Research Protocol

Title
A new therapeutic approach for somatosensory tinnitus

Investigators
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Specific Aims/Purpose
The purpose of this study is to address the immediate clinical need to improve the way the VA screens and evaluates tinnitus patients by piloting an approach modeled after what is done at the Cleveland Clinic. Results of this study will provide pilot data to be used in a large-scale Merit Review proposal. Long-term objectives are to adapt Cleveland Clinic's interdisciplinary approach to diagnose and treat somatosensory tinnitus for use in a new population: Veterans with tinnitus.

Scientific Rationale and Significance
Somatosensory tinnitus is suspected when the perceptual characteristics of tinnitus (e.g., pitch, loudness, timbre) are altered following certain head or neck maneuvers, forceful muscle contractions, or eye or jaw movements. Prevalence estimates range from 60 to 80% of tinnitus patients being able to somatically modulate their tinnitus in some manner (Ralli et al, 2017). The Cleveland Clinic, an institution at the forefront of tinnitus care in the United States, has developed a protocol for assessing if tinnitus can be somatically modulated and, when it can, implementing an established treatment regimen that has been successful in a majority of these patients. The prevalence and treatment of somatosensory tinnitus has not been studied in Veterans who suffer from tinnitus. The proposed research is the first step in achieving our long-term goal to develop a clinical framework for diagnosing, assessing, and treating somatosensory tinnitus in Veterans.

Of the millions of Veterans with tinnitus, many suffer negative consequences such as anxiety, insomnia, and concentration difficulties (Liu et al, 2015). Because the underlying mechanisms are still unclear, classification methods rely on categorizing tinnitus according to its characteristics. Many cases of somatosensory tinnitus involve concomitant pain or stiffness in the musculature of the head and neck. Other clinical features include tinnitus onset following head or neck trauma. Tinnitus and musculoskeletal disabilities of the head and neck are highly prevalent in Veterans (Veterans Benefits Administration, 2016); therefore, it is logical to postulate that a significant percentage of these Veterans have the clinical features suggestive of somatosensory tinnitus.

Current clinical practice at the VA Portland Health Care System (VAPORHCS) is for Veterans who report tinnitus to be seen in the audiology clinic to assess their hearing ability and communication needs. VA clinicians do not routinely perform an in-depth tinnitus assessment and no standard guidelines exist recommending questions or screening procedures to identify tinnitus fluctuations or triggers. Going one step further

and evaluating the influence of somatic factors on the Veteran's tinnitus perception is rarely done. Veterans whose tinnitus is influenced by somatic movements suggests the possibility of an underlying head or neck musculoskeletal deficit that is being overlooked, which if treated, would help the Veteran patient to regain normal functioning.

In general, there is a lack of understanding as to why some tinnitus patients report benefit from one treatment over another. One possible explanation is that some types of tinnitus are more responsive to select treatments. Therefore, a critical need exists to develop methodological and clinical tools capable of assessing and subtyping tinnitus so that controlled studies can be done to address this gap in our knowledge. In the absence of this knowledge, patient factors are often examined to determine the likelihood of successful treatment outcomes (Theodoroff et al, 2014). By examining patient factors of individuals who respond favorably to an intervention, including what "type" of tinnitus they have, insight is gained as to what aspects of the patient and types of tinnitus are best suited for particular treatments. The focus of this proposal is a specific tinnitus subtype known as somatosensory tinnitus.

