Research Plan: Clinical Trial of Transcranial Magnetic Stimulation for Relief of Tinnitus
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Objectives and Specific Aims
Our long-range goal is to develop a safe, practical, effective and cost-effective treatment for chronic tinnitus. The objective of this proposal, the next step toward attaining our long-range goal, is to conduct a well-designed, placebo-controlled clinical trial of rTMS in a large sample of tinnitus sufferers.

The central hypothesis of the proposed research is that rTMS can reduce the perception of tinnitus for prolonged periods of time with minimal adverse side effects. Our hypothesis has been formulated on the basis of supportive preliminary studies that are described in the Background section of this proposal.

We are well-positioned to undertake the proposed research because we have assembled a collaborative, multi-disciplinary team that combines the range of clinical and research expertise needed to achieve definitive outcomes. In addition, the study is strongly supported by preliminary data that validate the proposed approach. Finally, the investigation will be conducted in an environment that is conducive to its success. Participating organizations include the National Center for Rehabilitative Auditory Research at Portland VA Medical Center, the Tinnitus Clinic at Oregon Health & Science University (OHSU), the OHSU Department of Otolaryngology, the OHSU Department of Neurology, the Oregon Hearing Research Center, and the Department of Psychiatry, Psychosomatics and Psychotherapy at the University of Regensburg, Germany.

We will test our central hypothesis and accomplish the objective of this application by pursuing the following two specific aims:

1. Conduct a double-blinded, randomized, placebo-controlled clinical trial of repetitive transcranial magnetic stimulation (rTMS) in a large sample of people who experience chronic tinnitus.
   a. We hypothesize that application of rTMS daily for 10 successive work days will result in a statistically greater percentage of responders to treatment in the active stimulation group compared to the placebo group.
   b. We also hypothesize that the effectiveness of rTMS will be significantly greater when stimulation is delivered to the side of the subjects’ head ipsilateral to the side where their perception of tinnitus is loudest, compared to stimulation delivered to the side of the head contralateral to maximal tinnitus perception.

2. Track the progress of subjects who participated in the clinical trial for six months post-treatment.
   We hypothesize that improvements in tinnitus severity experienced by responders will be sustained during the follow-up period. Non-responders will not experience significant changes in tinnitus severity during the follow-up period.

This approach is innovative because it (a) applies current methods of transcranial magnetic stimulation to a large sample of tinnitus sufferers, (b) includes an improved placebo/control condition and blinding protocol, and (c) involves collaboration among experts from diverse disciplines, including tinnitus research, audiology, otology, neurology, psychiatry and psychology. The findings of the proposed clinical trial will facilitate the implementation of safe and effective treatment protocols to alleviate suffering from tinnitus.

Research Design and Methods
This will be a prospective, randomized, subject and clinician/observer blind, placebo-controlled parallel-group clinical trial of rTMS involving a large sample of people who experience tinnitus. Eligible subjects will be randomly assigned to receive either active rTMS treatment or placebo treatment. The group receiving active rTMS will be randomized to either left or right side of the head coil placement. Subjects will receive rTMS therapy on 10 consecutive work days. Outcomes will be measured prior to the start of treatment, immediately before and after each therapeutic session. Follow-up evaluations will be conducted 1, 2, 4, 13 and 26 weeks after the last treatment session. This design allows us to determine if rTMS reduces the severity and loudness of tinnitus (Hypothesis 1a), the long-term duration of relief (Hypothesis 2), and whether coil placement affects active rTMS efficacy (Hypothesis 1b).
The target population (to whom the study findings will be generalized) for this investigation includes people who experience bothersome, chronic tinnitus. A majority of people with chronic tinnitus have some degree of sensorineural hearing loss. Tinnitus is more prevalent among older people because hearing loss increases with age. However, a significant number of people with normal hearing also experience chronic tinnitus, especially if they have been exposed to loud sounds or blasts. The following methods for subject recruitment and enrollment will be implemented in order to enlist a study population that reflects the characteristics of the target population. Findings from the proposed clinical trial can then be applied directly to the target population, which includes Veterans and members of the U.S. Armed Forces who experience chronic tinnitus.

Subject Recruitment and Screening

All procedures for recruitment, informed consent, and conduct of the study will adhere to the requirements of the Institutional Review Boards at both the Portland VA Medical Center (PVAMC) and Oregon Health & Science University (OHSU) for protection of human research subjects.

Recruitment

Participants in this study will be adults who experience chronic tinnitus. Recruitment sources will include (1) referrals from clinics at the PVAMC and OHSU; (2) individuals who respond to study announcements at the PVAMC and OHSU; and (3) respondents to flier, internet or newspaper advertisements. Permission to advertise at OHSU will be obtained. In addition, recruitment will be facilitated by databases at the PVAMC and OHSU that contain contact information for approximately 10,000 tinnitus patients and study participants who have agreed to be contacted for potential participation in future tinnitus research. The databases can be searched for particular characteristics of patients or tinnitus required for our proposed research. The use of advertising will further ensure that the required numbers of study participants can be enrolled for each cohort. These methods have been used successfully by our team of investigators numerous times for previous research studies and clinical trials. The Study Audiologist will identify and recruit volunteers to participate in the proposed clinical trial. With an expected screening to inclusion ratio of 5:1, 840 subjects will be assessed for eligibility and 168 will be identified for study participation.

