DETAILED PROTOCOL:

Pilot Evaluation of auditory mirror-therapy for tinnitus

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BACKGROUND AND SIGNIFICANCE

Tinnitus, often referred to as 'ringing in the ears', is considered a perception of sound in the absence of external stimuli [1]. Approximately 50 million US adults report having any tinnitus, and 16 million US adults reported having frequent tinnitus in the past year [2]. Tinnitus is increasingly being recognized as a phantom auditory sensation [3], and recent neuroimaging studies indicate a substantial overlap between the neural circuits involved in tinnitus and those involved in neuropathic pain [4]. Antidepressants have insufficient evidence for the treatment of tinnitus [5], and while cognitive behavioral therapy [6] and sound/masking therapy [7] may be somewhat effective for improving function and quality of life, they are less effective in reducing the tinnitus percept *per se*.
As in phantom pain, the tinnitus percept does not appear to arise from increased cochlear signaling, but rather develops as a changes in central auditory and multisensory integration pathways [3]. Our brains continuously bind information obtained through many sensory channels to form solid percepts of objects and events. Usually these pieces of information complement and confirm each other, thereby improving the reliability of our perception, as demonstrated by audio-visual illusions like the McGurk effect [8], where lip-reading takes predominance over the interpretation of auditory input, or the audio-tactile parchment-skin illusion, where the sound of dry hands leads to a tactile perception of dry hands[9].
Notably, tinnitus can be evoked or modulated by somatosensory, somatomotor and visual-motor systems in as many as 65% of individuals with tinnitus [10]. Several behavioral and neuroimaging studies suggest that multisensory integration is altered in tinnitus[11-13]. Animal models of tinnitus indicate increased spontaneous firing rates and synchrony among neurons in central auditory structure, suggesting that maladaptive neural plasticity underlies these changes, possibly generating the phantom percept [3, 4].

The auditory olivocochlear system functions include noise protection on the one hand and mediation of selective attention and improvement of signal to noise ratio on the other hand. The efferent system also supports adaptation and frequency selectivity by modification of the micromechanical properties of outer hair cells. Consequently, the lateral and medial efferent system together form the basis for localization of a sound stimulus and enable to function in a three-dimensional auditory world. Tinnitus patients have a reduced ability to locate sounds, and that interference is worse for sound originating from the same side as the tinnitus [14].

This suggests that brainstem nuclei (olivary nucleus, inferior colliculi) involved in early interaural processing are altered in tinnitus.

Experiments performed 120 years ago by Stratton [15] suggest that after wearing inverting spectacles for 6 days, vision adapted and the world can be perceived as upright again. Subsequent research has shown that subject rapidly adapt to the upside-down world, but no such adaptation induces alterations in the retinotopy of early visual cortical areas[16]. Rather, the adaption is thought to involve changes in the subject´s spatial representation of the own body image[17]. Mirror therapy, where mirrors is placed so as to create a visual illusion of limb in amputees [18] exploits the brain's preference to prioritize visual feedback over somatosensory/proprioceptive feedback concerning limb position. In conditions such as phantom limb pain (PLP), stroke, or Chronic Regional Pain Syndrome Type 1 (CRPS1) where neuropathic processes cause issues with pain, related or unrelated to movement, this approach offers relief for a subset of patients[19]. A handful of studies (see [20] for a review) have investigated immediate and long-term CNS effects of mirror therapy. Mirrored visual feedback evokes a conflict between expected and actual somato-visual feedback, and typically leads to increased activation of the superior parietal lobe, the posterior cingulate cortex and ipsilateral lateral sulcus. Long term effects, examining neural representations of limb sensory and motor function after mirror therapy, indicate a gain in motor function, and enhanced excitatory function of the contralateral corticospinal pathways, suggestive of a reestablishment of hemospheric balance.

We propose adapting the mirror-phenomena to the auditory field, i.e., mirror box therapy for the ears to treat the auditory phantom of tinnitus. This is achieved by a) blocking sound input by acoustic earmuffs (a.k.a. ear defenders), and b) reintroducing sound from the left side of the body to the right side of the body, and vice versa, by means of two microphones outside the earmuffs, and two speakers inside the earmuffs, see Figure 1. This has been implemented in a prototype based on a commercial earmuff (Impact® Sport, Howard Leight by Honeywell, specifications attached as appendix I) with built in sound amplification. The modification consists of connecting the left microphone to the right microphone tab on the circuit board, and vice versa.

