Effect of rTMS on resting state brain activity in tinnitus with maintenance rTMS for chronic tinnitus relief (3/11/2017).

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BIOMEDICAL/BEHAVIOURAL* RESEARCH PROTOCOL

UAMS

UAMS 4301 W. Markham, Little Rock AR 72205-7101

Effect of rTMS on resting state brain activity in tinnitus with maintenance rTMS for chronic tinnitus relief

PROTOCOL

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Primary location (sites): TMS laboratory, 6th floor Bio Med II, UAMS

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ABBREVIATIONS AND DEFINITION OF TERMS

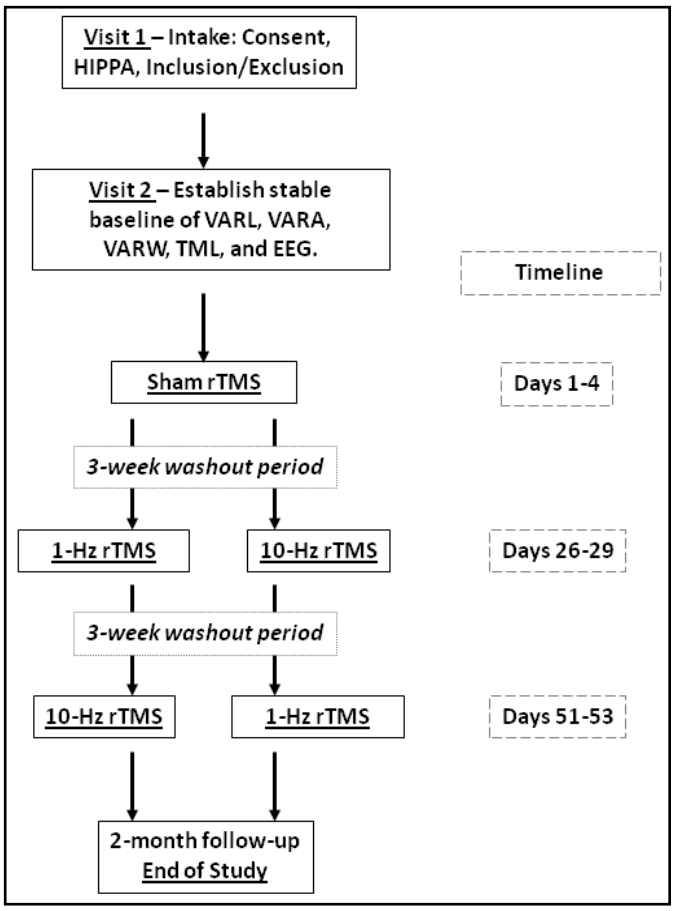
BA 22	Brodmann Area (secondary auditory cortex)
BDI	Beck Depression Inventory
C	Centigrade
cms	centimeters
CT	computed tomography
dB	decibel
ECT	electroconvulsive therapy
EEG	Electroencephalography
EMA	Ecological Momentary Assessment
EMG	electromyography
EMG	jaw movement
EOG	eye movement
Hz	hertz
I/R	forced-choice measure of improvement or relapse
kHz	kilohertz
kΩ	kiloohm
MEP	motor evoked potential
MRI	magnetic resonance imaging
msec	millisecond
MSO	maximum stimulator output
MT	motor threshold
µvolts	micro volts
OSHA	Occupational Safety and Health Administration
rTMS	repetitive transcranial magnetic stimulation
STAI	State Trait Anxiety Inventory
Secs	seconds
TAP	Tinnitus Assessment Procedure

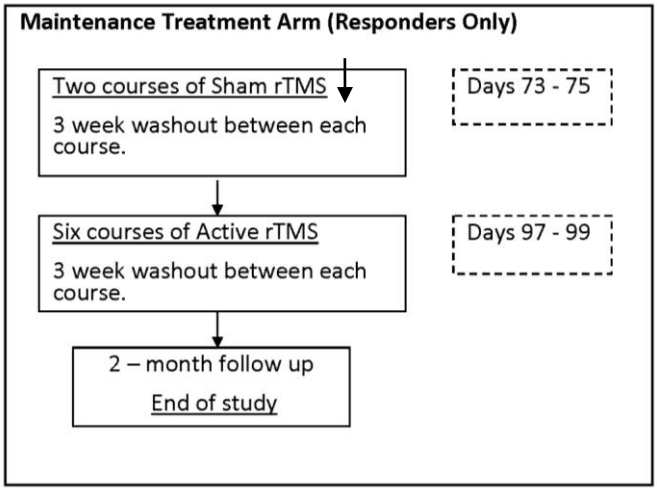
TASS	Tinnitus Adult Safety Screen
TCD	thalamocortical dysrhythmia
THI	Tinnitus Handicap Index
THQ	Tinnitus Handicap Questionnaire
TFI	Tinnitus Functional Index
TLM	Tinnitus Loudness Matching
TMS	transcranial magnetic stimulation
TSI	Tinnitus Severity Index
VARA	visual analogue rating of annoyance
VARL	visual analogue rating of loudness

PROTOCOL SUMMARY

This pilot study will use low and high frequency, repetitive transcranial magnetic stimulation applied over temporal cortex to treat tinnitus (1 and 10 Hz rTMS). Tinnitus refers to phantom sound perception (ringing in the ears). All participants must sign a written informed consent and meet inclusion/exclusion criteria designed to minimize risks associated with rTMS. It is well known that both 1 and 10 Hz rTMS can be used safely in carefully screened patients to relieve tinnitus temporarily [1-5]. About 50% of the people treated for one to two weeks achieve reduction in tinnitus that lasts from one to two weeks. This study will compare the effect of one week of active treatment (both 1 and 10 Hz) to one week of sham treatment using a realistic sham procedure[6]. Further, the study will compare whether the expected percentage of treatment responders is different among 1, 10 and sham rTMS. Finally, we examine if follow-up or maintenance rTMS can extend the duration of the effect. Cognitive function will be monitored throughout the study as a safety precaution. Tinnitus and associated co-morbidities like depression and inattention will be measured as outcome variables using rating scales and standardized questionnaires. Subjects will be retested on all behavioral pre-test measures 6 months after their last active rTMS session. The following diagram summarized study procedures.

Study Schema





BACKGROUND AND SIGNIFICANCE.

This project uses commercially available equipment purchased from Magstim. It uses a Magstim Super Rapid^2 Stimulator and an air-cooled 70 mm figure of eight stimulating coil. (The coil is called a figure-of-eight coil because the wires in the coil are wrapped in the shape of an 8 to focus the magnetic field.) A 70 mm air-cooled sham coil manufactured by Magstim to look and sound like the active coil but attenuate the magnetic field to a non-active level is being used. These are standard coils used in many rTMS treatment studies. The stimulator is approved for stimulating peripheral nerves for diagnostic purposes and rTMS of cortex recently gained approval for treating clinical depression. It will be used in this study to stimulate neurons in temporal cortex in order to decrease tinnitus perception.

This study examines the efficacy of using low and high frequency magnetic stimulation (1Hz – one pulse per second and 10 Hz – 10 pulses per second) to reduce tinnitus loudness similar to a previous investigation [5]. Khedr et al.[5;7] used low- and high-frequency stimulation to treat tinnitus in 66 tinnitus patients (i.e., 1500 pulses over temporoparietal cortex at 1-, 10-, and 25-Hz and 100% of MT x 10 days versus sham stimulation). Patients were followed for 4 months and 1 year. Each stimulation frequency except for sham was associated with lasting improvement on the tinnitus handicap questionnaire but not the tinnitus masking procedure. The highest percent of improvement (75%) was observed in the 10-Hz group, followed by the 25-Hz (60%), and the 1-Hz group (43%). Whereas all stimulation frequencies could improve tinnitus, we do not know if one is more effective because subjects only received one frequency of stimulation.

This study was important in revealing how "excessive activity in the temporal cortex of patient with tinnitus" (which was fundamental to our original protocol) may have misled investigators into believing that it was critical to use low-frequency rTMS to inhibit this activity. It now seems more important to understand how different frequencies of rTMS all work to suppress tinnitus and which are more effective. Also, we do not know of persons who failed one frequency of stimulation would have responded to another or if one frequency would be more effective for a given patient than the other. We aim to block randomize subjects to sham, 1 and 10Hz rTMS to learn if one frequency is more effective than the other.

Tinnitus can be present in one or both ears. Tinnitus can either be equal in both ears or unequal between ears [8]. Tinnitus is thought to be maintained by excessive neural activity in temporal cortex [9]. Increased activation leads to higher metabolic activity which can be measured using PET scans [10-12]. Low frequency rTMS at 1Hz has been shown to decrease neural activity beneath the stimulating coil when applied repetitively (rTMS) over several treatment applications [13-15]. Many studies, including those in our own lab, have shown that low frequency rTMS (1Hz) applied for 30 minutes over temporal cortex for 5 consecutive days can reduce tinnitus loudness in approximately 50% of people who receive rTMS [1-4;16-19]. The major problems are 1) determining where to target rTMS for treatment and 2) the fact that tinnitus often returns to its original loudness in most patients in one or two weeks after rTMS stops, and 3) whether one frequency of stimulation will work better than the other for a given patients. In previous studies, we found that some patients with tinnitus had obvious metabolic asymmetries in their PET scans between the two temporal lobes; however, many did not. The problem is that it is unclear where to target rTMS in patients who do not have clear PET asymmetries.