Screening and Enrollment

Individuals who volunteer to participate in the study will be screened by the Study Audiologist. Volunteers will be informed about the specifics of study participation, and will be asked to supply basic information about their tinnitus percept. If they have chronic tinnitus of at least 12 months duration and express a willingness to participate, they will be asked to rate the loudness of their tinnitus on a visual numerical scale (VNS: 0 labeled “No Tinnitus”, 10 labeled “Very Loud”). A minimum loudness rating of 6 or higher will be required for study participation.

Some study candidates will have disabilities for psychological function (e.g., anxiety, neurosis, psychosis, and post-traumatic stress disorder). Candidates who have confirmed, or a history of, psychological disorder, will be considered for study participation if their disorder will not interfere with their ability to serve as participants; that is, they must be able to respond competently to questionnaires and all testing (including a dementia screening test), and show no evidence that they could not complete the protocol.

Potential candidates will be selected using the following inclusion criteria:

- Diagnosis of chronic tinnitus.
- Able to provide written informed consent.
- Subject is naïve regarding rTMS.
- **Age/Gender:** minimum 18 years old, with an attempt to sample equal numbers of male and female subjects.
- **Other concurrent treatments:** A four-week washout from any other tinnitus treatment or management program is required prior to entering this study.
- **Psychological status:** Stable enough to complete this study per the opinion of the Study Physician.
- **Hearing function:** All degrees of hearing function can be included recognizing that profound, bilateral losses will not be able to perform tinnitus evaluations and hearing tests, but will be able to rate subjective tinnitus loudness, annoyance and impact on life. This is an important subpopulation because of the challenges in treating them with acoustic therapy and the need for a medical intervention.

- **Tinnitus characteristics:** All forms of tinnitus etiology will be accepted, providing the following criteria are met:
  
  o Tinnitus duration: Not less than 1 year. Cases of less than 1 year duration have increased likelihood of resolving spontaneously.
  o Stability: Constant (not pulsatile, intermittent, varying to a high degree in loudness or changing in location of perception). Fluctuating tinnitus reduces the reliability of test-retest measures for loudness.
  o Self-rated tinnitus loudness: ≥ 6 on a visual numerical scale (VNS: 0 labeled “No Tinnitus”, 10 labeled “Very Loud”). This outcome measure will provide a subjective indication of immediate changes in perceived loudness.
  o Location of tinnitus perception: Unrestricted. Tinnitus may be unilateral, bilateral, or perceived in the head.

**Exclusion Criteria**

- Objective Tinnitus – tinnitus that is audible to other people in addition to the patient. This type of tinnitus is rare and is unlikely to respond to rTMS because it is not associated with abnormal neural activity in the central auditory system.

- History or evidence of significant brain malformation or neoplasm, head injury, cerebral vascular events (such as strokes), neurodegenerative disorders affecting the brain (such as Parkinson’s Disease, ALS, Huntington’s Disease or Multiple Sclerosis) or prior brain surgery.

- Cardiac pace makers, other electronic implants (including cochlear implants), intracranial or intraocular metallic particles

- History of seizures or epileptic activity.

- Patients who cannot communicate reliably with the investigator or who are not likely to cope with the requirements of the trial.

- Participation in a clinical trial within the last 30 days before the start of this one.

- **Medications/drugs:** Not taking any of the following: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscamet, ganciclovir, ritonavir, amphetamines, cocaine, MDMA (“ecstasy”), phencyclidine (PCP, angel’s dust), ketamine, gamma hydroxybutyrate (GHB), theophylline. There are no restrictions on other medications, provided the dosages have been in place for at least 6 months.

- **Medical conditions:** No active neurologic or otologic disease processes that may impact tinnitus perception. No auto-immune diseases. No pregnancy or planned pregnancy during the study. No women who are lactating or are of child-bearing-age without using contraception.

- Maximum number of previous clinical trials for tinnitus in which subjects may have participated: two.

Individuals who pass a telephone screening will be scheduled for an initial appointment with the Study Audiologist. Subjects will be paid $20 for each appointment they attend during the study, including the initial appointment, each of the rTMS sessions, and each of the follow-up appointments that occur 1, 2, 4, 13 and 26 weeks post-treatment. Subjects will not be paid for missed appointments.
At the initial appointment, the Study Audiologist will:
(1) Obtain written informed consent.
Volunteers will be fully informed about the nature, purpose, possible risks and benefits of the study by the Study Audiologist at NCRAR before any study specific actions take place. There will be sufficient time for volunteers to ask questions and sufficient privacy to consider the information provided. Volunteers will be allowed to discuss the study with anyone of their choosing before making a decision regarding enrollment. If the volunteer is willing to participate in the trial, he or she will be asked to sign the informed consent form. Volunteers will be notified that they are free to withdraw from the study at any time without suffering any consequences or disadvantages for further clinical care. Subjects can be withdrawn from the study when this is deemed necessary by the Principal Investigator. Reasons for subject withdrawal can include safety concerns or severe non-compliance.

