

PROTOCOL

Role of the Auditory Efferent System in Auditory Perceptual Learning

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Study Synopsis

The goal of this study is to determine the impact of an auditory training program on the function of the inner ear and auditory brainstem. In normal-hearing individuals, the medial olivocochlear (MOC) branch of the auditory efferent system appears to aid with hearing signals in noise. A previous study in young normal-hearing adults found that auditory training strengthened the function of the MOC system in some participants in a way that coincided with their improvements in perceiving speech sounds in background noise (de Boer and Thornton, 2008, *J Neurosci*, 28:4929-4937). The MOC function measured at baseline also predicted the amount of success from the auditory training. Although these results are promising, it is not known if they generalize to populations that often have hearing-in-noise problems such as older and hearing-impaired adults.

This study will examine how an auditory training program impacts MOC activity in a group of older adults with normal hearing or mild hearing loss. This is a prospective study utilizing a repeated-measures design. Participants will participate in a computerized auditory training program taking place over a maximum of one year. Transient-evoked otoacoustic emissions (TEOAEs) will be used to measure the strength of MOC activity at each visit. Performance on untrained stimuli (words and sentences) will also be measured. A control group (no auditory training) will also be used to establish test-retest reliability for TEOAE measurements and performance on the word and sentence testing. A second “speech” control group will only participate in speech testing and the TEOAE testing. The results of this study may contribute to the improved diagnosis and treatment of hearing-in-noise problems in Veterans and in the civilian population.

Study Team

The study team will include the PI (Dr. Marjorie R. Leek), co-investigators (Dr. Ian B. Mertes and Dr. Glen K. Martin), and study staff (Dr. Erin C. Wilbanks and Barden Stagner). Co-investigator Dr. Ian Mertes and Study Staff members Erin Wilbanks and Barden Stagner are trained to obtain informed consent and will participate in the consenting process, answer participants’ questions about the study, and carry out data collection and analysis procedures. The PI, co-investigators, and Study Staff member Barden Stagner will be involved in data collection and data analysis and interpretation.

Barden Stagner was initially trained in consenting by Donna Strong in 2004 while working for Dr. Martin’s project “Otoacoustic Emission Cochleography”. He consented subjects for that project from 2004 until the end of 2015. He received additional training with Donna Strong around September of 2015 to work on Dr. Leek’s projects and practiced consenting several times under the supervision of Dr. Erin Wilbanks.

Test Site

This is a single-site study that will take place at the Auditory Research Laboratory, located at the VA Loma Linda Healthcare System (VALLHS) in Loma Linda, CA.

Participants and Eligibility

Veterans and non-Veterans, both males and females, between the ages of 35 and 89 with either normal hearing or mild sensorineural hearing loss will participate. Recruitment of non-Veteran participants is necessary because there is a high prevalence of hearing loss in the Veteran population, especially those 50 years of age and older

(http://www.publichealth.va.gov/docs/vhi/hearing_impairment.pdf). Past efforts by our laboratory to recruit a sufficient number of normal-hearing Veterans ages 35 and older have proven difficult. Women and minorities will be encouraged to participate.

We plan to screen up to 1000 participants. Up to 200 volunteers will be enrolled in the study. Each participant will participate in from 1 to 14 study visits.

The following exclusion criteria will apply: (1) a conductive hearing loss or other otologic pathology; (2) three-frequency pure-tone average >40 dB HL; (3) >15 dB asymmetry in hearing thresholds at more than two frequencies; (4) absent acoustic reflexes; (5) absent transient-evoked otoacoustic emissions (TEOAEs), defined as a signal-to-noise ratio of <6 decibels; (6) chronic disease or use of medication that might affect the auditory system or the participant's ability to perform the experimental tasks; (7) an inability to comply with test procedures; (8) an inability to read and speak English.

Participant Groups

Participants will be randomly assigned *a priori* to either the Experimental group (auditory training) or Control group (no auditory training) using simple random assignment. Because the third group (Speech Group) is added after the experimental and control groups have completed their participation, to provide additional power to the regression analysis, the Speech group will be assigned by the investigator. Because this study will detect whether or not significant changes in MOC activity and speech perception across time occurred as a result of auditory training, the Control group is needed to establish the test-retest reliability of our outcome measures in the absence of any training. Participants will be informed of which group they are assigned to at the initial visit, but they will not be allowed to change groups.