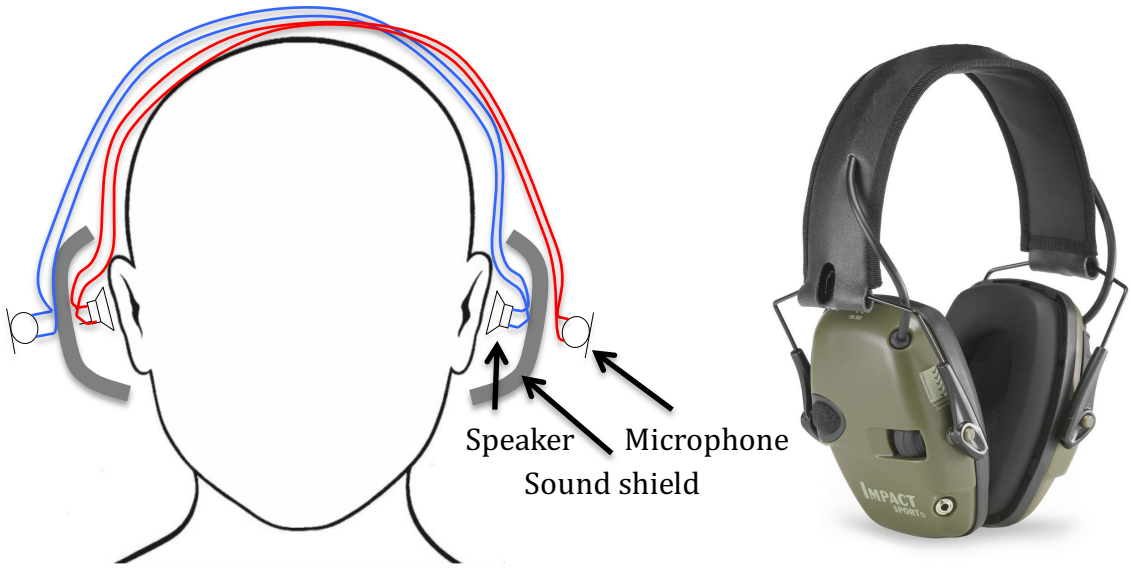

Figure 1. Schematic illustration of the auditory mirror headphones, and the implemented prototype based on a modified commercial hearing protection device with built in microphones and speakers.

We call this procedure Auditory Mirror Therapy (AMT).
In pilot trials, a sample of 20 subjects with chronic tinnitus, using the device for up to 3 hours per day for two weeks led to significant reductions in tinnitus awareness (-35%, p=0.00057) and on the Tinnitus Handicap Inventory (THI, -24%, p= 0.0014) (Linnman 2022, J American Academy of Audiology, *in press*). We seek to replicate and extend our proof-of-concept trial in an adequately powered and placebo-controlled study, with detailed audiometry and long-term follow up.

SPECIFIC AIMS

Aim 1: Determine the efficacy of a 21 day, 3 hours per day intervention of auditory mirror therapy (AMT) for chronic tinnitus. Hypothesis: AMT, as contrasted to a sham device, will significantly reduce symptom ratings on the Tinnitus Functional Index scale.
Aim 2: Determine AMT and placebo longitudinal response profiles using tablet- based, self-administered acoustic testing. Self-administered automated hearing measurements are statistically equivalent to manual measurements made by an audiologist in the clinic. By collecting serial measurements over the course of the AMT/placebo intervention, treatment/placebo responses and normal fluctuations in tinnitus will be captured. A six week follow up assessment post-treatment is done to evaluate if effects are sustained.

SUBJECTS SELECTION
Up to 80 subjects with tinnitus will be included in the study.
Written informed consent form will be obtained in all cases.
We are not planning to enroll subjects from at-risk population (e.g., children and minors, cognitively impaired persons, prisoners).