(2) Administer the Mini-Mental State Examination (MMSE). The MMSE is a 30-point questionnaire that is used to assess cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. The MMSE provides a total score that is used to assess cognitive function (Folstein et al., 1975). A minimum MMSE score of 24 will be required for participation in the study in order to identify and exclude subjects with dementia or other forms of cognitive impairment.

(3) Administer and check the baseline written questionnaires. These include:
   a) Tinnitus History Questionnaire
   b) Hearing History Questionnaire
   c) Medical History Questionnaire
   d) Visual numerical scale (VNS) for self-rated tinnitus loudness. This will be done in a quiet exam room, but not a sound booth. Careful instructions will be given to the subject to ensure that only a vertical line is drawn on the scale (as compared to a circle or shaded area). Folmer et al (2001) and others have determined that the self-rated loudness of tinnitus is positively and significantly correlated with measures of depression, anxiety, and tinnitus severity. Visual numerical scales are useful instruments to assess immediate changes in tinnitus perception post-treatment. Subjects will complete the visual numerical scale (VNS) for self-rated tinnitus loudness at baseline, before and after each session of actual or placebo rTMS, and at 1, 2, 4, 13 and 26 weeks post-treatment.

   On the scale below, please draw a vertical line to indicate the loudness of your tinnitus at this moment

   0               1               2               3               4               5               6               7               8               9               10
   NO                                                                                                                                                VERY LOUD
   TINNITUS

   e) Tinnitus Handicap Inventory (THI) is a 25-item questionnaire that is the most widely-used instrument for subject self-assessment of tinnitus severity (Newman et al, 1996). Newman et al (1998) and other researchers determined that THI has high test-retest reliability and repeatability, is psychometrically robust, and is therefore useful for assessing tinnitus severity and changes in tinnitus severity over time.

   f) Tinnitus Functional Index (TFI) is a 25-item questionnaire developed by Meikle et al (2007). Meikle et al (2009) demonstrated that the TFI is highly correlated with the THI, but the TFI has greater sensitivity for
changes in tinnitus severity because all of its responses are given on a 0-to-10 scale (in contrast to YES, SOMETIMES or NO response options for the THI).

b) Beck Depression Inventory II (BDI-II) is a 21-item multiple-choice self-report questionnaire that is one of the most widely used instruments for measuring the severity of depression (Beck et al, 1996). Its psychometric robustness, sensitivity, test-retest reliability and repeatability have been confirmed many times by multiple studies. Folmer (2002) reported that improvements in tinnitus severity were associated with reductions in Beck Depression Inventory scores.

c) State Anxiety Inventory (SAI) is a 20-item self-report instrument developed by Spielberger (1998). The psychometric robustness of this widely used anxiety assessment questionnaire has been confirmed numerous times by many researchers around the world. Folmer et al (2001) reported that State Anxiety Inventory scores were positively and significantly correlated with Beck Depression Inventory scores, self-rated tinnitus loudness scores, and measures of tinnitus severity.

Participants who meet all requirements during their initial appointment with the Study Audiologist will receive an otolaryngological and physical exam by a physician. Each subject’s medical condition, concurrent treatments, medications, psychological status and other health information will be obtained by the Study Physician through medical history and physical exam.

Subjects will then undergo a hearing evaluation by the Study Audiologist. The hearing evaluation will include pure tone air and bone conduction testing, immittance measures, and speech audiometry. Folmer et al (2006) and other researchers reported that rTMS does not affect hearing thresholds of subjects receiving active or placebo stimulation. However, the effects of rTMS on hearing have not been studied in a large sample population and will therefore be monitored in this clinical trial.

Tinnitus evaluations will also be conducted by the Audiologist and will include tinnitus pitch and loudness matching per Johnson (1998), taking care to identify and account for octave confusion. Tinnitus loudness matching will be performed using a 1 kHz tone presented to the ear contralateral to the side of tinnitus perception. Loudness matching has been hampered in some previous studies because the loudness match at the pitch of the tinnitus was often too high a level to test (beyond the limits of the equipment). This problem occurs less often when using a 1 kHz comparison tone because most subjects have reasonable auditory thresholds at that frequency. Tinnitus loudness matching will provide a somewhat objective measure of changes in subjects’ perception of tinnitus following rTMS treatment.

The Audiologist will determine minimum masking levels (MMLs) by measuring the level at which a 2 kHz-12 kHz band of noise completely masks tinnitus in the ipsilateral ear. This test is conducted because MMLs are correlated with tinnitus severity and might provide useful information as secondary outcomes measures (Andersson et al, 1999; Andersson, 2003).