Sample Size

Based on power analyses, the study will require participation of at least 12 participants in the experimental group. Sample sizes were estimated using data from studies that reported differences in MOC activity or speech perception before and after an auditory training program. Pre- and post-training means and standard deviations were used to compute the minimum sample sizes (n) needed to detect a mean difference in paired samples (i.e., mean results for pre- versus post-training performance in the same participants), using methods described in Dupont and Plummer (1990, *Control Clin Trials*, 11:116-128). Sample sizes were calculated using a type I error rate of 0.05 and 80% power to detect differences in mean performance between pre-training and post-training. For MOC activity, the results of de Boer and Thornton (2008, *J Neurosci*, 28:4929-4937) indicated a minimum of $n = 10$. For word recognition, the results of Henshaw and Ferguson (2014, *Proc ISAAAR 2013*) indicated a minimum of $n = 12$. For sentence recognition, the results of Song et al. (2011, *Cereb Cortex*, 22:1180-1190) indicated a minimum of $n = 11$. An

equal number of participants will be assigned to the control group. To account for possible subject attrition, we tentatively plan to recruit up to 40 total participants (20 each in the Experimental and Control groups).

Recruitment

Potential participants will be recruited through several methods. One method will include a contact list of current and former participants of the Auditory Research Laboratory who agreed to be contacted regarding future studies. This [REDACTED] is stored on [REDACTED] and is password-protected so only authorized study staff has access. Personal information stored on this list consists of first and last name, date of birth, last 4 numbers of the SSN, phone number, and results of the hearing screening conducted during their participation in an earlier study. Potentially eligible participants from this list will be contacted by phone. Information about the study will be discussed and if they are interested, an initial study visit will be scheduled at their convenience.

Other recruitment methods include electronic billboard advertisements placed throughout the VALLHS, volunteer fliers placed in the VALLHS audiology clinic, word-of-mouth referral from VALLHS audiologists, and special events held on VALLHS property such as health fairs and research events.

For all forms of recruitment, interested individuals will be provided the laboratory phone number to call if they are interested. The research team will describe the study in more detail and answer any questions the individual may have. If they continue to be interested, the research team will conduct an initial screening over the phone. Individuals will provide their first and last name and last 4 of the SSN to authorized study staff. This information will be stored in the [REDACTED] password-protected document stored on [REDACTED] accessible only to authorized study staff. Authorized study staff will ask the individual a series of questions related to the inclusion and exclusion criteria for this study. They will be asked if they are between ages 35-89, have normal hearing or mild hearing loss, have the ability to read and speak English, have no history of conductive hearing loss or otologic pathology, and have no chronic disease or use of medication that affects the auditory system or ability to perform experimental tasks. The answers to these questions will not be stored in the screening log, but are used solely to determine if the person is eligible for an initial study visit. For individuals who have had a previous hearing test at the Loma Linda VA, this information will be accessed in CPRS by authorized study staff to determine if the individual's hearing thresholds fall within the inclusion criteria. If the test indicates that their hearing falls within the allowable range, a laboratory visit will be scheduled if they are interested in being in the study. If the individual has not had a hearing test at the Loma Linda VA but reports normal hearing or mild hearing loss, an initial visit will be scheduled at the individual's convenience.

Participant Compensation

All eligible participants will be paid for their time and effort for participating in this research project. Each participant will be paid \$10 per hour of participation. Participants can receive a maximum of \$420 (14 study visits × 3 hr/visit × \$10/hr). If, for any reason, a participant wishes to stop the session before all the data are collected, he or she will still receive payment for the time of participation, with each partial hour paid as a full hour.

The participant will receive the payment by check from the Loma Linda Veterans Association for Research and Education (LLVARE). Checks will be mailed to the participant

after every study visit in which he or she participates. In order for the participant to be paid for participation, the first and last name, mailing address, and social security number will be provided to LLVARE on a payment form signed by the participant at each visit. Additionally, each participant will complete an IRS W-9 form at the initial visit; this form will be sent to LLVARE, who requires this form in order to report the participant's income received for this participation.

Study Timeline

The experiment will be carried out over the course of 3 years. Disbursement of research funds from NIH is expected to occur on or before 12/1/2015. Participant recruitment and data collection will begin immediately after disbursement of funds. Using a conservative estimate of recruiting one new participant per week, it will take 40 weeks to recruit all 40 participants. The last participant will therefore be tested approximately 15 weeks from that point, for a total of 55 weeks to complete data collection. We will allot an additional 12 months for data collection to account for potential delays in participant recruitment and attrition.

This study consists of one experiment that will last 3 years total. Each participant is expected to complete all study procedures in from 1 to 14 study visits, ideally over a 10-week period. However, we will allow for the visits to take place across a one year period to account for participants needing to miss or reschedule some visits. Additionally, we will allow each subject to make-up a maximum of 2 study visits. All study visits will last between 2-3 hours. Thus, the maximum amount of participation for each participant is 42 hours during a maximum one year window for data collection.