Inclusion/ Exclusion Criteria
General Inclusion Criteria:

- Male or female
- Age 18–80
- No significant medical history; seizure disorder, diabetes, alcoholism, cardiac disease including coronary artery disease, psychiatric problems; drug addiction, respiratory problems, liver disease, etc.)
- No signficant medication history
- Chronic (≥3 months), tinnitus

Exclusion Criteria:

- Significant alcohol or drug history (> 7 glasses of alcohol per week) per self-report
- Use hearing aids
- Pregnancy
- Current or past history of major medical, neurological, or debilitating psychiatric illness as per self-report
- Current or past history of balance-, vertigo- and/or vestibular- symptoms including Ménières disease

SUBJECT ENROLLMENT
Tinnitus participants will be recruited through physician and audiologist contacts in the Harvard Medical School area. We may also recruit patients and controls by advertising by flyers and printed announcements posted within as well as outside of our Partners community. In addition, email, web and bulletin board announcements posted within our hospital network community may be used. We may also use the Partners' RSVP for Health and RPDR systems. If necessary, auxiliary backup methods such as Craigslist, posting flyers at community billboards in the greater Boston area, emails to physicians and family medicine centers, and advertisements in newspapers etc. may be adopted. Advertisements will briefly describe the study and invite subjects to call if they are interested.

At initial contact, potential participants will be fully informed of the purpose and activities involved in the research study. Interested subjects will be scheduled for an in-person visit where written informed consent will be immediately obtained, by the study coordinator or one of the co-investigators, prior to starting any study procedures. One copy of the signed consent form will be given to the patient, and one will be kept in the study files for documentation. No time limits will be imposed on the informed consent process. Participants are encouraged to take as much time

as they would like during the informed consent process, and all their questions will be answered. It is anticipated that obtaining written informed consent will take approximately 15-25 minutes, on average. Comprehension of the consent information will be assessed via solicitation of answers to questions throughout the process. If comprehension appears to be limited, participants will be actively queried to determine whether they need further explanation.
Necessary data will be gathered for the subject identification and remuneration, including date of birth, gender, years of education, address, telephone number, and social security number.

STUDY PROCEDURES

For all studies, the following questionnaires will be administered initially

Tinnitus Reaction Questionnaire [21]. The TRQ provides a useful index of distress related to tinnitus for subject selection and clinical assessment and has potential as a measure of change in coping ability. Note: Those who score a 78 or higher on the TRQ (classified Grade 5: Catastrophic) will be excluded from the study due to risk of worsening tinnitus symptoms. Subjects with catastrophic tinnitus will be referred to the study audiologist for clinical follow-up.

Tinnitus Handicap Inventory [22]: THI is a brief and psychometrically robust self-report measure used to quantify the impact of tinnitus on daily living.

Visual Analogue Scales [23]. Scale from 0 to 100 for tinnitus awareness, loudness and annoyance, on separate VAS. VAS loudness and annoyance are valid and effective measurements for capturing reductions in tinnitus severity in patients with chronic tinnitus.

Tinnitus Functional Index [24] The TFI is a 25 question inventory that developed to provide a scaling of tinnitus severity, an identification of tinnitus domains with impact on the tinnitus severity, and a responsive measurement of change in tinnitus severity

Sound Reactivity Questionnaire. Developed by the Polley Lab, SRQ is an iteration of the TRQ, however shifts the questions to focus on sensitivity to sound rather than tinnitus. Note: Those who score a 3 or greater on Questions 24 26 ("My sensitivity to sound has caused pain in my ears and head") and 26 ("Sensitivity to sound has led me to think about suicide") then subject is disqualified to participate.

Minimum Masking Level and Residual Inhibition [27]. MML is defined as the lowest tone intensity level required to cover or mask and individual's tinnitus. Correspondingly, the RI is considered the temporary decrease of tinnitus after a prolonged acoustic stimulation.

Auditory Mirror Therapy Questionnaire. AMT Questionnaire was developed to qualitatively analyze how AMT is affecting participants' tinnitus throughout the intervention study.

After obtaining informed consent, subjects will be instructed to rate their tinnitus intensity and aversiveness on VAS scales~~,~~ and rate their tinnitus experience on tinnitus rating instruments~~.~~ questionaries. Thereafter, subjects will be instructed on how to use a tablet device for audiology measurements. The tablet and software are described in Chen et al, Otology & Neurotology, 202. Briefly, tablets and calibrated headphones are provided to participants to complete this study. Tablets are loaded with tinnitus research software programmed by the Polley lab (Mass Eye and Ear). Subjects are shown how to use the tablet-based study application. Additionally, participants will be given a detailed instruction packet on how to use the tablet at home throughout the study.