Additionally, the number of patients who can identify an ear with louder tinnitus is roughly equal to those who cannot. Finally, we found that it was feasible and safe to use maintenance rTMS to increase the durability of treatment in a patient who show an initial response to active rTMS [20]. Maintenance treatment consisted of 1-3 additional rTMS sessions on consecutive days when tinnitus returned to its baseline loudness. This pilot study compares the efficacy of active rTMS (1 and 10 Hz) with a realistic sham or placebo rTMS procedure. We aim to learn how rTMS should be targeted for treatment by using a decision flow chart to guide the application of rTMS as follows:

1. rTMS will be targeted to one hemisphere based on the following flow chart:
    a. rTMS will be targeted to the temporal cortex opposite the ear with loudest tinnitus.
    b. failing this, rTMS will be targeted to the left temporal cortex - a treatment option used in several studies [3].

Participants will receive sham, low and high frequency active rTMS treatment according to a block randomized schedule. This ensures every participant has an equal chance of benefiting from rTMS because we expect that 50% of patients will fail to respond to active stimulation. It also allows us to compare stimulation frequencies within subjects. Persons whose tinnitus is decreased by active stimulation, will proceed to a maintenance rTMS treatment arm (either 1 or 10 Hz which ever produced the lowest ratings of tinnitus loudness) that delivers courses of sham (n=2) and active (n=6) maintenance treatment, with three week washout periods between each course of treatment..

INFORMATION ABOUT RISK DETERMINATION IN TMS STUDIES.

Both the sponsor (UAMS) and the IRB must make a decision about whether this study is one of non-significant risk (NSR) or significant risk (SR). In May of 2008 the director of the TMS laboratory at UAMS, Dr Mennemeier, and members of the Research Support Center (RSC) including Drs Thomas Wells and Raymond Anderson held a conference call with Dr Bernard Berne, M.D., Ph.D. who is the Medical Officer of the Restorative Devices Branch Division of General, Restorative, and Neurological Devices (HFZ-410) in the Office of Device Evaluation Center for Devices and Radiological Health at the FDA. Dr Berne oversees studies that use TMS. Dr Berne provided documents about SR and NSR determinations for medical device studies using rTMS. These documents are included in the appendix. They state the following:

- According to FDA regulations and guidance, the sponsor (UAMS) is initially responsible for determining whether medical device investigations are SR or NSR. Sponsors should make their own SR/NSR determinations for their proposed investigations and then ask the investigational review boards (IRBs) at all investigational sites to review and confirm their determinations.

- The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.

- The IRBs should make the SR or NSR determination about a study by reviewing relevant information at a convened meeting. This information includes the description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. If it so desires, an IRB may consult with FDA when making its determination for studies that involve the use of rTMS (Dr Berne's phone 240 276-3735 & fax 240 276-3602).

- The documents listed a number of items to consider with NSR and SR studies. I listed these items below and provided answers/responses for the IRB's consideration.

ITEM 1. REGULATIONS UNDER 21CFR812.3(M) STATE A **SR DEVICE** MEANS AN INVESTIGATIONAL DEVICE THAT:

- Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject.
    - The device used in this study is not an implant.
- Is purported or represented to be for use supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject.
    - The device is not for use in supporting or sustaining human life.
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.
    - The device as used in this study is for use only in learning how asymmetries in cortical metabolism are influenced by rTMS and whether symptom and cognitive improvement relate to change in cortical activation. The data are also used to determine if the device is functioning for its intended purpose and to determine the optimal operating parameters.
- Otherwise presents a potential for serious risk to the health, safety or welfare of a subject.
    - In general, studies using low frequency (1Hz) rTMS have a good margin of safety and most are considered NSR when used in accordance with established guidelines as does our study. The following considerations pertain to NSR device investigations.

ITEM 2. SOME TMS STUDIES MAY BE **NSR DEVICE INVESTIGATIONS** BECAUSE PUBLISHED AND UNPUBLISHED INFORMATION FROM SIMILAR STUDIES DEMONSTRATES THAT THE RISK TO HUMAN SUBJECTS IN THE PROPOSED STUDY WILL BE NONSIGNIFICANT. The following information shows that the procedures used in our study have been well-tolerated when used in other studies.

- Our proposal uses low and high frequency rTMS (1 and 10 Hz) with an intensity and amount of stimulation that falls within a range of parameters considered safe for use in human subjects [21-23]. (see also section on risk later in the protocol for a table listing the acceptable parameters).

- Low and high frequency rTMS, i.e., , has been well tolerated in literally 100s of studies of both normal subjects and in clinical populations [24-26]. There has only been one report of a seizure in a healthy subject during 1Hz rTMS [27]. It is unclear if this was, in fact, a seizure or a syncopal episode [28].

- One study compared the efficacy of low and high frequency rTMS in moderate-sized samples of patients with tinnitus (N=66 patients) [5]. This study compared 1, 10 and 25 Hz stimulation with sham stimulation. Each stimulation frequency besides sham was associated with improvement. There was a trend toward greater efficacy with 10 Hz stimulation and perhaps a longer duration of treatment. All stimulation frequencies were safely used with no adverse events reported.

- We recruit male and female participants with tinnitus who are between the ages of 19-89 years old. There is no age limit for TMS to our knowledge. Several rTMS treatment studies of depression have included patients up to 74, 75 and 89 years of age without indication that advanced age placed them at greater risk for complication [29-31].

- Five published studies, including two from our laboratory, have already used PET to guide the application of 1-Hz rTMS, at comparable levels of intensity and number of pulses, delivered over areas of increased cortical activity in the temporal lobe in patients with tinnitus [1;2;4;17;32;33]. Two large studies targeted 1Hz rTMS over left temporal cortex without guidance by either PET or anatomical imaging [3;5]. Over 100 patients were tested in these studies. There has been no indication of detrimental change in cognition or mood and no report of seizure resulting from either high or low frequency rTMS in these studies. We have uniquely examined change in PET following rTMS [4] and found a reduction in metabolic activity beneath stimulating coil.

- Regarding the use of follow-up or maintenance rTMS treatments for tinnitus, one study applied 1Hz rTMS in daily sessions lasting 4 weeks in a patient with tinnitus [17]. Another case study applied 7 maintenance sessions of 1Hz rTMS as tinnitus returned. Maintenance treatment was well tolerated in both studies and it increased the length of time before tinnitus returned [20]. One study of six patients applied 1Hz rTMS every day for a total of 10 days over two weeks [33]. No adverse effects were reported.

- Maintenance treatment has been used safely in rTMS studies of depression which place subjects at greater risk for seizure than does our study because stimulation is delivered at much higher frequencies and greater intensities than we propose. One study (n=38) examined the safety of twice-daily sessions of rTMS for two weeks (10-Hz rTMS delivered over the prefrontal cortex) followed by once-daily sessions for 6 weeks [34]. A second study (n=7) used once per week maintenance rTMS sessions (high-frequency rTMS delivered over the prefrontal cortex) [35]. A third study (n=15) [36] used maintenance rTMS sessions 1–3 times per week from between 6 months to 6 years (patients in the study received an average total of 257 rTMS sessions – by contrast we are proposing up to 18 maintenance sessions). In general, these studies revealed improvement in mood

after active but not sham rTMS, no adverse effects were found in terms of neuropsychological test performances or seizure.

ITEM 3. SOME TMS STUDIES HAVE UNIQUE CHARACTERISTICS THAT IMPOSE RISKS THAT OTHER STUDIES LACK WHICH MAY MAKE THEM **SR DEVICE INVESTIGATIONS.** These characteristics are listed below with are responses to them.