Residual inhibition (RI) or post-masking change testing will be conducted after the other tinnitus tests. RI is a temporary suppression or reduction of tinnitus following subjects’ exposure to masking sounds. To test for RI, the intensity of the 2 kHz-12 kHz band of noise will be set 10 dB above the MML and played continuously in the ear ipsilateral to the subject’s loudest perceived tinnitus for 60 seconds. At that point, the masking sound will be turned off and subjects will be asked to identify any changes in their perceived tinnitus. If partial or complete residual inhibition occurs, its duration will be timed with a stopwatch and recorded. One possible consequence of rTMS treatment is an increase in the duration of RI.
1) Initial Appointment: written consent, baseline questionnaires, medical exam, audiometric testing, tinnitus testing.
2) 10 sessions of active or placebo rTMS applied to a specific temporal region on one side of the head (sessions take place once daily over 10 consecutive work days)
3) Follow-up assessments will take place 1, 2, 4, 13 and 26 weeks after the final rTMS session.
4) After the follow-up period is completed, subjects in the placebo group will undergo 10 sessions of active rTMS applied to a specific temporal region on one side of the head (sessions take place once daily over 10 consecutive work days). Follow-up assessments will take place 1, 2, 4, 13 and 26 weeks after the final rTMS session.

Outcome Measures
The primary outcome measure will be the Tinnitus Functional Index (TFI).

- In addition to the primary outcome measure, audiometric evaluations, the Tinnitus Handicap Inventory (THI), the Beck Depression Inventory (BDI), the State Anxiety Inventory (SAI), Minimum Masking Level and matched tinnitus loudness (re: a 1 kHz pure tone) results will be recorded seven times during the study: At the initial visit, at the end of the first 10 rTMS sessions, 1, 2, 4, 13 and 26 weeks after the final rTMS session. The visual numerical scale (VNS) for self-rated tinnitus loudness will be completed before and after each session of actual or placebo rTMS, and again 1, 2, 4, 13 and 26 weeks after the final rTMS session. Tinnitus loudness matching will be conducted (using a 1 kHz tone presented to the ear contralateral to the side of tinnitus perception) before and after each session of actual or placebo rTMS, and again 1, 2, 4, 13 and 26 weeks after the final rTMS session.

These secondary outcome measures will be used for multiple linear regression analysis.

Randomization
At the beginning of the study, subjects will be stratified by left-dominant, right-dominant, and equal/centrally-located tinnitus. The expected proportion of randomized subjects in each tinnitus laterality group is 32% right side dominant, 40% left side dominant, and 28% central or left=right. These estimates are based on data collected from 1629 patients in the Tinnitus Data Archive at Oregon Health & Science University. Subjects will then be randomized according to a stratified 2x2 design, corresponding to active vs. placebo and left side of the head vs. right side of the head positioning of the rTMS coil. Subjects will be allocated according to a stratified block schedule, with randomly permuted block lengths of 4, 8, 12, and 16 subjects. We will use 1:1:1:2 allocation of subjects to placebo/active and left/right rTMS coil placement treatment conditions at the start of the study (see Figure 4).
Sample Size and Power Analysis

Hypotheses 1a and 1b will be tested by comparing subject responses to active vs. placebo rTMS averaged over strata and coil placement conditions, using a 2-sample t-test. Hypothesis 1b will be tested among subjects receiving active rTMS by comparing outcomes among subjects with ipsilateral coil placement to those randomized to contralateral coil placement. Placebo group subjects and subjects who do not have lateralized perception of tinnitus will not be used for testing Hypothesis 1b.

The number of subjects needed to detect a significant effect of rTMS therapy compared to a placebo is based on improvements in two primary endpoints: visual numeric scale (VNS) for self-rated tinnitus loudness, and Tinnitus Handicap Inventory scale improvements from baseline to post-treatment time points. A one-sided test for efficacy at the 0.05 test level will be used and we require 90% power to detect a significant difference. Since two outcomes are measured simultaneously, we will employ a Bonferroni correction so that a one-sided p-value of 0.025 or less on either scale is required to show efficacy. Effect sizes for the VNS score improvement are based on a study by Rossi et al (2007), who reported that active rTMS therapy subjects had a mean post-treatment VNS score of 47.1 on a 100-point scale (standard deviation [sd] =24.6) compared to sham treatment subject VNS scores of 60 (sd=25.9). Effect sizes for the THI scale improvements are based on a study by Khedr et al (2008), who reported that subjects receiving active rTMS therapy experienced a 30% improvement from baseline compared to a 10% average improvement among sham treatment controls. The variability of the response is estimated as sd=37 from a preliminary evaluation of tinnitus laterality effects by these same authors. We will require 62 subjects per group for analysis of the VNS tinnitus loudness scale responses and 75 subjects per group for analysis of the THI scale responses. Using the larger of the two projections (75 subjects per treatment condition) and assuming a 10% loss to follow-up, we will randomize a total of 168 subjects in this stratified 2x2 design.

Power analysis for Hypothesis 1b will be two-sided and based on a 2-sample t-test of the average TFI score improvement comparing subjects randomized to ipsilateral rTMS coil placement with those randomized to contralateral rTMS coil placement. If the full sample is subjected to complete randomization in the 2x2 design, then there will be 29 ipsilateral coil placements and 29 contralateral coil placements among subjects receiving active therapy. Accordingly, we can detect a 21% difference in TFI scale improvement with 50 subjects per ipsi-/contra-lateral group, a 24% difference in TFI scale improvement with 41 subjects per group, and a 28% difference with 29 subjects per group.
**rTMS intervention:** Half of the subjects will be assigned to the active treatment group and the other half of the subjects will be assigned to the placebo group. All subjects will be treated daily with either active or placebo rTMS over a period of 2 weeks. rTMS will be administered according to safety guidelines established by Wassermann et al (1998). Two Magstim Rapid² (The Magstim Company Ltd, Whitland, Carmarthenshire, Wales, UK) transcranial magnetic stimulators will be used in this study. Over the last 20 years, this brand and type of transcranial magnetic stimulator equipment has been used safely by numerous investigators in more TMS studies than any other brand of equipment. For example, Magstim brand transcranial magnetic stimulators were used in TMS studies of tinnitus conducted by Eichhammer et al (2003), Langguth et al (2003), De Ridder et al (2005), Kleinjung et al (2005), Rossi et al (2007), Smith et al (2007), Lee et al (2008), and Plewnia et al (2003, 2007) among others.