At study visit 1, participants, with study staff assistance, will complete the first tablet based at-home audiogram (125 to 16000 Hz) in a quiet space, which had previously been shown to have good validity compared with clinical audiograms. On days 2, 4, 6, 8, 10,12,15 and 18~~,~~ participants will complete the audiogram, TFI, VAS, AMT Questionnaire, and tinnitus masking and residual inhibition. Each session lasts approximately ~~30~~ 90 minutes. Participants rate tinnitus intensity on a sliding visual analog scale (VAS) that ranged from "not audible" to "extremely loud". Loudness discomfort levels (LDL) are assessed with pure tones (125–16000Hz in 1 octave increments) in each ear. In the tinnitus matching interface, participants use sliders controlling the center frequency, level and bandwidth of a sound output from the tablet until they generate sounds that matched their tinnitus. Once a sound is locked in, participants then rate how similar this sound is to their current tinnitus percept on a slider that ranges from "sounds nothing like my tinnitus" to "sounds exactly like my tinnitus" Each participant creates 10 tinnitus-matching sounds per session over 7 sessions.

After collection of baseline questionnaires and audiology, subject will be randomized to either AMT or sham treatment.

Randomization will be done using the Microsoft Excel function rand(), with a 50% chance of being assigned to the AMT arm and 50% chance of being assigned to the sham arm. Up to 40 subjects will be assigned to the AMT arm, and up to 40 subjects will be assigned to the sham arm.

Then, each participant will be fitted with the assigned device, and instructed to adjust the volume a comfortable level. Subjects will be allowed to walk around in the lab and cafeteria area. Participants are allowed to stop wearing the device at any time if they feel uncomfortable, confused, experience vertigo or nauseas, or experience their tinnitus worsening.

After walking around, if subjects are still comfortable and do not experience any adverse effects, they will be sent home with an instructions packet and use the device for up to 3 hours per day for a total of 21 days. Throughout the study, the participants will be asked to complete brief surveys about their tinnitus symptoms, as well as at-home audiometry measurements. Reminders via email and or text message will be sent to the participants on days 2, 4, 6, 8, 10,12,15 and 18 to complete these measurements. Furthermore, subjects will be asked to record how much they use the device and any effects they may experience. After 21 days, the participant will return to the lab for audiology measurements, tinnitus rating forms, and then return the device, headphones, and tablet.

Six weeks after the end of the intervention, subjects will be contacted to rate their tinnitus.

Difference between AMT and sham device.

The AMT device and the sham device will look identical, with the only difference that the AMT device will be modified so that sound recorded at the left ear is played back at the right ear, and sound recorded at the right ear is played back at the left ear. Both the AMT and sham device have high fidelity microphones and speakers, but a slight modification of sound, as compared to not wearing a device, is inevitable.

There will be no difference in research procedures for those assigned the sham device.

BIOSTATISTICAL ANALYSIS

The VAS, TFI, TRQ and THI scores and audiological measures pre and post the intervention will be evaluated in Excel/SPSS using a within subject repeated measures t-test.

Power:
We will compare the AMT device to a sham control device. To estimate the magnitude of placebo effects, we extracted placebo responses in prior comparable studies. Across sham device and placebo pharmaceutical studies, in 111 tinnitus subjects, the average withing subject reduction in THI induced by placebo was 7%. In our pilot trial, we observed an average reduction on the THI of 24% (σ = 24%). Thus, the total sample needed to detect a difference between AMT and sham at 80% power and a 5% level of significance is 25 subjects per arm.

RISKS AND DISCOMFORTS

We reviewed the literature and clinicaltrials.gov for adverse effects of behavioral and acoustic interventions on tinnitus.

One acoustic stimulation trial reported a worsening of tinnitus symptoms in 8% of subjects (4 of 50 subjects in clinical trial NCT01541969), while music therapy and Progressive Tinnitus Management report no adverse effects.

In a prospective, open-label, nonrandomized, noncontrolled multicenter clinical study with 200 chronic tinnitus patients, acoustic stimulation treatment led to worsening of tinnitus in one patient [25].

Other types of acoustic stimulation treatment of tinnitus, do not report adverse effects [26].

A Cochrane review of six trials with auditory masking therapy concluded no adverse effects [7].

Taken together, we conclude that a brief exposure to AMT has a low risk of adverse effects, but the possibility of worsening of tinnitus symptoms must be closely monitored.

We anticipate a slight risk of vertigo, confusion and nausea associated with wearing the earmuffs. The participant will be informed that if this happens, he or she should take the earmuffs off and may stop the experiment at any time if they wish.

