 Weeks	Baseline	Post-rTMS	Post-sham	4 Weeks	Baseline	Post-rTMS	Post-sham	4 Weeks
1	38	33	50	39	44	25	38	35	22	19	24	40
2	36	47	50	41	41	46	46	32	35	48	48	31
3	70	91	87	78	74	85	85	90	80	85	85	88
4	40	45	50	69	55	48	48	73	35	48	48	74

*Maximum score is 100, with higher scores indicating greater perceived tinnitus.
rTMS = repetitive transcranial magnetic stimulation.

rTMS administered for 5 consecutive days could have a significant effect on tinnitus that persisted up to 6 months after treatment. Our results differ in that we found only a transient improvement. Similarly, a more recent study now confirms that the effects of rTMS on tinnitus perception may be shorter lived than originally believed.[15] This does not diminish the importance of examining the effect of rTMS on tinnitus perception because such studies have theoretic significance for understanding tinnitus pathophysiology, and we can now focus on varying the treatment parameters to promote lasting change.

In our study, we showed that change in tinnitus was typically greatest in the ear contralateral to stimulation and that low-frequency rTMS can be expected to effect change by the fourth to fifth treatment session. Several procedural observations were made. First, most patients are not used to rating the subjective nature of their tinnitus; therefore, it is necessary to establish a stable baseline of tinnitus ratings before starting a clinical trial. Ratings should also be made daily because relying on pre- and postexperiment measures may miss real change that occurs during the course of the experiment. In fact, the most likely reason that our pre/postglobal measures of tinnitus failed to detect change was that tinnitus returned shortly after treatment. Another procedural observation is that it may be necessary to stimulate both hemispheres in persons with bilateral tinnitus. All our patients had bilateral tinnitus, but perceived change in tinnitus was most likely to occur in only one ear. On a related note, given our sample size, it is unclear how useful PET asymmetries are in guiding the application of rTMS. The pretreatment PET scans of subjects 2 and 3 lateralized to the hemisphere ipsilateral to the ear with louder subjective tinnitus (Table V). It is simply premature to guess what the PET asymmetries represent, even though most tinnitus patients appear to have them. We know that a majority of auditory fibers cross to project from the cochlea to the contralateral auditory cortex, and our experience in this trial demonstrates that subjective improvement appears to occur in the ear opposite stimulation. An alternative to PET-guided rTMS may be to choose a stimulation site opposite the ear with the louder tinnitus.

The use of PET/CT after treatment is novel. We believed that the increased activity used as an indication for the site of stimulation would be decreased after active treatment, producing a symmetric finding on posttreatment imaging. Two subjects nearly completely resolved the pretreatment asymmetry; however, the other two subjects were also noted to have a decreased asymmetry index after treatment. This may indicate that, in patients with tinnitus, areas in the primary auditory cortex that are stimulated with low-frequency rTMS have decreased activity on PET imaging after treatment. Interestingly, the patient who did not show much of a change in his asymmetry (subject 3) was the patient who arguably had the least response to active rTMS as measured by subjective scores. The two subjects who had complete resolution of their tinnitus at their best rating (subjects 1 and 4) had improvement in their asymmetry index. These findings point toward an association between tinnitus improvement and improvement in functional imaging after rTMS that will have to be corroborated with a larger series of patients.

The use of reaction time testing (PVT) to measure sustained attention is also novel. In a previous study, we demonstrated that patients with tinnitus have deficits in

TABLE V.
Ear-Specific Ratings of Tinnitus.*

	Ipsilateral Ear†			Contralateral Ear		
Subject	Baseline	Post-rTMS	Best Tinnitus	Baseline	Post-rTMS	Best Tinnitus
1	65	47	0	65	47	0
2	50	40	30	10	30	5
3	100	100	100	60	50	50
4	5	5	1	55	60	0
Mean	55	48	32.8	47.5	46.8	13.8

*Ratings out of 100, with higher number denoting greater perceived tinnitus.
†Ear on same side as increased uptake of F-18-fluorodeoxyglucose seen by positron emission tomography/computed tomography and, subsequently, side of repetitive transcranial magnetic stimulation (rTMS).

TABLE VI.
Audiometric Data.