- Some studies may involve specific patient populations, such as children, post stroke or epileptic patients, which may be at higher risk than others.
    - We do not enroll high risk patients. Our exclusion criteria and screening instruments are specifically designed to exclude persons at increased risk.
- Some studies may utilize devices with new features that FDA has not previously evaluated for investigational use.
    - The stimulator and coil(s) used in this study are commercially available and were purchased from a leading company (MagStim). This equipment is used commonly in rTMS studies.
- Some studies may stimulate portions of the brain that have never been stimulated before.
    - We stimulate temporal cortex in patients with tinnitus which is the standard procedure in most studies (see review by [3]).
- Some studies may involve rTMS treatments of clinical disorders that few or no publications have previously described.
    - The review by Rossi [3] shows that many studies have now applied low frequency rTMS over temporal cortex in patients with tinnitus.
- Some studies may lack personnel who have adequate training or experience in the administration of TMS or in seizure monitoring and management procedures.
    - Our group has published four manuscripts on the use of rTMS to treat tinnitus [4;19;20;37]. The PI and Dr Mennemeier worked collaboratively with two other experts in rTMS to develop this protocol - Dr Kimbrell (Psychiatry, UAMS) who trained in TMS at the NIH and Dr Triggs (Neurology, University of Florida) who trained Dr Mennemeier and has a long career in TMS. Dr Berne's documents state that appropriate risk precautions for seizure management include a study physician or nurse trained in seizure management be present during all active rTMS sessions. Sham rTMS sessions do not require the presence of a nurse because there is no active stimulation and no possibility of seizure. Single pulse TMS delivered during EEG recording does not require the presence of a nurse because it is not rTMS (repetitive) and because it is an assessment rather than a treatment procedure. Our study physician (Dr Dornhoffer) and nurses (from the Clinical Research Center at UAMS) will be trained in seizure precautions and management by Dr Kimbrell. A trained study physician or nurse will be present during every active rTMS session. An active rTMS session will not be conducted unless a trained physician or nurse is present.
- The investigational plans of some studies may lack procedures and exclusion criteria that will adequately prevent the inadvertent enrollment of subjects who are at increased risk of injury, seizure or other potential complications of TMS.

  - As recommended by Dr Berne, we use the Transcranial Magnetic Stimulation Adult Safety Screening Questionnaire (TASS, in appendix) to evaluate participants prior to TMS. Our exclusionary criteria and screening methods are specifically designed to exclude subjects with any factor know to increase the risk of injury, seizure or complications due to rTMS.
- The investigational plans of some studies may lack adequate seizure monitoring and management procedures.
  - Our monitoring procedures during rTMS are comprehensive including electromyographic recording of the hand contralateral to stimulation, video monitoring, and behavioral monitoring by trained study personnel during and after rTMS.
- The investigational plans of some studies may lack procedures that will adequately minimize the risk of transient or permanent hearing loss.
  - Our study participants receive audiometry before and after rTMS, they wear foam ear plugs during rTMS, and we monitor subjects to ensure that ear plugs stay in place and we tell subject to inform us if an ear plug falls out. rTMS is stopped if an ear plug falls out.
- The investigational plans of some studies may not adequately comply with published recommendations and guidelines that minimize the risks of TMS.
  - Our study parameters are compliant with published recommendations [21].

STUDY OVERVIEW

1. All subjects must sign an informed consent, pass screening, and meet inclusion/exclusion criteria. The study procedures can be summarized as follows:

PLEASE NOTE THAT WHILE ALL STUDY PARTICIPANTS ARE EXPECTED TO TAKE PART IN THE FIRST 15 VISITS, PERSONS WHO FAIL TO RESPOND TO TREATMENT WILL COMPLETE A 2-MONTH FOLLOW UP VISIT WHILE THOSE WHO RESPOND POSTIVELY TO TREATMENT GO ON TO A MAINTENANCE TREATMENT ARM. THE MAINTENANCE TREATMENT ARM IS DESIGNED TO COMPARE SHAM AND ACTIVE MAINTENANCE TREATMENTS AND TO DETERMINE IF ADDITIONAL MAINTENANCE TREATMENT CAN EXTEND THE DURATION OF THE TREATMENT EFFECT. SUBJECTS IN THE MAINTENACE ARM WILL COMPLETE TWO COURSE OF SHAM MAINTENANCE TREATMENT FIRST FOLLOWED BY SIX COURSES OF ACTIVE TREATMENT. A THREE WEEK WASHOUT PERIOD SEPARATES EACH COURSE OF MAINTENANCE TREATMENT.

2. All participants enter a counterbalanced, placebo-controlled treatment that entails 15 visits to the TMS laboratory. Subjects are assigned to received sham treatment first (half at 1 and half at 10 Hz according to a counterbalanced schedule. Next, they are block randomized to receive either 1 or 10 Hz stimulation. A minimum of three weeks (21 days) will intervene each treatment. The rest period may be longer than 21 days. Details for active and sham stimulation are provided below under the study flow diagram.

A minimum dose of 4 rTMS treatments, within 5 days is acceptable. Minimum doses are established to accommodate the practical concern of scheduling participants who may have to miss a session. Sham stimulation is delivered first to avoid any potential carry forward effects of active treatment into the sham week. The order of 1 and 10 Hz active stimulation is counterbalanced across subjects to control order effects. Subjects are kept blind to active or sham treatment. Subjects are not informed which week is active or sham until after they receive both conditions.

3. All participants receive all types of treatment according to a block randomized schedule.

4. Only persons who respond to active treatment of one or both frequencies of rTMS - those who rate their tinnitus as improved (i.e., rating it as less loud, annoying or noticeable on analogue rating scales relative to baseline and/or indicating that it is better either at the end of the active treatment week or during the week following active treatment) will be entered into the maintenance treatment arm. These visits are also to the TMS laboratory. Maintenance treatment will consist of 3 active treatment sessions on consecutive days (a dose of 3 treatments within 5 days is acceptable). Patients will receive two, 3-day courses of sham treatment first followed by six, 3-day courses of active treatment with a three week washout period separating each course of treatment. Patients will be contacted for their tinnitus ratings (either via phone or e-mail) three times during the washout period (approximately 2, 9, & 16 days after maintenance treatment). Subjects will not be told what type of maintenance treatment they are receiving. .
5. Participants who do not enter the maintenance treatment arm will be re-assessed 2 months after their last course of either 1 or 10 Hz treatment. Subjects who enter the maintenance treatment arm will begin three weeks after day 53. Their 2-month follow up visit (i.e., rating scales, questionnaires and reaction time) will occur after subjects complete maintenance treatment.
6. Ten participants from our waitlist of people who volunteered for the study will be invited to receive four assessments of tinnitus and brain activity prior to entering the counterbalanced, placebo-controlled treatment described above in steps 2-5. As we can only treat a limited number of participants at a time, many are already waiting to be enrolled and treated. We will simply ask the participants who are waiting if they are willing to enter the pre-intervention assessment phase prior to receiving treatment.

The significance of this study is great. Tinnitus affects approximately 1 in 6 people in the US (men and women, adults and children) and there is no widely effective treatment. rTMS has already been shown to be a safe and effective at reducing tinnitus temporarily in about half of people tested [1-4]. This pilot study aims to learn if the percentage of responders can be increased and if the durability of the rTMS effect can be extended with maintenance rTMS.

HYPOTHESIS/ SPECIFIC AIMS

Observations and theories of tinnitus have posited a connection between tinnitus and over-activity of auditory processing areas in the temporal cortex [9]. Low frequency rTMS reduces neural activity beneath the stimulation coil [13;15]. We originally hypothesized that low frequency rTMS applied over temporal cortex would decrease tinnitus loudness and annoyance by

inhibiting neural activity. However, recent studies have shown that both high (10 and 25 Hz) and low (1Hz) frequency rTMS applied over temporal cortex reduces tinnitus[5]. Our revised hypothesis is that rTMS works by "normalizing" thalamocortical rhythms that promote conscious awareness of tinnitus perception. We will use EEG recordings collected at baseline and following each treatment week to examine change in thalamocortical rhythms. We want to go farther than the Khedr et al study by examining whether 1 versus 10 Hz stimulation has a greater effect on tinnitus and whether individual subjects differ in response to 1 and 10 Hz stimulation.

Our aims and sub-aims are to determine:

Specific Aim 1: Conduct a double blind, placebo (sham)-controlled study with treatment crossover to compare how standard, sham and active maintenance rTMS alter tinnitus perception and treatment duration.

1. We will determine whether active 1 Hz rTMS or 10 Hz stimulation is more effective than either sham rTMS or no treatment for altering tinnitus. **Primary outcome measures include questionnaires, subjective measures of tinnitus loudness, annoyance, and awareness and a forced-choice measures of improvement/worsening, and physically anchored measures of tinnitus frequency and loudness.**
    a. If rTMS alters cognitive processing relative to sham. We will examine changes in memory (the three words at 5 minutes test), manual dexterity (the finger tapping test), and coding (the digit symbol test) before and after each treatment condition.
    b. If rTMS alters depression and anxiety relative to sham. We will examine change in the Beck Depression Inventory and State Trait Anxiety Inventory before and after each treatment condition.
    c. If rTMS alters thalamocortical oscillations in the resting state EEG and in brain connectivity on fMRI after treatment and in association with tinnitus improvement. (see appendix for each measure).
2. ***Sub-aim: Explore which patient characteristics predict a treatment response***. Subjects will be divided empirically into those who respond to treatment and those who do not based upon a series of predictors that include: 1. tinnitus characteristics (frequency, pitch, loudness and chronicity scores on standardized questionnaires (Tinnitus Handicap Inventory [THI], 2, Tinnitus Handicap Questionnaire THQ measures of hearing loss, tinnitus loudness matching and hyperacusis and on the Beck Depression Inventory (BDI), and State Trait Anxiety Inventory (STAI), 3, risk factors for tinnitus including age, race/ethnicity, hypertension, smoking history, and loud noise exposure, 4, EEG measures of spectral power and coherence and 5, change in resting state fMRI.
3. We will determine if maintenance treatment can improve the durability of 1 or 10 Hz rTMS. We compare change on analogue ratings of tinnitus before and after rTMS. Additionally, we will count the number of days from the end of active treatment until tinnitus returns and compare them across maintenance sessions (i.e., sham versus active maintenance rTMS).