A potential risk of using the earmuffs is a reduction in situational awareness. It is therefore paramount that subjects do not wear the earmuffs wile in traffic or near traffic, or while bicycling or operating a motor vehicle. Subjects will be instructed to only use the earmuffs in safe environments. Study staff will supervise initial wear.

In the pilot evaluation, two subjects experienced a worsening of their tinnitus symptoms. Subjects will be made aware of this risk, and subjects will be instructed to discontinue use immediately if they experience a worsening of symptoms. Likewise, in the pilot evaluation, some subjects experienced that the device was warm and or too tight to wear for a prolonged period. The new prototypes are more comfortable, but subjects will be made aware of this risk.

POTENTIAL BENEFITS

It is possible that individual subjects will benefit from taking part in this study if the auditory mirror therapy is indeed effective. If the proposed auditory mirror therapy has similar effectiveness as mirror therapy of phantom limb pain, effects may be observable in single subjects. However, while the pilot study suggests a reduction in tinnitus handicap and awareness, there are no established benefits of AMT. If successful, this study will benefit tinnitus patients by providing a simple and readily accessible therapeutic option.

EQUITABLE SELECTION OF SUBJECTS

This research includes adults aged 18-80 years old of all identities; including race, ethnicity, class, sexuality, gender, religion, etc. Children are excluded from the study to minimize risk. In accordance with NIH guidelines, efforts will be made to attain a mix of study participants, in terms of age and racial/ethnic representation. In the present study, the assessment of symptoms will include the self-report of complex sensory, cognitive and emotional experiences. Non-English speakers will not be actively recruited, but should a non-English speaking subject express interest, they will not be denied participation

REMUNERATION

Subjects will be paid $100 at the completion of the study for their participation. Once all devices are handed back, an electronic payment will be made to the participant. If the subject choses to stop participating in the study at any time for any reason, they will still receive the payment for their time.

DATA AND SAFETY MONITORING

The study will regularly monitor for safety, including periodic staff meetings to review any adverse events and treatment outcomes. The PI will also routinely monitor and assure the validity and integrity of collected data and adherence to the IRB-approved protocol. The team will evaluate the progress of the study and verify that the rights and well-being of the participants are protected. Likewise, the lab will confirm that the reported study data are accurate, complete, and verifiable from source documents and ensure that the conduct of the study follows the approved protocol.

Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines. The PI and/or the study staff will take the necessary steps to ensure the recovery and comfort of the patients. Any adverse events will be reported to the IRB within the required timeframe, using the appropriate forms. The principal investigator will provide an interim report of all adverse events to the IRB at the time of continuing review. The seriousness, expectedness, and relationship of any adverse event to the study procedures will be evaluated and documented by the study staff. The study staff will also, in consultation with Partners IRB and the subject, take action to determine whether it is safe for the participant to continue with the study protocol.

MONITORING AND QUALITY ASSURANCE

All study procedures will be in accordance with the MGH subcommittee on Human Studies. The principal investigator will oversee the collection, maintenance, and analysis of the data. Research Affairs will be contacted immediately in the case of unexpected adverse events.

The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data and adherence to the IRB-approved protocol. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well-being of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study follows the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee.

PRIVACY AND CONFIDENTIALITY

All data collected during the study will only be accessible to study personnel. The study protocol has been designed to ensure the privacy and confidentiality of the study participants. Codes are generated to substitute for the name and other identifying information from all study instruments and questionnaires. Confidentiality of subjects is maintained by use of these individual coded identifiers and removal of any identifying information from shared data. The information linking coded identifiers and individual subjects will be stored in the locked offices of the study staff members. Information gathered as part of this study will not be included in the subjects' medical record and will be maintained separately. All study data will be analyzed within the Partners system and will not be transferred or sent to outside institutions. In addition, no subject names will be used in any publication to be generated from the data collected as part of this study. Only the Principal Investigator and co-investigators have access to the study data that is stored in locked cabinets. Due to the nature of the intervention, it is not possible to conceal treatment allocation to the participants or to the study staff.