**Placebo Stimulation**

Lack of adequate placebo control conditions has plagued most rTMS studies, including those involving subjects with tinnitus. rTMS produces characteristic sounds and sensations when stimulation is applied to a subject’s scalp. Although some studies have attempted to provide a placebo condition by positioning an active coil perpendicular (or at an angle) to the subject’s scalp (Rossi et al, 2007; Smith et al, 2007), it was still relatively easy for subjects to distinguish between active and placebo stimulation because the placebo condition did not replicate the sounds and sensations of active stimulation. Some subjects undoubtedly reported greater tinnitus suppression during active rTMS because it was obvious when they were receiving active vs. placebo stimulation (Folmer, 2005). Several studies of rTMS for tinnitus (Langguth et al, 2006; Kleinjung et al, 2007; Lee et al, 2008) did not employ a placebo condition at all. It is difficult to interpret the positive results reported by these studies because the “placebo effect” among subjects with tinnitus is high (Dobie, 1999).

The proposed clinical trial will utilize a greatly improved placebo control design that includes the following elements:

1. A Magstim placebo rTMS coil which looks identical to the active coil and produces identical sounds and sensations for subjects, but does not deliver electromagnetic stimulation to the subject’s brain.
2. Blinding of all subjects, clinicians and observers except the Principal Investigator (PI). Only the PI will know which subjects receive active rTMS.

**Blinding**

Blinding has presented a substantial methodological challenge in previous rTMS studies, primarily because clinicians delivering treatment always knew when active or placebo stimulation was being administered. In most studies, it was also easy for subjects to distinguish between active and placebo rTMS conditions. In
this proposed clinical trial, a blinded design will be used in which everyone except the PI will be blind to
treatment conditions. Subjects will be naïve regarding rTMS treatment and will not be informed about
technical details of rTMS application. At the beginning of each rTMS session (active or placebo), the PI will
obtain the resting motor threshold (rMT) for each subject according to procedures described in the following
sections of this application. After rMT is assessed, the PI will set the appropriate stimulation intensity and
position a rTMS coil to contact one side of the subject’s head at the location specified in Figure 5. The PI
will then summon the Study Audiologist to administer pulses of rTMS to the subject’s head. Neither the
clinician nor the subject will be able to distinguish between active and placebo stimulation because, a) the
coils are identical in appearance, and b) the sounds and sensations produced by the active coil are
replicated by the placebo coil. To assess the effectiveness of the placebo coil and blinding of the trial, each
subject will be asked at the final visit whether or not he or she guesses to have been treated with active or
placebo rTMS.

**Hearing protection**: Prior to active or placebo rTMS, subjects will have foam ear plugs inserted into each of
their ear canals to minimize the effects of rTMS sounds on their hearing thresholds and tinnitus. Ear plugs
will not be worn during tinnitus testing that will take place before and after each TMS session.

Subjects will be randomized to one of two parallel groups with the following stimulation parameters:

**Treatment group** – 84 subjects. A subgroup of 42 subjects will receive active rTMS on the left side of the
head during daily sessions for 10 consecutive work days. Stim rate: 1 or 10 Hz; stimulation intensity: 110%
of the individual resting motor threshold or lower; with the figure-of-eight coil positioned over left primary
auditory cortex. The coil will be placed in an adjustable stand that will hold it against the subject’s head in a
fixed location. During rTMS sessions, subjects will sit in a comfortable chair with head and neck supports
which will help them to minimize movements.

At the beginning of the first treatment session, the individual resting motor threshold (rMT) for the right first
dorsal interosseus muscle (FDI) of each participant will be determined by the Principal Investigator (PI)
according to procedures described by Silbert et al (2006). This is accomplished by placing the figure-of-
eight magnetic stimulating coil over the region of left motor cortex that controls right thumb movement. A
skin surface electrode will be placed over the belly of right FDI and a reference electrode will be placed
distally at the muscle tendon insertion point. The TMS coil will be oriented to induce current in the brain that
flows in a posterior-anterior direction over the hand area of motor cortex. Motor evoked potential (MEP)
signals will be recorded and amplified using an electromyographic (EMG) system built into the Magstim
Rapid² stimulator. rMT will be defined as the lowest stimulus intensity capable of eliciting at least 5 MEPs in
the contralateral FDI muscle with an amplitude of 50 µV or higher in 10 consecutive trials using an
incremental step size intensity of 1% maximal stimulation output. In this active rTMS condition of the study,
rTMS will be delivered at 110% of rMT or lower intensity.