Aim 2: Explore mechanisms by analyzing change in resting state thalamocortical oscillations and connectivity after treatment and in association with tinnitus improvement.

1. We will determine how brain oscillations on EEG and brain connectivity on fMRI change from baseline to the completion of the sham, 1 Hz, and 10Hz treatment weeks.

STUDY POPULATION:

Recruitment plan: Eighty subjects, male and female aged 19-89 years old, will be enrolled to obtain 30 subjects that complete the study design endpoints. Following a press release of a recent publication [20], over 100 people contacted either Dr. Dornhoffer or Dr. Mennemeier directly to express an interest in participating in our rTMS study. Some of these subjects already participated in an earlier TMS protocol and expressed interest in returning for future studies. We plan to recruit patients from both of these sources. Finally, we will contact study participants who already completed the 6 month follow up for the earlier version of this study protocol and offer them the opportunity to participate in the 10 Hz crossover trial. They will be required to go through the informed consent process again and to complete and pass all inclusion and exclusion criteria again. They will not be required to complete the active 1Hz and sham stimulation conditions again. Only the 10 Hz and maintenance sessions will be offered to subject who completed an earlier version of this protocol which compared 1Hz rTMS and sham stimulation. Subjects who enrolled in the study prior to March 2012 and are in open label maintenance treatment will continue to receive open label maintenance treatment under this protocol

CONSENT PROCESS AND INCLUSION/EXCLUSION CRITERIA.

1. All subjects will be thoroughly informed of the risks associated with the procedures and an approved, written informed consent will be obtained. The consent process will take place in a quiet and private room in a location that is convenient for the subject and the person authorized to obtain informed consent such as a research office in Bio Med II or the Stephens Building.

Description of the informed consent process: Potential participants will be given adequate time to read the written informed consent. The person obtaining consent will thoroughly explain to the prospective participant each element of the protocol and outline the risks and benefits, alternate treatments, and follow-up requirements of the study. The information will be given in language understandable to the participant. Prospective participants will be given sufficient opportunity to consider whether or not to participate. Participants will be given an opportunity to ask questions about the protocol. Participants will be encouraged to take the consent home to review and to obtain family/friends input prior to signing consent. Participant privacy will be maintained. All participant questions will be answered. No coercion or undue influence will be used in the consent process. No research related procedures will be performed prior to obtaining informed consent. All signatures, dates, and times will be obtained. A copy of the signed consent will be given to the subject. A copy of the consent will be sent to Medical Records.

2. All subjects must meet Inclusion Criteria: All subjects must report experiencing the presence of their phantom auditory perception for at least 6 months and must meet the following additional criteria:
    - Sign the informed consent to participate in this research study and sign the HIPAA form for this study.
    - Complete a Tinnitus Handicap Inventory (THI).

- Complete and pass the Transcranial Magnetic Stimulation Adult Safety Screen (TASS). (Appendix)
- Female subjects of childbearing age must take a pregnancy test to rule out pregnancy prior to participating in this study.
- Individuals taking SSRIs and benzodiazepines or for depression or anxiety related to tinnitus must be stable on doses of these medications for 3 months and not change medications during the course of the study.

3. <u>All subjects must not meet Exclusion Criteria: Individuals presenting with the following will be excluded from enrolling in the study because rTMS may not be tolerated by them.</u>
   A clinical, personal or history of
   - epilepsy, including a first degree relative diagnosed with epilepsy
   - head injury that resulted in the loss of consciousness for more than 10 minutes
   - aneurysm, stroke, previous cranial neurosurgery, diagnosed neurological or major psychiatric disorders (excluding depression or anxiety related to tinnitus),
   - ferromagnetic metal implants in the head or neck,
   - pacemaker (because of possible interference with magnetic field)
   - pregnancy (or the possibility of pregnancy)
   - medications that lower seizure threshold or reduce cortical excitation (i.e., tricyclic antidepressants, bupropion or anticonvulsants)
   - significant neurological disease, acoustic neuromas or glomus tumors, active Meniere's disease, or profound hearing loss (>90 dB at 4000 Hz)
   - Bipolar Disorder.
   - Patients who cannot speak English will be excluded because they will not be able to complete questionnaires and may not understand instructions.
   - Failing the claustrophobia screening questionnaire (exclusionary for fMRI only).
   - Abnormalities present on an acquired or existing CT or MRI image of the head.

   Persons under 19 years of age (children) are excluded because the effect of rTMS on children is unknown, in contrast to adults, who have been well studied.

4. <u>Subject withdrawal criteria for all subjects.</u>
   - Subjects experiencing a serious adverse event (SAE) related to rTMS would be withdrawn from the study by the PI. (Procedures for reporting an SAE are described below.) The PI would inform the participant of the decision and reason for withdrawing them from the study. Serious adverse events would include, but are not limited to, a seizure or an event mimicking a seizure, hearing loss, or excessive complaints of pain related to rTMS.
   - Persons experiencing SAE would be withdrawn from the study.
   - Participants who are withdrawn from the study would be replaced by selecting the next person on the list or next suitable replacement until a study population of 30 subjects completes the study or an enrollment of 80 is reached.

STUDY PROCEDURE AND LOCATION(S)

Screening: Screening and a review of existing medical records will occur for new participants. For subjects being seen for tinnitus by an outside physician, records will be reviewed by Dr. Dornhoffer to determine if diagnostic screening criteria are met. Subjects who participated in previous rTMS studies for tinnitus will not be required to be seen again in the Hearing and Balance Clinic but they must pass the screening questions and measures and meet inclusion and not meet exclusion criteria again. If the subject meets all inclusion and no exclusion criteria, he/she will complete all pretest assessments and baseline measures**.**

Pre-test assessments. (scheduling by appointment prior to beginning study procedures)

a. Baseline testing: (35 - 50 minutes). Location is a research office in the Stephens Building or in the TMS research lab in BioMed II.
   i. Tinnitus Handicap Questionnaire (THQ)
   ii. Tinnitus Handicap Inventory (THI)
   iii. Beck Depression Inventory (BDI)
   iv. State Trait Anxiety Inventory (STAI)
   v. Rating of tinnitus loudness (0-100)
   vi. Rating of tinnitus annoyance (0-100)
   vii. Ratings of tinnitus awareness (0-100)

Pharmacy requirements:
One-time Pharmacy cost for on-site Ativan, 2mg vial – to stock lab for the safety plan which is outlined below under risk prevention. The dose will be kept in a locked refrigerator that is locked to a cabinet the TMS laboritory - room 654-2, on the 6th floor of BioMed II. (see letter in appendix from Jennifer Roberts).

rTMS Treatments: All rTMS and sham treatments will take place in the TMS laboratory, room 654-2, on the 6th floor of BioMed II.

INVESTIGATIONAL PLAN

STUDY FLOW DIAGRAM

PARTICIPANT RECRUITMENT. (As described above).

VISIT 1. (SCREENING)

- Obtain informed consent.
- Screen for inclusion/exclusion criteria.
- TASS - TMS Adult Safety Screening Questionnaire

- THQ - Tinnitus Handicap Questionnaire
- THI - Tinnitus Handicap Inventory
-
- Schedule behavioral testing. (scheduling by appointment must be completed prior to beginning study procedures).

VISITS 2: Training/Baseline Assessments. At the second study visit, participants will complete the Tinnitus Assessment Procedure and the Tinnitus Loudness Matching (TAP & TLM) and they will be trained in the laboratory on the following tests, which will be completed at baseline and during the study as indicated in the schedule of events, (these tests are included in Supplemental Documents). The VARL, VARA, VARAw, I/R, and THQ will be completed at least 2 times after the baseline assessment for training and to ensure stability in the data.

- VARL – visual analogue rating of tinnitus loudness.
- VARA – visual analogue rating of tinnitus annoyance
- VARAw – visual analogue rating of tinnitus awareness.
- THQ – Tinnitus Handicap Questionnaire
- TFI – Tinnitus Functional Index
- I/R – Improvement/Relapse measure
- The TAP and TLM are recorded as follows: TLM is part of an integrated, multi-dimensional tinnitus assessment package (TAP). The TAP runs on a PC with peripheral hardware. It is used to obtain objective measures of tinnitus and it includes co-morbidity assessments of hyperacusis, quality of life, and emotional disturbance; psychophysical measures of hearing threshold; and objective measures of tinnitus loudness using the TLM. The full TAP will be administered at baseline and during the 2-month follow-up. The TLM will be used repeatedly to assess tinnitus as indicated in the schedule of study events.
- EMA – Eccological Momentary Assessments - (sent via text to subject's smart phone between 9a.m. and 8p.m., 3 x per day for 1 day).