When attributes of the tinnitus percept change following certain maneuvers or muscle contractions and somatosensory tinnitus is suspected, it suggests an interaction between the somatosensory and auditory systems (Levine, 1999; Shore et al, 2007; Ralli et al, 2017; Marks et al, 2018). Numerous studies have revealed that tinnitus can be somatically modulated in many people (see Ralli et al, 2017 for a review). Tinnitus modulations associated with the somatosensory system and somatic disorders are often attributed to cortical neuroplasticity initiated by subcortical changes occurring at the auditory brainstem level (Shore et al, 2007). The anatomical and physiological connections between the somatosensory and auditory pathways have been well documented (Dehmel et al, 2008; Shore et al, 2007; Shore et al, 2016; Wu et al, 2016) and are shown in Figure 1 (Cherian et al, 2013). The fact that somatic manipulations can directly influence the tinnitus perception for many patients (Shore, 2011) suggests somatosensory tinnitus is an indicator of an underlying musculoskeletal deficit of the head or neck which warrants taking a non-traditional approach to tinnitus management (Sanchez & Rocha, 2011). The Cleveland Clinic, an institution that is at the forefront of providing tinnitus rehabilitative services, has developed a protocol for assessing if tinnitus can be somatically modulated; when it can, the clinic provides these patients with individualized physiotherapy as part of the treatment regimen.

Research Design and Methods

General Summary of Procedures. To accomplish the goals of Aim 1 (address the prevalence of somatosensory tinnitus in Veterans with tinnitus), individuals who are enrolled for care at a VA facility or clinic will be contacted and screened over the phone. Based on the phone screening, a subset of Veterans will be invited to attend one in-person visit. To accomplish the goals of Aim 2 (develop a clinical framework to diagnose, assess, and treat Veterans with somatosensory tinnitus), a subset of Veterans identified with somatosensory tinnitus (knowledge gained at visit 1) will be given the option to attend 3 in-person individualized physiotherapy sessions from the

study physical therapist using an abbreviated therapy protocol modeled after protocols used at the Cleveland Clinic.

Subject Identification/Recruitment

We will use a variety of recruitment methods including any of the following:

NCRAR Data Repository: Veteran subjects will be recruited from a pool of participants who previously participated in research projects at the NCRAR and gave their consent to be contacted for future studies. These authorized data can be found in the NCRAR data repository (MIRB#2874) and the audiology and rehabilitation research data repository (MIRB #3750). The NCRAR data repository and audiology and rehabilitation research data repository's SOP indicates that any investigator who has an approved IRB protocol and consent form can contribute and retrieve data from the repository.

Corporate Data Warehouse (CDW): Data in the CDW are generated, in part, from Veterans' electronic health records within the VA and include healthcare use, diagnoses, and prescription drug dispensation for those receiving VA care nationally. The CDW will be used to identify demographic information and diagnoses for health conditions of interest relevant to accomplish the aims of this research (e.g., audiologic test data, tinnitus). CDW data will be accessed and linked via the VA Informatics and Computing Infrastructure (VINCI) Data Application Request Tracker (DART). Once VA data are linked within the VINCI environment, they will be securely moved to a VA Portland Health Care System research server. Dr. Theodoroff has worked on other projects that have successfully used this method for similar recruitment efforts.

Recruitment Letters: Veterans who are enrolled for care at a VA facility or clinic, and have tinnitus, will be mailed a recruitment letter informing them about the opportunity to participate in this research study.

Outreach and Other Activities: Veterans may learn about the possibility of study participation through newspaper advertisement, online advertising, recruitment flyers, from health care professionals, or word-of-mouth. When advertising and discussing the study at outreach events, IRB approved study personnel can collect names, email addresses, and phone numbers of people who would like us to contact them to learn more about the study for screening purposes. A full screening will be done over the telephone to ensure as much as possible that callers who are invited for an assessment are suitable candidates. IRB approved staff will access Veterans' medical records in the computerized patient record system (CPRS) to determine if they meet the study's eligibility criteria. We have conducted this type of screening for numerous clinical studies and have refined the techniques for efficiency.

To identify eligible candidates, study personnel will administer a phone screening to interested callers. This phone screening will be conducted from a VA or non-VA networked telephone. If a non-VA networked telephone is used to conduct the screening, additional precautions will be taken to maintain the privacy of the Veteran. These precautions include calling from a private and secure location, and only leaving the contact information of study team member's VA telephone extension, should a call back be required.