Subject	Baseline PTA-AS (dB)	Baseline PTA-AD (dB)	Post-rTMS PTA-AS (dB)	Post-rTMS PTA-AD (dB)	Baseline Discrim AS (%)	Baseline Discrim AD (%)	Post-rTMS Discrim AS (%)	Post rTMS Discrim AD (%)
1	23	18	27	23	100	100	92	96
2	15	15	15	15	92	96	92	96
3	10	15	—	—	96	92	—	—
4	12	10	8	5	96	96	100	100

*Pure tone average (PTA) and discrimination scores (Discrim) are reported for baseline, pre-enrollment audiograms, and posttreatment audiograms. Subject 3 did not return for posttreatment audiogram.
AS = left ear; AD = right ear; rTMS = repetitive transcranial magnetic stimulation.

attentional vigilance compared with controls.[6] The study reported here indicates that vigilance improves with rTMS treatment. Either attention improved as tinnitus improved, or improved reaction time may be a nonspecific effect of rTMS. Alternatively, rTMS might affect tinnitus perception secondary to altering attentional processes. A recent rTMS study using PET and lidocaine injections concluded that activity in brain systems related to emotion and attention may contribute to or promote tinnitus.[15] It is plausible that rTMS alters tinnitus perception secondary to altering attentional systems, which might be responsible for the observed change in reaction time.

One of the limitations of this trial included its crossover design. There may be carryover effects of active rTMS on the subjects who received active treatment first, which could hide statistical significance in differences noted in tinnitus severity or slowest reaction times when compared with sham treatment. Furthermore, 3 of the 4 subjects were able to correctly identify the active week, calling into question the effectiveness of the sham stimulation. Because of these hindrances, we are now planning to conduct a larger study that uses a parallel treatment design and a more advanced sham stimulation.

CONCLUSION

This pilot study corroborates the findings of others and indicates that tinnitus can be alleviated in some cases by rTMS; however, with our protocol, these effects appear to be short lived. We have demonstrated that vigilance is improved in patients with tinnitus after active rTMS and that cortical asymmetry is decreased in a majority of subjects. Results of this trial indicate directions for future clinical studies of rTMS in tinnitus, including variations in treatment duration for individual sessions and the number of days of stimulation, use of a parallel study design, and the need for a more technically advanced sham stimulation. Stimulation on the side opposite the loudest tinnitus with optimization may be the best choice in asymmetric patients, and bilateral patients may require bilateral stimulation to obtain adequate relief. We plan to continue to evaluate these variables in search of the most appropriate role for rTMS in the treatment of tinnitus.

Acknowledgments

The authors thank Mary K. Dornhoffer for editorial assistance during the preparation of this paper.

BIBLIOGRAPHY

1. Jackson P. A comparison of the effects of eighth nerve section with lidocaine on tinnitus. *J Laryngol Otol* 1985;99: 663–666.
2. Melcher JR, Sigalovsky IS, Guinan JJ Jr, Levine RA. Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. *J Neurophysiol* 2000;83:1058–1072.
3. Arnold W, Bartenstein P, Oestreicher E, et al. Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: a PET study with [18F]deoxyglucose. *ORL J Otorhinolaryngol Relat Spec* 1996;58:195–199.
4. Langguth B, Eichhammer P, Wiegand R, et al. Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. *Neuroreport* 2003;14:977–980.
5. Kleinjung T, Eichhammer P, Langguth B, et al. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. *Otolaryngol Head Neck Surg* 2005;132:566–569.
6. Dornhoffer J, Danner C, Mennemeier M, et al. Arousal and attention deficits in patients with tinnitus. *Int Tinnitus J* 2006;12:9–16.
7. Sturm W, Longoni F, Fimm B, et al. Network for auditory intrinsic alertness: a PET study. *Neuropsychologia* 2004; 42:563–568.
8. Plewnia C, Bartels M, Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. *Ann Neurol* 2003;53:263–266.
9. De Ridder D, Verstraeten E, Van der Kelen K, et al. Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. *Otol Neurotol* 2005;26:616–619.
10. Bear MF. Homosynaptic long-term depression: a mechanism for memory? *Proc Natl Acad Sci U S A* 1999;96:9457–9458.
11. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997;48:1398–1403.
12. Tai Y-C, Lin K, Hoh CK, et al. Utilization of 3-D elastic transformation in the registration of chest x-ray CT and whole body PET. *IEEE Trans Nucl Sci* 1997;4:1606–1612.
13. Wang H, Tian J, Yin D, et al. Regional glucose metabolic increases in left auditory cortex in tinnitus patients: a preliminary study with positron emission tomography. *Chin Med J (Engl)* 2001;114:848–851.
14. Folmer RL, Griest SE, Martin WH. Chronic tinnitus as phantom auditory pain. *Otolaryngol Head Neck Surg* 2001;124: 394–400.
15. Plewnia C, Reimold M, Najib A, et al. Moderate therapeutic efficacy of PET-navigated repetitive transcranial magnetic stimulation against chronic tinnitus: a randomized, controlled pilot study. *J Neurol Neurosurg Psychiatry* 2006; Aug 4, Epub ahead of print.