REFERENCES

1. Mahboubi, H., et al., *The prevalence and characteristics of tinnitus in the youth population of the United States.* Laryngoscope, 2013. **123**(8): p. 2001-8.
2. Shargorodsky, J., G.C. Curhan, and W.R. Farwell, *Prevalence and characteristics of tinnitus among US adults.* Am J Med, 2010. **123**(8): p. 711-8.
3. Shore, S.E., L.E. Roberts, and B. Langguth, *Maladaptive plasticity in tinnitus - triggers, mechanisms and treatment.* Nat Rev Neurol, 2016. **12**(3): p. 150-60.
4. Rauschecker, J.P., et al., *Frontostriatal Gating of Tinnitus and Chronic Pain.* Trends Cogn Sci, 2015. **19**(10): p. 567-78.
5. Baldo, P., et al., *Antidepressants for patients with tinnitus.* Cochrane Database Syst Rev, 2012. **9**: p. CD003853.
6. Cima, R.F., et al., *Cognitive-behavioral treatments for tinnitus: a review of the literature.* J Am Acad Audiol, 2014. **25**(1): p. 29-61.
7. Hobson, J., E. Chisholm, and A. El Refaie, *Sound therapy (masking) in the management of tinnitus in adults.* Cochrane Database Syst Rev, 2012. **11**: p. CD006371.
8. McGurk, H. and J. MacDonald, *Hearing lips and seeing voices.* Nature, 1976. **264**(5588): p. 746-8.
9. Jousmaki, V. and R. Hari, *Parchment-skin illusion: sound-biased touch.* Curr Biol, 1998. **8**(6): p. R190.
10. Sanchez, T.G. and C.B. Rocha, *Diagnosis and management of somatosensory tinnitus: review article.* Clinics (Sao Paulo), 2011. **66**(6): p. 1089-94.
11. Levine, R.A., M. Abel, and H. Cheng, *CNS somatosensory-auditory interactions elicit or modulate tinnitus.* Exp Brain Res, 2003. **153**(4): p. 643-8.
12. Lanting, C.P., et al., *Neural correlates of human somatosensory integration in tinnitus.* Hear Res, 2010. **267**(1-2): p. 78-88.
13. Lockwood, A.H., et al., *The functional anatomy of gaze-evoked tinnitus and sustained lateral gaze.* Neurology, 2001. **56**(4): p. 472-80.
14. An, Y.H., et al., *Does tinnitus affect the sound localization ability?* Otol Neurotol, 2012. **33**(5): p. 692-8.
15. Stratton, G.M., *Some preliminary experiments on vision without inversion of the retinal image.* Psychological Review, 1896. **3**: p. 611-617.
16. Linden, D.E., et al., *The myth of upright vision. A psychophysical and functional imaging study of adaptation to inverting spectacles.* Perception, 1999. **28**(4): p. 469-81.
17. Yoshimura, H., *A hisotrical review of long-term visual-transposition research in Japan.* Psychological Research, 1996. **59**: p. 16-32.
18. Ramachandran, V.S. and D. Rogers-Ramachandran, *Synaesthesia in phantom limbs induced with mirrors.* Proc Biol Sci, 1996. **263**(1369): p. 377-86.
19. Thieme, H., et al., *The Efficacy of Movement Representation Techniques for Treatment of Limb Pain-A Systematic Review and Meta-Analysis.* J Pain, 2016. **17**(2): p. 167-80.
20. Deconinck, F.J., et al., *Reflections on mirror therapy: a systematic review of the effect of mirror visual feedback on the brain.* Neurorehabil Neural Repair, 2015. **29**(4): p. 349-61.
21. Wilson, P.H., et al., *Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus.* J Speech Hear Res, 1991. **34**(1): p. 197-201.
22. Newman, C.W., G.P. Jacobson, and J.B. Spitzer, *Development of the Tinnitus Handicap Inventory.* Arch Otolaryngol Head Neck Surg, 1996. **122**(2): p. 143-8.
23. Adamchic, I., et al., *Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus.* Am J Audiol, 2012. **21**(2): p. 215-25.
24. Meikle, M.B., et al., *The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus.* Ear Hear, 2012. **33**(2): p. 153-76.
25. Hauptmann, C., et al., *Acoustic Coordinated Reset Neuromodulation in a Real Life Patient Population with Chronic Tonal Tinnitus.* Biomed Res Int, 2015. **2015**: p. 569052.
26. Davis, P.B., B. Paki, and P.J. Hanley, *Neuromonics Tinnitus Treatment: third clinical trial.* Ear Hear, 2007. **28**(2): p. 242-59.
27. Fournier P, Cuvillier AF, Gallego S, Paolino F, Paolino M, Quemar A, Londero A, Norena A. A New Method for Assessing Masking and Residual Inhibition of Tinnitus. Trends Hear, 2018.