The active rTMS coil will be positioned on the subject’s scalp using a 10–20 EEG-system that has been
proven to guarantee exact placement of the coil over the auditory cortex without the need of using magnetic
resonance or positron emission tomography (PET) guidance (Langguth et al, 2006 -- see Figure 5). The
spread of the electromagnetic field beneath the coil guarantees stimulation of all areas of auditory cortex
that contribute to tinnitus suppression or reduction.
A second subgroup of 42 subjects will receive active rTMS on the right side of the head during daily sessions for 10 consecutive work days, 1 or 10 Hz rTMS, stimulation intensity 110% or lower related to the individual resting motor threshold, with the figure-of-eight coil positioned over right primary auditory cortex. The coil will be placed in an adjustable stand that will hold it against the subject’s head in a fixed location. During rTMS sessions, subjects will sit in a comfortable chair with head and neck supports which will help them to minimize movements.

Procedures for determining resting motor threshold (rMT) will be as described above, but the TMS coil will now be positioned over right motor cortex and skin surface electrodes will be placed on the left hand. In this active rTMS condition of the study, rTMS will then be delivered to the right side of the subject’s head at 110% of rMT or lower intensity.

Subjects will complete the visual numerical scale (VNS) for self-rated tinnitus loudness before and after each session of rTMS. Tinnitus loudness matching will also be conducted before and after each session of rTMS. At the conclusion of 10 rTMS sessions, assessments of subjects’ hearing and tinnitus will be conducted and all questionnaires will be administered.

Control group -- 84 subjects will receive placebo stimulation during daily sessions for 10 consecutive work days, 1 or 10 Hz rTMS, placebo stimulation intensity 110% or lower related to the individual resting motor threshold, with figure-of-eight coils positioned over left or right primary auditory cortices.
A subgroup of 42 subjects will undergo the same procedure to determine left motor cortex/right thumb rMT as described above for the treatment group. A second subgroup of 42 subjects will undergo the same procedure to determine right motor cortex/left thumb rMT as described above for the treatment group.

After the PI establishes rMT, and positions a placebo coil against the subject’s head, he will set the stimulation intensity on the Magstim unit. The Audiologist will then be summoned to observe the subject while pulses of placebo stimulation are delivered to one side of the subject’s head during one session.

The coils will be positioned using a 10–20 EEG-system that has been proven to guarantee exact placement of the TMS coil over the auditory cortex without the need of using magnetic resonance or PET guidance (Langguth et al, 2006 – see Figure 5).

Placebo stimulation will be provided by a Magstim Rapid² “sham coil.” These coils are identical in appearance to the coil used for active rTMS. The placebo coils produce the same sounds and sensations as the active coil. Therefore, subjects will not be able to determine if they are receiving active rTMS or placebo rTMS.

Subjects will complete the visual numerical scale (VNS) for self-rated tinnitus loudness before and after each session of rTMS. **Tinnitus loudness matching will also be conducted before and after each session of rTMS.** At the conclusion of 10 rTMS sessions, assessments of subjects’ hearing and tinnitus will be conducted and all questionnaires will be administered.

**Follow-up**

All subjects will return to NCRAR 1, 2, 4, 13 and 26 weeks after the conclusion of their final rTMS session. At each of these appointments, assessments of subjects’ hearing and tinnitus will be conducted and all questionnaires will be administered.

After they complete the 26-week follow-up appointment, subjects who received placebo rTMS will be asked to return to NCRAR to participate in another series of rTMS sessions. Subjects will not be told that they first received placebo rTMS and they will not be told that the next series of sessions will be active rTMS. Subjects who choose to participate in additional rTMS sessions will follow procedures described previously for the Treatment group.

**Subject safety and adverse effects:** Subjects will be instructed to contact the Study Physician or the PI (work, home, cell phones, pager and email addresses will be available) in case of any adverse effects from the procedures. At that time, a course of action will be determined including reassurance and/or a physician examination and/or medical treatment at the emergency department and/or discontinuation of treatment and withdrawal from the study.

**Roles and Responsibilities of the Medical Monitor**

Sarah M. Theodoroff, Ph.D., CCC-A, who is credentialed and privileged at the Portland VA Medical Center, will serve as Medical Monitor for the study. Dr. Theodoroff will observe all volunteers during the remainder of the clinical trial, maintain communication with members of the study team, and monitor the safety and performance of all study participants.

**Safety of rTMS**

Applied under previously published safety guidelines (Wassermann, 1998), rTMS has been proven to be safe and well tolerated by subjects in a broad range of studies for conditions including depression (Gershon et al, 2003), some forms of epilepsy (Tergau et al, 1999; Kinoshita et al, 2005), post-traumatic stress disorder (Grisaru et al, 1998), auditory hallucinations in schizophrenia (Hoffman et al, 2000), stroke (Takeuchi et al, 2008), movement disorders such as Parkinson’s Disease (Khedr et al, 2006) and dystonia (Lefaucheur et al, 2004). As described in the Background section of this application, rTMS has also been used safely in numerous studies around the world involving subjects with tinnitus.
The risk of greatest concern with TMS is the induction of seizures. The neurophysiological excitability induced even by focal rTMS can spread beyond the site of stimulation, causing seizure activity. In most instances, seizures have been relatively localized, causing only movements of the hand or arm, for example. Generalized seizures leading to loss of consciousness have also been observed, however. The risk of seizures is influenced by a number of factors, the most important of which is the state of the subject’s brain. Seizures are far less likely to occur in normal, healthy subjects than in subjects with neurologic disease such as stroke, brain tumor, or Multiple Sclerosis. For this reason, most studies – including this one – employ strict guidelines in an attempt to exclude subjects with neurologic disorders or other conditions that would be associated with an increased risk of seizures (see Exclusion Criteria).