EEG recordings will be made at baseline, the end of each treatment session, and at 2 month follow-up. During EEG, data will be acquired using a 128 channel electrode cap (ES 301 eego mylab 128+24 channel EEG system with 128 channel wavegaurd cap from ANTneuro. Electrode impedances will be <30 kΩ. Mild abrasion of the scalp at each recording site and application of conductive gel is required to keep impedances low. Vigilance will be monitored online for alpha slowing, drop-out and the appearance of vertex sharp waves or sleep spindles. Spontaneous EEG will be recorded in two stages. First, spontaneous EEG will be acquired using the ES 301 eego mylab 128+24 channel EEG system with 128 channel wavegaurd cap from ANTneuro for a minimum of 12, 10 second epochs (120 secs) in both eyes open and closed conditions with subjects instructed to stare forward. Alpha frequency and mean amplitude will be examined in each epoch for consistency. Next, EEG will be recorded while single TMS pulses are delivered over temporal cortex. One hundred TMS pulses will be delivered using the MagStim figure-of-8 coil and stimulator- set to 80% maximum output. Each TMS pulse will be separated by a two-second interval. EEG will be recorded with eyes open and eyes closed (~3

minutes each). This procedure is referred to as EEG frequency tuning[38]. It is used in this protocol, to enhance EEG as a biomarker of change in thalamocortical oscillations. Averaging the EEG responses evoked by TMS helps to eliminate state-dependent fluctuations present in the spontaneous EEG. Additionally, spectral power and coherence of the EEG can be examined in direct response to a TMS pluse. Subjects will be seated in a slightly supine position. EEG signals will be acquired using the extended 10-20 system and linked mastoid reference. Impedances will be below 30 kΩ. Two electrode channels at the left inferior and right superior canthus will record eye movement (EOG) and one channel over the masseter muscle will record jaw movement (EMG). Records showing artifact at acquisition will be rejected and the epoch will be repeated.

Up to twenty subjects may be asked to have a resting state fMRI scan following the training/baseline assessment and following the sham and active rTMS treatment weeks depending on whether they meet eligibility criteria and the availability of funds for obtaining fMRI scans. Persons who meet inclusion and exclusion criteria but who are not receiving fMRI may be asked to have an MRI structural scan after the first or second study visit depending on eligibility and the availability of funds. The structural scan will be used to guide coil placement and performed only once. Resting state fMRI data will be acquired using a scanner located in the Brian Imaging Research Center in the Psychiatric Research Institute at UAMS. Subjects will be escorted to this facility by study staff. Procedures for a resting state fMRI are identical to an MRI obtained for clinical purposes. Each subject will lie still in the scanner for approximately 20-40 minutes while the image is acquired. They are instructed first not to let their mind wander but to stay focused an activity like breathing or keeping their eyes steady. Second, a scan is acquired while subjects perform a task that focuses attention. The subject's head is secured by a head holder to prevent motion artifact in the scan. The subject wears head phones to mitigate the noise of the scanner and to allow communication with study staff. Female subjects of childbearing potential will be screened for pregnancy prior to each imaging session. Subjects testing positive for pregnancy will not be imaged and will be withdrawn from the study.

Visits 3-6; 7-10; 11-14: Treatment Visits.
At each treatment visit, subjects will receive either active or sham rTMS (as described in the Experimental Intervention section above) according to their assigned treatment group.

TFI will be completed at baseline and the beginning (prior to the first treatment) and end (following the fourth treatment) of each treatment week. An EEG will be recorded on the last day of each treatment regimen (fourth day) and an fMRI will be completed following the last day of each treatment regimen.

Each treatment session will be videotaped to provide documentation in case of adverse events during rTMS. Videos will be deleted if no significant adverse events occur during the session.

EMA – Eccological Momentary Assessments - (sent via text to subject's smart phone between 9a.m. and 8p.m., 3 x per day on treatment visits 3 and 4).

Wash-out Periods. A 3-week washout period will follow each 4-day course of treatment. During this washout period, subjects will not receive any treatments for tinnitus. At 2, 9, and 16 days following the end of each treatment course, subjects will complete the following assessments which will be administered remotely via online questionnaires or by telephone:

- VARA
- VARL
- VARAw
- THQ
- TFI
- I/R
- EMA – Eccological Momentary Assessments - (sent via text to subject's smart phone between 9a.m. and 8p.m., 3 x per day on day 16 of washout).
-

Treatment protocol:

1. Begin daily procedure checklist. (Appendix 3)
2. Cognitive testing before and after rTMS.
    a. Recall of 3-words after 5 minutes.
    b. The digit symbol test (90 seconds).
    c. The Finger Tapping Test – three 10 second trials using the index finger of each hand (3 minutes).
    d. Rating of tinnitus loudness (1 minute).
    e. Rating of tinnitus annoyance (1 minute).
    f. Ratings of tinnitus awareness (1 minute).
3. Apply scalp electrodes 3cm anterior and 2cm posterior to the top of the ear (these electrode are present during active stimulation merely to keep the sham and active conditions identical.) Apply hand/wrist electrodes over the thumb abductor muscles. (3 minutes).
    a. Establish motor threshold (MT) to determine the intensity of rTMS (5-10 minutes). The face of the coil will be oriented perpendicular to motor cortex with the handle parallel to the sagittal plane and the handle pointing toward the back of the subject's head. Deliver single TMS pulses (starting at either 60% of max stimulator output or at the MT intensity established during the participants last test session) of increasing intensity over the motor cortex to evoke a muscle movement of the thumb or fingers of the hand on the opposite side of the body to rTMS that is sufficient to record a motor evoked potential from the thumb abductor muscle of 50 micro volts in 3 out of 6 trials. If the motor evoked potential is obscured by electrical noise (which sometimes happens) or if it is not consistent with evoked movements of the contralateral thumb, hand or fingers after stimulation (i.e., being negligible or absent when a thumb or hand movement is clearly present) a visible movement of the thumb or fingers in 3 of 6 trials will be accepted in place of the motor evoked potential. If a subject was missing a

thumb, then visible movements of the fingers on the same hand would be used to establish MT. The coil may be moved around motor cortex and intensities may be decreased as well as increased to find the lowest level of stimulation required to activate the contralateral hand.

4. Apply Treatment (either sham, 1 or 10 Hz active).
    a. Active rTMS sessions (30 or 37 minutes of stimulation for 1 and 10Hz rTMS).
        i. Set stimulator intensity to 110% of MT.
        ii. Navigate TMS coil over temporal cortex based on targeting algorithm. RTMS will be targeted over BA 22 in the temporal cortex either using Brainsight Frameless Stereotaxy System (Rouge Research) in subjects who have a clinically obtained MRI or CT scan or using the 10-20 system for EEG placement in subjects who do not have a clinical scan. RTMS will be delivered opposite the ear with loudest tinnitus or over the left temporal lobe when no asymmetry is present.
        iii. Orient the coil perpendicular to temporal cortex.
        iv. Apply 1800 magnetic pulses at 110% of MT at a rate of either 1 Hz (one pulse per second for 30 minutes) or 10 Hz (10 pulses per second) - 72 trains of 2.5 seconds duration with an inter-train interval of 30 seconds (i.e., 2.5 seconds "on" and 30 seconds "off") for 37 minutes. Total of 7200 pulses will be applied over 4 sessions.
        v. Reduce intensity of stimulation and adjust coil position as necessary if participant indicates that stimulation is uncomfortable to them.
        vi. Monitor subject for abnormal muscle activity during rTMS via:
            1. Examine electrical activity of the thumb abductor muscle contralateral to stimulation (used to establish MT).
            2. Video monitoring of subject during session.
            3. Inspection of subject for muscle contractions or after discharges by study physician or nurse during session.
        vii. Remove equipment and electrodes after rTMS, monitor subject for after discharges and ask whether there are any complaints.
        viii. Readminister cognitive tests.
    b. Sham rTMS sessions (30 or 37 minutes of stimulation to match 1 and 10Hz)
        i. Procedures are identical to those for establishing MT and for active stimulation, except that a sham TMS coil is used in place of the active coil. A staff member will be present during sham stimulation to collect information that a nurse normally collects, i.e., checking that ear plugs are in place and asking subjects whether or not they experienced discomfort. The following procedures which are unique to sham stimulation merely describe how the electrical stimulator and rTMS machine are set for sham stimulation.
            1. Set electrical scalp muscle stimulator to deliver a weak current of electrical stimulation to the temporalis muscles (i.e., between .2 and 15 mA. The level of electrical stimulation is set below the muscle twitching felt by magnetic stimulation at MT. Settings are based on a previous methodology development study in our

laboratory which replicates results of a published study in another lab [3].