If candidates fail to meet the selection criteria during the phone screening they can be re-screened at a later date at the discretion of staff. This will be tracked in the study tracking database used for recruitment by recording their screen status (i.e. “Re-screen”) and will also include the date that the participant needs to be contacted. When a candidate is re-screened, they will be contacted via the phone and re-asked the phone screening questions following the IRB approved script. If they meet the criteria to be invited for the in-person screening, they will be scheduled at that time.

Aim 1: Eligibility Criteria

- Veteran
- Chronic tinnitus (≥ 6 months) that can typically be heard in a quiet room

Aim 2: Inclusion Criteria

- Veteran
- Chronic tinnitus (≥ 6 months) that can typically be heard in a quiet room and is experienced at least daily or weekly.
- Positive screen for somatosensory tinnitus (i.e., tinnitus pitch or loudness that changes during somatic maneuvers and/or limited range of motion suggestive of mechanical deficits associated with a somatic component)

Aim 2: Exclusion Criteria

- Non-Veteran
- Not able to attend 3 weekly physiotherapy sessions at the VAPORHCS
- Not a good candidate for physical therapy
- Participation in new (i.e., < 1 month) tinnitus management or treatment
- Current participation in tinnitus research involving an intervention
- Inability to read and respond appropriately to instructions, and/or to perform all of the study procedures

Informed Consent & HIPAA Authorization

The study will be reviewed with the participant one of two ways: 1) over the telephone using the IRB-approved Information Sheet, with a review and signature of the HIPAA authorization during the first study visit, or 2) if the participant prefers to be consented in-person, the IRB-approved Informed Consent Form and HIPAA authorization will be reviewed at the beginning of the screening visit. For both options, IRB-approved testing procedures will only occur after the appropriate consent and/or authorization have been obtained.

After the phone screening, if a participant appears to be eligible for the study, they will be given the option to complete the consenting process over the telephone rather than in-person as indicated above, in an effort to limit close, person-to-person contact in accordance with COVID-19 precautions. In that case, a member of the research team will then mail the IRB-approved Information Sheet to the participant, and at a mutually agreed upon time, the participant will be contacted by phone to review each section of

the form. Participants will be given ample time to review the Information Sheet and decide if they would like to participate in the study. Following this discussion and the clarification of any questions, the study member will ask “Based on the information we have reviewed in this form, would you like to participate in this study?” If the participant answers “Yes,” this affirmation will serve as their consent to participate in the study. They will be advised to keep a copy of the Information Sheet for their records. It will be made clear to the participant that providing consent is not the same thing as being enrolled in the study, which will be determined during the in-person visit.

Screening/Baseline Tests

For participants who choose to be consented in-person, after the informed consent and HIPAA authorization forms are reviewed and signed, they will complete a screening evaluation to confirm eligibility for the study. For participants who consented via the IRB-approved Information Sheet, they will be reminded they provided consent over the phone and be asked if they want anything about the nature of the study to be reviewed with them prior to starting the screening procedures. The HIPAA authorization will then be reviewed and signed prior to any study procedures being conducted. In some cases, procedures will be repeated on later visits. Baseline testing includes tinnitus loudness-matching using an audiometer (optional) and a musculoskeletal screening exam. The following questionnaires will also be administered: Tinnitus Screener, Health History Questionnaire, Tinnitus History Questionnaire; Hospital Anxiety and Depression Scale; and the Tinnitus Functional Index, which is the primary outcome measure.

Data Analysis (Statistical Analysis Plan)

A Bayesian approach will be used to estimate the prevalence of somatosensory tinnitus in the VA population conditional on the phone screening data. The Bayesian prior probability distribution (i.e., “prior”) for this analysis is the meta-analysis based prediction derived from 4 published studies (Sanchez et al, 2002; Abel & Levine, 2004; Sanchez et al, 2007; Simmons et al, 2008). A sensitivity analysis will be conducted using a flat prior and a prior concentrated below 40% prevalence to evaluate the effects of the prior on the Bayesian posterior probability distribution.