**Data Collection**
This clinical trial will collect epidemiological data, information from medical exams and histories, scores on self-report questionnaires associated with tinnitus and psychological assessments, evaluations of audiometric thresholds and tinnitus characteristics. Data will be collected and recorded by the Study Physician and the Study Audiologist.

**Information Management**
Electronic data will be kept in a database that resides behind the VA firewall at: S:\NCRAR\Folmer\rTMS. Hardcopy data and records (including ICFs, etc.) will be stored in in a locked file cabinet in a locked office (Building 103/104 P5F-175).

Information (e.g., research data) participants authorize to be kept for future use will be stored in the MIRB #3644 data repository.

**Data Management**
The Data Manager will collect all data from the clinical trial, organize and code it for data entry. A double data entry system will be utilized to minimize errors. The Data Manager will check the accuracy of recorded data and data entry, organize and summarize data for review by the PI and Biostatistician.

**Confidentiality**: All data entered into the database will be de-identified. Some measures are computerized and will automatically be stored in a database. These data will be de-identified also through use of a subject code system. The key code will be kept in a locked filing cabinet. The database will be kept on a VA server. A password is required to access the server. The statistician will see only de-identified data. Data accuracy of manually-entered data will be verified by double data entry. That is, following initial data entry, the Data Manager and Audiologist or PI will verify the data. Data verification will take place prior to any analysis of data.

**Data Analysis**
Outcome measures include a self-rated VNS score for tinnitus loudness, Tinnitus Handicap Inventory score, Tinnitus Functional Index score, Minimum Masking Level (MML), and matched tinnitus loudness re: a 1kHz pure tone. The primary endpoint for evaluation of efficacy of rTMS for tinnitus will be the change from baseline in the Tinnitus Functional Index score. Subjects receiving active rTMS will be compared to subjects receiving placebo rTMS using a two-sample t-test on each endpoint to evaluate the efficacy of rTMS therapy. Bonferroni adjustments will be used to ensure that the risk of one or more type I errors is controlled at the 0.05 test level.

Linear mixed models (Fitzmaurice et al, 2004) will also be fit to the entire dataset to statistically test treatment effects over the course of therapy and over the long term after therapy has ended. The mixed model approach allows us to adjust for the inherent correlation among repeated outcome measures on each subject using random intercepts and random time coefficients. In addition, we will test for potentially important confounders such as duration of tinnitus prior to enrollment, age, gender, employment status, other medications used, and other baseline measures. Interactions between important baseline characteristics and treatment condition will be evaluated to determine if certain patient subpopulations benefit more than others from rTMS therapy. The mixed modeling approach will allow us to describe
average change in tinnitus severity/loudness over time and across demographic categories for each treatment assignment.

The following factors will be analyzed for all subjects who complete the study:

**Subject factors (independent or predictor variables):**
1. Duration of tinnitus prior to study
2. Residual inhibition duration
3. Age
4. Presence or absence of any other medications during this trial (yes/no)
5. Marital status
6. Gender
7. Employment status
8. Use of amplification or sound generating device (yes/no)
9. Other chronic illness (> 6 months) resulting in multiple physician visits (yes/no)
10. Beck Depression Inventory score
11. State Anxiety Inventory score
12. Pure-tone air conduction hearing threshold averages (500Hz, 1kHz, 2kHz, 4kHz and 8kHz)
13. Minimum Masking Level (MML)

**Outcome measures (dependent or criterion variables):**
1. Tinnitus Functional Index score
2. Self-rated VNS score for tinnitus loudness
3. Matched tinnitus loudness re: a 1 kHz pure tone
4. Tinnitus Handicap Inventory score

Step 1: Pearson r correlation analysis using SPSS to determine which subject factors are correlated ($r > 0.2$) to the outcome measures.
Step 2: Determine co-linearity between subject factors. Those with high co-linearity ($r > 0.8$) will be considered redundant and one will be eliminated from the regression model.
Step 3: Perform multiple linear regression using SPSS.

Weighting of the subject factors will be used to generate hypotheses for future studies on optimizing patient selection for rTMS treatment. The same information will be useful in the design of clinical protocols using rTMS for tinnitus relief.