2. Target the sham coil in same manner as the active coil for establishing MT.
3. Apply 1800 attenuated magnetic pulses using the sham coil at a rate of 1 Hz (one per second) and 10 Hz (ten pulses per second). The rTMS stimulator is set at 45% of its maximum output because the sham coil best mimics the sound of active coil at this setting. However, the sham coil attenuates the magnetic field to only 5% of the stimulator output. So, the sham coil delivers 2.25% of the simulator's maximum output (.05 x 45% = 2.25%). This level of magnetic energy does not stimulate the scalp muscles or brain. This is why electrodes are used to produce the sensation of muscle twitching during sham stimulation.

ii. Readminister cognitive tests.

5. Reassess ratings for tinnitus loudness and annoyance at the end of each session (0-100).
6. Assess patient's impression of whether tinnitus is improved – either the same, worse or improved relative to baseline.
7. Complete and sign daily procedure checklist.

Follow-up Visit. Approximately two months following completion of the final treatment course, subjects who do not enter maintenance treatment will return for a final study visit. At this final visit, all study measures completed at baseline will be repeated. These include:

- TAP and TLM
- THQ
- THI
- TFI
- BDI
- STAI
- VARL
- VARA
- VARAw
- I/R
- EEG

Repeat assessments prior to treatment. Ten participants from our waitlist of people who volunteered for the study will be invited to have tinnitus assessments at regularly scheduled intervals prior to beginning the placebo controlled treatment trial. The time course for these assessments parallels that for the treatment protocol which are provided in the Schedule of Events Table on page 23. Participants will complete the baseline assessment described for visits 1 on page 16 and the assessments described for visit 2 on page 17, including EEG and fMRI, in one day if possible. They will complete the assessments described for visits 6, 10, and 14 (described on page 18) at intervals that correspond to the treatment protocol. After completing these assessments, participants will simply enter the treatment protocol.

Maintenance treatment arm: Participants who report that tinnitus is improved from baseline following an active course of rTMS will be entered into the maintenance treatment arm.

1. Subjects reporting improvement on analogue ratings and/or the I/R index during the three week wash out period will be entered into the maintenance treatment arm.
2. Maintenance treatment sessions follow the same procedures for active stimulation described above except that only 3 active treatments will be delivered (either on consecutive days or 3 treatments within 5 days to accommodate schedules).
3. All subjects will receive 2, 3-day courses of sham maintenance treatment followed by, 6 3-day courses of active treatment at either 1 or 10 Hz (which ever showed better improvement or tolerance in the initial trial) separated by a three week washout with assessment.

VISIT AT MAINTENANCE COMPLETION

A 2 month follow up visit for subjects receiving maintenance treatment will take place when the subject has completed all maintenance visits or has discontinued maintenance. The following tests will be repeated:

1. Tinnitus Handicap Questionnaire (THQ).
2. Tinnitus Handicap Inventory (THI).
3. Tinnitus Functional Index (TFI).
4. Beck Depression Inventory (BDI).
5. State Trait Anxiety Inventory (STAI).
6. Rating of tinnitus loudness (0-100).
7. Rating of tinnitus annoyance (0-100).
8. Ratings of tinnitus awareness (0-100).

END OF STUDY DATA COLLECTION.

Schedule of Events

	Visit 1 Day 1	Visit 2 Day 2	Visit 3 Day 3	Visit 4 Day 4	Visit 5 Day 5	Visit 6 Day 6	w/o[2]	Visit 7 Day 26	Visit 8 Day 27	Visit 9 Day 28	Visit 10 Day 29	w/o[2]	Visit 11 Day 51	Visit 12 Day 52	Visit 13 Day 53	Visit 14 Day 54	w/o[2]	2-Month Follow-up
Informed Consent	X																	
Medical History	X																	
Screening Tests	X																	
Subject Training		X																
Treatment A, B, or C[1]			X	X	X	X		X	X	X	X		X	X	X	X		
EEG		X				X					X					X		X
MRI*		X				X					X					X		
TASS	X																	
VARL		X	X	X	X	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X[3]	X
VARA		X	X	X	X	X	X[3]	X	X	X	X	X[3]	X	X	X	X	X[3]	
TLM		X																X
TAP		x																X
I/R							X	X				X	X				X	X
THI		X																X
TFI		X	X			X	X	X			X	X	X			X	X	X
EMA		X			X	X	X			X	X	X			X	X	X	
THQ	X						X					x					X	X
BDI		X																X
STAI		X																X
Digital Video Recordings			X	X	X	X		X	X	X	X		X	X	X	X		

[1]Treatment A = sham rTMS; Treatment B = 1.0 Hz; Treatment C = 10.0 Hz; [2]w/o = 3- week washout period; [3]To be performed at 2, 9, and 16 days following the end of each treatment. *Only for the 10 subjects who selected for an MRI.

Subjects receiving assessments prior to treatment will complete the procedures shown for days 1 & 2 and for days 6, 29 & 54.

RISK / BENEFIT:

Risks to participants include those associated with high and with low frequency (1 and 10 Hz) rTMS, 1800 pulses delivered at 110% of the motor threshold. The potential benefit to subjects is a decrease in tinnitus loudness and annoyance that could be either temporary or longer lasting. A

temporary effect is expected to last between one week and several months. We will learn if maintenance treatment can increase the durability of the rTMS effect.

Possible risks and precautions associated with rTMS are as follows:

1. **Seizure.** There is a very low risk of seizure associated with 1 Hz and 10 Hz rTMS delivered at 110% of the motor threshold. Seizures associated with TMS have been reported more frequently in subjects with brain lesions (e.g., stroke) but have rarely been reported in subjects with no history of seizures or neurologic disease. One healthy subject with no apparent risk factors for seizure associated with TMS may have had a seizure with loss of consciousness during 1 Hz rTMS [27]. This is the only reported such case to our knowledge. More frequently, seizures in healthy subjects during rTMS have been association with stimulation frequencies that exceeded 1 Hz. The table below lists stimulation parameters that are deemed safe for use in human subjects. The table was derived during a conference on TMS safety in 1996 at the NIH (Wasserman et al, Eletroenceph Clin Neuropshysiol 1998; 108: 1-16). Using these guidelines, there have been very few reports of seizures or evidence of after discharge or spread of excitation in normal subjects receiving rTMS. The level of stimulation in this study - 1800 pulses at 1 & 10 Hz frequency and 110% of the motor threshold lies within the guidelines for safe use. Further, we are not proposing to use any new rTMS equipment, stimulation parameters, methods or patient populations, that might increase risk to participants. A detailed plan for monitoring and handling seizure and its related consequences is provided below.

Freq (Hz)	**INTENSITY (% of motor threshold)**													
	80-100	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

2. **Effects on Cognition**: There have been several studies in which a number of cognitive tasks were administered before and after TMS [24;26]. In these studies, there were no adverse effects of TMS; in fact, both studies demonstrated a trend for performance to be better on measures such as delayed story recall. The data from Wasserman [24] may be of particular relevance as they employed stimulus parameters (frequency of 1 Hz and amplitude of 125% of MT) similar to those that we propose to use. Three studies, however, have demonstrated possible adverse effects lasting up to one hour but both studies involved high frequency stimulation [39] (cited in Wasserman 1998[21 40;41] They found a significant decrease in logical memory one hour after testing.

3. **Effects on Mood**: Dysphoria with crying has been induced after left prefrontal stimulation[42] In contrast, high-frequency stimulation of the right prefrontal cortex may transiently improve mood. Some studies have reported that rapid-rate rTMS has been shown to be a safe and effective treatment in patients with depression who were unresponsive to other types of treatment. TMS

delivered to temporal cortex has not been associated with mood changes in patients with tinnitus (see review [3]).

4. **Effects on Hearing**: Animals have shown permanent increases of the auditory threshold after single-pulse TMS[43] and humans have shown transient increases. Foam earplugs were effective in avoiding changes in the auditory threshold in a safety study of TMS[26]. Foam earplugs will be used in our investigations. One study reported permanent hearing loss following 1 Hz TMS using an H-coil after the subject's ear plug fell out during stimulation[44]. Another study reported increased hearing thresholds in subjects who wore earplugs after 4 to 6 weeks of high frequency TMS[45]. Some patients reported an increase in tinnitus loudness following rTMS (Rossi, 2007d) that declined after rTMS was terminated.

5. **Scalp Burns**: Rapid rate and high-stimulus–intensity TMS may cause the coil to heat, resulting in scalp burns[46]. The electrodes used in our study are rubber and will not heat up during TMS. The Magstim stimulator that we use is air-cooled and incorporates a temperature sensor in the coil; it will cease operation should the internal temperature of the coil exceed 140°C.

6. **Neck Pain, Headache and Dental Pain:** Head and neck pain related to stimulation of underlying muscle and nerves occurs in approximately 10% of subjects. The incidence and severity is a function of stimulus site and intensity but is most common over fronto-temporal regions. The symptoms are self-limited and usually treated with minor over-the-counter analgesics. One subject reported dental pain during TMS delivered over left prefrontal cortex, presumably due to stimulation of the trigeminal nerve [47].