We will evaluate the feasibility and tolerability of individualized physiotherapy performed in ~10 Veterans with somatosensory tinnitus. We will use the pilot data from questionnaires (e.g., TFI) and if available, 1 kHz loudness-matching results to document any reductions in tinnitus-related distress and perceived loudness following individualized physiotherapy. The change from baseline TFI score and 1 kHz loudness-match (in dB Sensation Level; dB SL) observed in this sample will provide the basis for sample size calculations in a subsequent large-scale Merit Review proposal.

Risks and Side Effects

There are only minimal risks associated with these research procedures. The sound booth used for testing is extremely quiet, and some people find such quiet environments to be disconcerting/annoying. Subjects will be told they do not have to participate if this is a problem. All of the testing equipment is checked and calibrated according to a required schedule, so any risk of equipment malfunction is minimized. For all measurements, sound

levels are below those known to cause hearing damage. There is a small possibility, however, that certain sounds in the tests may seem loud to a subject and cause them temporary discomfort. In addition, some discomfort is occasionally associated with wearing earphones during audiologic and tinnitus testing. To minimize these risks, subjects will be told they can stop at any time and do not have to listen to any sounds they do not want to.

Minor anxiety and fatigue may be experienced when carrying out the testing and when completing questionnaires. People could react emotionally to some of the items on the questionnaires. These items ask about how people react to tinnitus and how it affects their life. To minimize this risk, individuals will be told they do not have to answer any questions they do not want to.

People with tinnitus have been known to report their tinnitus becoming louder following auditory testing. Usually these individuals report some discomfort during testing. Participants will be informed of this potential risk and told to report any discomfort during testing, which would result in testing being terminated immediately.

The musculoskeletal screening exam will be performed by a trained clinician. It is possible that the screening procedures could aggravate the subject's tinnitus, underlying dizziness, headache, ear discomfort, or neck symptoms. To minimize these risks, subjects will be told to let the clinician know immediately if symptoms appear or worsen in any way during the exam.

For the individualized physiotherapy, Veterans will be working one-on-one with the physical therapist who will provide both exercises and manual treatments (i.e., physiotherapy) to correct any deficits that are identified using standard of care clinical procedures. After a treatment session, there is a minimal risk that the subject may experience an increase in tinnitus, discomfort associated with the cervical spine, jaw, or thoracic spine. To minimize subjects experiencing discomfort, they will be educated on: 1) proper form of the exercises and expectations; 2) how to prevent worsening of symptoms; and 3) what to do if symptoms worsen.

Participant Safeguards

This study does not include vulnerable populations. Additional safeguards have been established to minimize risk of noise exposure.

Suicidality

It is not expected that potential subjects will be suicidal. In the unlikely event that an individual expresses suicidal ideation during the screening phone call or if he/she indicates that he/she is suicidal at any time during the study, a "warm transfer" procedure will be implemented to connect the individual with a person at the Suicide Hotline. All research staff will be informed of the warm transfer procedure and phone number for the National Crisis Hotline 1-800-273-8255 (Veterans press "1" and non-Veterans stay on the line).

Language is included in the informed consent form that if participants express thoughts about wanting to harm themselves or others, the Principal Investigator or study team member may call the National Crisis Hotline at 1-800-273-8255 (Veterans press “1” and non-Veterans stay on the line) or walk them to the Emergency Department as appropriate.

Benefits

Tinnitus is the most prevalent service-connected disability for Veterans and currently has no “cure.” Hearing loss is the second most prevalence service-connected disability for Veterans. Subjects may or may not personally benefit from participating in this study. However, by serving as a subject, they will contribute new information expected to benefit patients in the future. Data generated from this research will help to assess the effectiveness of a new therapeutic approach to reduce tinnitus distress and partially, or completely, suppress the tinnitus perception.

Subjects will benefit by learning about tinnitus. In some cases, people who are bothered by their tinnitus are helped simply by receiving information and having their questions answered.