**Non-compliance:** This is an intent-to-treat study investigating the effects of rTMS therapy on tinnitus when applied to a clinically relevant population. However, any therapy runs the risk of subject non-compliance due to perceived effect of the assigned therapy or other subject characteristics. Non-compliance does not interfere with the ability to identify the clinical utility of rTMS therapy, which is suitably addressed with an intent-to-treat analysis. However, inferences regarding the causal association between rTMS and tinnitus may be biased by non-compliance. Non-compliance will be directly measured for each subject as the number of therapy sessions attended and completed. Subjects will be allowed to miss only one of ten TMS sessions. Reasons for non-compliance will be documented for each subject. Average compliance will be summarized by randomization group and demographic features (age, gender, ethnicity) and baseline tinnitus severity and loudness, and compared non-parametrically using the Kruskal-Wallis test. Logistic regression models will be fit to the session counts to determine important predictors of compliance with the assigned treatment conditions. We will also measure the extent to which non-compliance results from concurrent tinnitus self-rated loudness at each session. Since session counts and tinnitus severity/loudness are measured repeatedly on each study subject, coefficients will be estimated using generalized equations (Fitzmaurice et al, 2004). The resulting regression coefficients are the population-averaged log odds ratio of therapeutic session attendance given concurrent tinnitus severity/loudness and treatment allocation. This analysis framework will allow us to estimate the acceptability of the treatment protocol, as well as to measure important predictors of compliance that will estimate the feasibility of utilizing rTMS with novel populations.
We will evaluate two alternatives to the intent-to-treat analysis for assessing the causal relationship between rTMS and tinnitus severity/loudness. The first alternative is a “Per-Protocol” analysis that restricts analysis to subjects who are compliant with the therapeutic protocol. The second alternative is an “As-Treated” analysis that adjusts analyses of the effects of treatment condition by the number of rTMS sessions actually completed. Since this analysis involves a certain degree of self-selection into treatments actually received, we will adjust for self-selection bias in the treatment condition actually received using propensity score methods (Rubin, 2001). Two subjects with the same propensity scores are effectively identical with respect to those observed features (such as demographics and baseline tinnitus severity/loudness) that determine treatment received, and that may confound estimates of the causal relationship between the treatment conditions and outcomes. These analyses, in addition to the intent-to-treat analysis, will be performed for each outcome to test the different analysis procedures used to address non-compliance.

**Loss-to-follow up:** Missing outcome data due to loss-to-follow up is a serious concern in any longitudinal study. Loss-to-follow up does not necessarily pose any technical problems for the statistical analysis framework to be used (other than loss of information), but it can cause serious errors in the conclusions drawn if the mechanisms for attrition are not carefully considered. If loss-to-follow up is a direct result of tinnitus severity that is otherwise effectively mitigated by rTMS, then the estimated effect of rTMS on each outcome may be underestimated. This is because placebo subjects suffering from tinnitus may be more susceptible to drop-out and less represented in the longitudinal outcome measurement data. Such a situation is described as “non-ignorable missingness,” and inferences regarding the estimated effect size must be subjected to careful sensitivity analysis.

Several methods can be used to evaluate and address subject dropout. Dropouts will be compared to complete cases on all baseline characteristics, including baseline tinnitus severity/loudness, demographic characteristics, treatment condition, and previously observed tinnitus outcomes during therapy. Logistic regression models will be fit to determine the most important predictors of subject dropout. The goal is to determine the composition of the subject population that is most likely to complete the study, so that more efficient tracking can be implemented or so that subsequent large-scale trials can identify populations within which retention will be more effective. These procedures will allow us to determine the extent to which these randomized controlled trial findings can be generalized to future populations of treatment-seeking tinnitus sufferers.

Several imputation methods will also be considered to adjust for loss-to-follow up. Specifically, if loss-to-follow up is significant in this sample, we will analyze each outcome using an array of imputation methods and compare results to complete-case only analyses (Fitzmaurice et al, 2004). One imputation strategy commonly used is to assume that dropouts have the highest observed tinnitus severity or loudness level over the missing outcomes. Another imputation strategy is to use the last observed tinnitus outcome measure carried forward. More sophisticated methods such as propensity score multiple imputation will also be considered. This method uses the propensity score (defined as the probability of dropout at each time point) derived from the logistic regression model of subject dropout described above. Dropouts and complete cases are stratified on the propensity score, and missing responses for the dropouts are filled in by randomly sampling from the complete cases. The imputation is repeated 10 or more times, and the tinnitus data are modeled using the linear mixed model described above. The results are combined across iterations and standard errors of the regression coefficients are adjusted using methods described by Fitzmaurice et al (2004).
Study Organization and Management Plan

Organizational Chart:

- CO-INVESTIGATORS AND COLLABORATOR
- PRINCIPAL INVESTIGATOR
- STUDY PHYSICIAN
- STUDY AUDIOLOGIST
- DATA MANAGER
- BIOSTATISTICIAN
### Study Timetable

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<th>STUDY YEAR</th>
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<td>Project start-up functions, including IRB approvals</td>
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<td>Recruitment and screening of subjects</td>
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<td>Implementation of rTMS protocols and subject assessments</td>
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<td>Follow-up evaluations 3 and 6 months post-treatment</td>
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<td>Analyses, preparation of reports and publications, presentation of results</td>
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### References


Siebner HR, Filipovic SR, Rowe JB, Cordivari C, Gerschlager W, Rothwell JC, Frackowiak RS, Bhatia KP. Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. *Brain* 2003;126:2710-2725.


Additional References