7. **Histotoxicity**: Studies from animals as well as a study of subsequently resected anterior temporal lobes of humans subjected to direct cortical stimulation or TMS have failed to demonstrate evidence of histotoxicity. For reasons reviewed by Wasserman [22] there appears to be very little chance of histotoxicity. It is also noteworthy that MRI examinations done minutes and hours after occipital stimulation with rTMS sufficient to cause phosphenes have failed to demonstrate edema or diffusion changes [48].

8. **Kindling**: Kindling is a process by which repeated administration of an initially subconvulsive stimulus results in a progressive intensification of induced neuroelectrical activity resulting in a seizure. This has not been reported with TMS and appears unlikely for several reasons. Kindling is most readily obtained with high-rate repetitive stimulation (e.g., 60 Hz), requires a pulse duration of 1 msec (longer than that of TMS), and is easiest to produce in the amygdala and hippocampus. Kindling of the neocortex in animal models of epilepsy is very difficult to achieve. There is no evidence that kindling can be produced by rTMS.

9. **Exposure to Magnetic Fields**: The maximal field strength generated by commercially available stimulators, such as the Magstim machine to be used in our laboratory, is in the 2-Tesla range. The field is induced for a brief period only, and the strength of the field falls off rapidly with distance from the coil. There is no evidence of adverse effects from magnetic field exposure during TMS; however, the long-term effects of TMS are not known.

10. A **seizure** caused by rTMS could place subjects at financial risk secondary to cost of medical care. Having a seizure might also influence driving privileges, employment, and the ability to obtain insurance. Subjects are informed of these risks during the consent process. The PI and study physician would provide documentation that the seizure was triggered by rTMS, that it does not constitute epilepsy, and that seizures caused by rTMS have not resulted in future seizures.

11. Syncope may occur in association with rTMS (Rossi, 2007d).

Procedures for minimizing these risks have been established [21]. A stock of Tylenol and Advil (ibuprofen) is kept in the lab to be dispensed by the study nurse or physician if a subject complains of pain due to scalp muscle contraction. Subjects are fully informed of this possibility during the informed consent process. The intensity of rTMS stimulation can also be decreased for subjects who report discomfort during the rTMS treatment. Participants who report dental pain due to trigeminal nerve stimulation would be withdrawn from study (this has never happened in our experience but we would not continue to test patients who complained of dental pain).

Our study also incorporates the following procedures for **minimizing risk associated with active rTMS**:

1. Subject exclusion criteria listed below will greatly eliminate subjects with a higher risk for seizure.
2. We use stimulation procedures that fall within the guidelines recommended at the conclusion of the NIH Panel on TMS [21].
3. Subjects will be monitored by a study physician or nurse trained in seizure management and in monitoring for subjects after discharges (that is, muscle contraction persisting after stimulation) by inspection of body parts that might be affected (e.g., the left arm after right frontal stimulation) or for symptoms that might occur (visual disturbance after occipito-temporal stimulation). Dr. Dornhoffer is the study physician. The study nurse(s) will be registered nurses in the Clinical Resource Center at UAMS. The study physician or nurse will attend the rTMS sessions conducted in the TMS laboratory in the BioMed II building. Dr. Kimbrell will train the study physician and nurse in seizure monitoring and management during rTMS. Should indicators of seizure be observed, the session will be terminated, and the participant will not be tested again using the same stimulation parameters.
4. The study physician or nurse will be present when a subject is receiving active rTMS. The laboratory is stocked with an oxygen supply, CPR equipment and muscle relaxing medication if needed (see below).
5. All subjects will wear foam earplugs during testing sessions. They will be questioned about changes in hearing before and after testing. Earplugs will be monitored during TMS and TMS will be terminated if a subject reports or if the study personnel observe that an earplug has fallen out. Subjects will be told to report when and if an ear plug falls out.
6. The study physician or nurse will stock and maintain the laboratory with the emergency equipment and supplies described below.
7. If a subject were to have a seizure during or immediately following the study, the study physician or nurse would attend to the subject and administer standard precautionary procedures for seizures. The following precautions will be performed:
    a. The stimulator coil will be removed from the subject's head.
    b. The subject will be supported to physically guard against injury.
    c. The subject will be placed on his/her side, on a flat surface away from sharp edges.
    d. The subject will be given nasal oxygen and observed for airway maintenance.

KNOWING THAT ALL TMS-INDUCED SEIZURES TO DATE HAVE SPONTANEOUSLY RESOLVED WITHOUT INTERVENTIONS IN APPROXIMATELY ONE MINUTE, THE

FOLLOWING WILL BE DONE ONLY IF THE SEIZURE OR EVENT PERSISTS PAST 5 MINUTES SUGGESTING STATUS EPILEPTICUS (THIS IS AN EXTREMELY UNLIKELY EVENT):

a. A 911 emergency call will be made to assist the participant.
b. Ativan 2 mg will be given IM.
c. The participant will be transport to the emergency room via ambulance.
d. The study physician or nurse will accompany the subject to the ER and recommend the post-event assessment as follows:

After the seizure is over, the subject will be examined for injuries and a neurological exam will be completed. Routine studies, including calcium, magnesium, and prolactin, will be completed and urine will be sent for a drug screen. An MRI scan of the head will be performed to rule out underlying epileptogenic pathology. An EEG will be performed with hyperventilation and anterior temporal leads. The subject will be advised that following a seizure provoked by TMS, the likelihood of further spontaneous seizures is not significantly increased unless other pathology is discovered. The subject will be scheduled for a neurology consultation. The subject will not be allowed to drive himself/herself home.

11. Prior to the study, participants will be fully informed of the possibility of seizure, the plan for care in event of a seizure, and any foreseeable financial or medical consequences resulting from a seizure. Subjects will be videotaped during active TMS and sham as a safety precaution in case of an adverse event.
12. If the subject experienced nausea, vertigo or fainting during TMS the stimulator would be stopped and the coil removed and the nurse will elevate the subject's feet. The study physician will be called for monitoring and further instruction.
13. If a subject reported that their tinnitus increased beyond a level that is typical for them, rTMS treatment will be stopped and the study physician will review the subject and determine whether the subject should be removed from the study.

RISKS ASSOCIATED WITH EEG.

A cap with 128 electrodes is used to record the EEG. It is necessary to lightly scrub the scalp at each electrode location to lower electrical impedance for good recording. Scrubbing the scalp can be mildly painful to some subjects and it could leave a red mark or minor cut. Additionally, electrode gel is applied at each location which is messy. We inform subjects of these risks prior during the informed consent process. We minimize these risks by training personnel to scrub locations lightly and to rescrub lightly when impedances need to be lowered. We have towels and water on hand to clean off electrode gel. We inform subjects that their hair may have residual gel after testing and that they will need to wash their hair to remove all the gel.

Risks associated with MRI scanning.

1. MRI scans are performed in small enclosures that could cause anxiety. We exclude participants who report claustrophobia on the claustrophobia questionnaire.
2. MRI scans can reveal an undiagnosed brain abnormality or process that would exclude the participant from study. Participants are informed of this possibility during the consent process. Dr Dornhoffer will examine each MRI scan to rule out brain abnormalities. A neuroradiologist associated with the Brain Imaging Research Center will review any MRI or fMRI studies were abnormalities are suspected or noted either by Dr Dornhoffer or study staff at the Brain Imaging Research Center. We inform participants during the consent process that any findings from the MRI scan will be made known to them. We refer participants for follow up with an appropriate medical specialist if abnormalities are discovered. We inform subjects that they and their insurance provider will be responsible for the cost of and any medical care associated with investigating an abnormality on the fMRI or MRI.

ASSESSMENT OF EFFICACY WITH STATISTICAL PLAN.

THIS IS A PILOT STUDY WITH ONLY 80 SUBJECTS. THE MAIN PURPOSE IS TO GATHER DATA THAT CAN BE USED TO ESTIMATE EXPERIMENTAL POWER FOR A LARGER STUDY. WE PRESENT AN OPTIMAL PLAN FOR STATISTICAL ANALYSIS BELOW BUT RECOGNIZE THE NUMBER OF SUBJECTS MAY NOT PROVIDE SUFFICIENT POWER. WE INTEND TO USE THE MEANS AND STANDARD DEVIATIONS FROM OUR ANALYSES TO DERIVE POWER ESTIMATES FOR OUR AIMS. AT THE END OF THIS SECTION, WE REPORT A POWER ANALYSIS BASED ON PREVIOUS PILOT WORK WHICH DEMONSTRATES THE FEASIBILITY OF THE AIMS FOR THIS PROPOSAL.

Comparing sham and active treatment (1 and 10 Hz). The analysis involves comparisons between groups on continuous variables – the tinnitus questionnaires, analogue ratings of loudness and annoyance, and awareness and on measures of resting state brain activity assessed with EEG and fMRI. To control variability due to differences in the initial level of baseline measures between subjects, we will transform the raw data into z-scores prior to analysis. If there are not enough observations to use standardized scores, the data will be log-normalized prior to analysis. Between-group differences in the dependent variables will be examined using MANOVA with planned contrasts. For example, we expect active treatment to have a greater effect than sham treatment and, based on a published study [5], we expect 10 Hz rTMS to have a greater effect than 1 Hz. These expectations will be tested using planned contrasts.