Protected Health Information

HIPAA identifiers will include names, geographical subdivisions smaller than a state, dates (study contact dates), telephone numbers, email addresses, and last four digits of participants’ social security numbers (SSNs). This information is the minimum necessary to contact potential subjects, enroll them in the study, and carry out the study protocol. Phone numbers, addresses, and email addresses are needed to ensure that subjects may be reached for follow-up visits and other study-related communication.

All test results from this study, including behavioral data and responses to questionnaires, date(s) of study session, and all contact information will be banked in Dr. Theodoroff’s data repository “Sensory Perception, Physiology and Outcomes Data Repository" (#4635). Information will be shared with repository #4635 only after the participant is enrolled in the study and has given consent to bank their data for future research. Participants must agree to bank their data in repository #4635 in order to participate in this study; this banking of research data is mandatory.

Subject Compensation

Subjects will receive a VA payment voucher for $30 for each visit they attend at the NCRAR. This amount is consistent with our other studies, which will cover typical travel costs associated with attending the appointments. If subjects show up, but are unable to complete the session (or are disqualified), they will still receive the entire payment ($30) for their participation in that session. If subjects withdraw from the study prior to finishing all of the required sessions, they will only be compensated for the number of visits they attended. For subjects who qualify to receive individualized physiotherapy and attend all scheduled visits, they will receive a total of $120.

Privacy and Confidentiality

The information gathered for this study will be kept confidential as required by law. The results of participation in this study may be used for publication or for scientific purposes, but the results will not include any identifying information. A subject's identity will not be disclosed unless they provide specific, separate consent or if required by law. All VA research records will be held in accordance with the VA records control schedule.

Subject data confidentiality will be maintained throughout the clinical study, but in a manner that ensures the information can always be tracked back to the subject if necessary. All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. Only unique subject numbers in case report forms will identify subjects.

All study personnel, who have been authorized by the PI, will have access to the subject identification log which will be kept as an electronic version and will be password protected; this will not be copied or removed from the study center. All records with personal information will be kept in a locked cabinet at the study center according to national legal requirements or hospital requirements, whichever period is longer.

Transfer of Data Ownership

No PHI data will be transferred away from the VAPORHCS.

Data and Safety Monitoring Plan (DSMP)

1. ***What safety information will be collected including serious adverse events and unanticipated problems involving risk.***
   Adverse events and unanticipated problems will be recorded by the PI or study team member and documented according to VA guidelines.

2. ***How the safety information will be collected, e.g., case report forms, at study visits, by telephone, etc.***
   The data will be collected and recorded by study staff. Any unexpected safety issues will be collected and reported on the appropriate IRB forms.

3. ***The frequency of data collection including when safety data collection starts.***
   Information will be collected at each visit, and as necessary between visits.

4. ***The frequency or periodicity of review of cumulative safety data.***
   Summary reports of subjects' data will be generated for discussion at weekly meetings. Safety information will be reported to the PI as it is collected.

5. ***If there will not be a data monitoring committee, and if applicable, what statistical tests will be used to analyze safety data and determine if harm is occurring?***

Because this is a minimum-risk study, a data monitoring committee is not required.

6. ***Who will oversee safety data?***
   Any safety issues that arise will be reported immediately to the PI who reviews all data collected. In accordance with VA guidelines, any Serious Adverse Event will be reported in writing to the IRB within 5 business days of awareness.

7. ***Which conditions would trigger an immediate suspension of the research, if applicable.***
   For this minimal risk study, there are no forseeable conditions or events that would trigger an immediate suspension of the study or stopping it prematurely.

Data Storage

Any identifiable information collected at the NCRAR will be kept on a password protected computer, in a password protected MS Access database, and/or password protected excel spreadsheet, which will be stored in a restricted folder on the VA server behind the firewall. Folder access will be restricted to IRB-approved study team members. Data collected during study visits and on questionnaires will be kept in separate MS Access databases/excel spreadsheets. These databases will also be stored on the VA server in the restricted study folder. These data will be coded by unique study ID numbers. Paper files containing identifiable (e.g., ICF) data will be kept in a separate locked file cabinet within a locked room.

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