Comparing 1 and 10 Hz treatment within subjects. Treatment comparisons will be analyzed using MANOVA for repeated measures in SAS (SAS Institute, Cary, NC) which treats a crossover design as a special case of repeated measures analysis of variance. Each record in a subject's data will be ordered by treatment (1Hz -active versus 10 Hz -active stimulation) and time period (first or second treatment). A significant effect of "treatment" on tinnitus ratings would indicate that either 1 or 10 Hz stimulation leads to greater change on tinnitus perception. A significant effect of period on tinnitus would indicate that it is important to match patients with the correct type of stimulation. Crossover designs have the advantage of

increased statistical power associated with repeated measures and the opportunity for each subject to receive each type of active treatment; however, the disadvantage is to introduce carry-over effects (the possibility that the effect of one treatment can carry over to the next). Carry over effects into sham treatment are eliminated by presenting sham treatment first. Carry over effects into active treatment will be prevented using a 21 day treatment washout period. The possibility of carry-over effects will be evaluated statistically by examining the treatment by period interaction.

Analyses for sub Aim: we will compare responders and non responders to determine what patient characteristics predict outcome. Predictors for 80 subjects include 1) tinnitus characteristics including duration, frequency, pitch, and loudness, 2) questionnaires (the TSI, THI, and THQ), 3) the range of measured hearing loss; and co-morbidities such as hyperacusis, depression (BDI), and anxiety (STAI) and 4) risk factors including age, race/ethnicity, hypertension, smoking history, and loud noise exposure. Power and coherence ratios from EEG and fMRI recorded at baseline can be examined for 20 and 20 subjects, respectively. A series of regression analyses will be conducted to reduce the overall number of predictors and to build an initial model, to assess the predictive value or weight of remaining variables, and to cross-validate predictors.

Examining the efficacy of maintenance treatment: A 3-factor ANOVA for repeated measures will be used to determine whether a fixed schedule of maintenance rTMS improves and delays the return of tinnitus. All types of treatment are repeated for all subjects. Summary variables include change scores from baseline; calculated from the pre- and post-treatment assessments of tinnitus (i.e., TSI, VARL, VARA, and TLM). The analysis will proceed as follows.

Planned contrasts comparing treatment conditions will be used to analyze a significant main effect of treatment with appropriate corrections for multiple comparisons. Planned contrasts will be used to determine whether active maintenance treatments (M3 thru M8) has an incremental effect on tinnitus, improving with each successive course of treatment, or cumulative, depending on a critical number of treatments. Based on our preliminary study of 7 subjects, the statistical power to detect differences in the mean VARL (loudness) rating between standard and maintenance treatment was high (.88) with a very large effect size (1.19). Analysis of the VARA (annoyance) ratings for three subjects and of the TSI for twelve subjects (comparing standard treatment to baseline) revealed medium effect size (d=.54 & 51, respectively). Sample size of 15 and 22, respectively, would yield power of .80 to detect a rTMS induced change.

A one-way analysis of variance model will be used to determine if maintenance treatment extends treatment duration. We will calculate, the number of days between the end of treatment and the date on which the subject indicates, on the I/R measure, that tinnitus increased following the six courses of active maintenance treatment. A significant omnibus effect will be examined using planned contrasts to learn if a delay in tinnitus is incremental, cumulative, or dependant on a critical number of treatments.

Analysis of the follow-up data will use repeated measures ANOVA (with appropriate statistical corrections) to compare measures obtained at baseline to those collected 2 months

after all treatment ends. This analysis will address long-term effects of rTMS treatment on clinical, behavioral, emotional, and perceptual aspects of tinnitus.

Power analyses. The power to detect an rTMS-induced change in tinnitus loudness was calculated directly from a previous pilot study (n=7) using SAS. We examined power to detect change in ear-specific tinnitus ratings following active rTMS using a 0–100 scale comparing ratings taken at baseline to the best rating achieved during the week of active treatment (day 4 for most patients). We found that a sample of 16 subjects would yield power >.99 to detect a change after one week of rTMS (10 subjects yields power = .92). Power analyses to detect rTMS-induced change in the Tinnitus Severity Index (TSI) showed that 20 subjects will yield experimental power of >.81 to detect an rTMS-induced change in the total score of the TSI immediately following treatment (10 subjects yields power = .42). Power to detect change in PET asymmetry ratios (PETAR: change in PET activity between homologous regions of the temporal lobes) following rTMS was examined using a paired t-test to compare baseline PETARs and those immediately following the fifth day of active rTMS. A sample size of 15 would yield experimental power of >.98 to detect an rTMS-induced change in PETAR (a sample size of 10 yields experimental power of .87). (Also, Wang [49] investigating cortical asymmetries in patients with tinnitus compared with healthy controls and indicated that 10 subjects were sufficient to detect significant cortical asymmetries in patients with tinnitus using PET. Experimental power = **.92**.) Power estimates for maintenance treatment could not be calculated because only one subject to date has had maintenance treatment; however, the data indicate that the beneficial effect of rTMS can be reproduced in the same subject at multiple later points in time (i.e., it is reliable)[20]. Additionally, the duration of the treatment effect increased from the first to the second and third follow-up treatments and further treatment was not required after the third round of maintenance treatment.

ASSESMENT OF SAFETY

The Research Support Center will conduct independent data safety and monitoring before the first subject is entered, after the first subjects is tested and following the next 3-6 patients entered according to a plan that has been uploaded with this application. The Data and Safety Monitoring Plan (which is included in the appendix) describes operating procedures that will be in place to monitor study data validity and integrity, participant safety, individuals and/or entities (e.g., IRB) that will be involved in monitoring these procedures, and the frequency/regularity of this monitoring. All staff involved in the conduct and/or monitoring of this study will have completed the UAMS Human Subject Protection Training and the HIPAA Research Training. Documentation of training will be uploaded in ARIA in documents. UAMS IRB regulations will be strictly adhered to in the conduct of the proposed research. Specifically, prior to implementation of any protocol changes, amendments will be submitted to the IRB for approval. The PI will be responsible for continuous data and safety monitoring of all subjects enrolled in this study. In terms of standard operating procedures, all assessments will be administered by trained research staff members.

In terms of participant safety, in the unlikely event that a participant experiences an adverse reaction during the course of a study, guidelines in the UAMS IRB Investigator's Handbook for adverse event and serious adverse event reporting will be followed. The PI will report all such activities to the IRB and the sponsor (as appropriate). Additionally, the PI will inform the sponsor of any actions taken by the IRB resulting from its continuing review of this study. In terms of reporting mechanisms of IRB actions to regulatory agencies, the following UAMS IRB policy (#2.6) applies:

> The IRB reports any unanticipated problems involving risks to human participants or others; any instance of serious or continuing noncompliance with the IRB regulations, requirements, or determinations; and any suspension or termination of IRB approval to the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), and the Office of Research Oversight (ORO) according to appropriate regulations and the terms of the UAMS IRB Federal Wide Assurance (FWA).

Monitoring of the aforementioned procedures will be overseen by the PI, Project Director(s), and the IRB. These procedures will be reviewed regularly by the Project Director in a number of settings. For instance, issues pertaining to data validity and integrity and subject safety will be addressed during regular research staff meetings. Moreover, the Project Director and PI will meet on a regular basis to discuss these topics further. In addition, the IRB, in collaboration with the Office of Research Compliance (ORC), during its yearly continuing review process, will evaluate procedures in place to effectively monitor data integrity and validity and participant safety.

QUALITY CONTROL AND QUALITY ASSURANCE

As previously mentioned, we will follow the NIH guidelines by Wasserman and the NIH International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. We developed this protocol in collaboration with Tim Kimbrell, M.D., who trained with Dr. Wasserman at the NIH. As mentioned above, Dr Kimbrell will train the study physician or nurse to carry out safety procedures in the event of a seizure during or after TMS.

PUBLICATION POLICY

This study will be registered on clinicaltrials.gov.

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Appendix

A1 Ratings scales of tinnitus loudness and annoyance.

A2 Better / worse rating.

A3 Daily log of tinnitus.

A4 Tinnitus severity index.

A5 Tinnitus handicap questionnaire.

A7 Three words at five minutes memory test and finger tapping test forms.

A8 The Digit Symbol test form.

A9 The Beck Depression Inventory.

A11 Psychomotor vigilance test (example test printout).

A12 Transcranial magnetic stimulation adult safety screen.

A14 Claustrophobia scale and scoring information.

A15 e-mail from Jennifer Roberts, M.D regarding Ativan.

A16 rTMS session procedural checklist.

A17 SRC Data Safety Monitoring Plan.

A29 Information from Dr Berne - SR and NSR device studies related to rTMS.

A37 Information from Dr Berne - suggested items in rTMS submissions.