Instrumentation

Standard-of-care screenings and experimental testing will be carried out in a double-walled sound-isolated audiometric chamber adjoined to a single-walled room in the Auditory Research Laboratory, located at the VALLHS. Initial audiometric testing using standard-of-care procedures will be conducted to verify eligibility for the study and will be carried out using standard clinical equipment. A Grason-Stadler (GSI 61) clinical audiometer calibrated to standards (American National Standards Institute, 1996) will be used to deliver the pure-tone signals for threshold testing through Etymotic Research ER-3A insert earphones. Speech audiometry will be achieved by presenting words (pre-recorded or live voice) through insert earphones via the audiometer. A Grason-Stadler Tymptest Middle Ear Analyzer acoustic-immittance meter will be used for immittance measurements to verify normal middle ear function. A visual inspection of participants' ear canals and tympanic membranes will be performed using a Welch-Allyn otoscope.

Experimental tests will consist of TEOAE testing, word/sentence recognition testing, and an auditory training program (only participants in the Experimental group will undergo the auditory training). For all experimental testing, participants will be seated in the sound booth. TEOAE testing uses an Etymotic Research ER-10D microphone and loudspeaker assembly. The hardware is controlled by a computer-based otoacoustic emissions system (Intelligent Hearing Systems) that interfaces with the MATLAB programming language. The software allows for the selection of sounds, as well as parameters of the testing such as duration, amplitude, and rate of stimulus presentation. For word and sentence testing, pre-recorded speech stimuli (saved as digital computer files) are presented through insert earphones using custom MATLAB software. Participants will make responses either by

pressing a button on an ELO TouchSystems touch screen monitor (for word testing) or by verbally repeating back the sentences (for sentence testing). The computerized auditory training program (Speech Perception Assessment and Training System; SPATS) will be run from a computer. The SPATS stimuli are digital computer files that are presented through insert earphones. Participants will make their responses concerning what they heard by mouse click or keyboard entry. At the end of each session, the response data will be stored on the local computer. No patient identifiable information will be included in the data files.

As part of the experimental set-up, all stimuli will be verified as to their spectral and temporal characteristics using a Tektronix oscilloscope and a Signal Analyzer. The stimulus intensity levels will be checked weekly using a Larson-Davis 824 sound level meter and a standard 2-cc coupler. Biologic calibrations will also be performed weekly, where study team members will listen to the sounds presented through earphones to ensure that the volumes are appropriate.

Testing Procedures

Standard of Care Procedures

At the beginning of the initial study visit (after informed consent is obtained), routine audiometric tests will be administered by trained Study Staff (primarily co-investigator Dr. Mertes, with assistance from Study Staff members Dr. Erin C. Wilbanks and Barden Stagner as needed). Dr. Mertes and Dr. Wilbanks are trained clinical audiologists with an advanced degree in audiology and are licensed to practice in either California or another state. This is the same requirement as for audiologists who work in the Audiology clinic at the VALLHS. Barden Stagner has over 30 years of experience testing human and animal subjects in auditory research settings. The purpose of this evaluation is to verify hearing eligibility for the study. If a participant recently had a hearing test at the VA Loma Linda audiology clinic (within 6 months), this audiometric information may be used for the study and so it may not be necessary to repeat the initial hearing screening for the study. The following standard-of-care procedures will be conducted:

Interview: An initial interview will be conducted to obtain case history information about current and past hearing and ear-related problems, family history of hearing loss, history of noise exposure, current health status, and present and past hearing-aid use (if any). The purpose of this history is to establish eligibility to be in the study, to aid in the interpretation of the experimental data, to provide case history information concerning probable etiologies of participants' hearing losses in articles and presentations emerging from the study.

Otoscopy: The ear canal and tympanic membrane of the patient will be visually inspected for abnormalities, such as earwax blocking the ear canal.

Pure-tone audiometry. Air conduction and bone conduction thresholds will be measured using recommended procedures (American Speech-Language-Hearing Association, 1978). Pure tone thresholds will be used to define degree and type of hearing impairment. Pure-tone audiometry will be repeated at visits 6, 11, and 12 to detect any changes in hearing thresholds over the course of the study (not due to participation in the study itself because all sound levels are presented at safe volumes).

Speech audiometry. Speech recognition thresholds will be measured using standard clinical procedures. Word recognition scores in quiet will be measured in each ear by presenting pre-recorded word lists through insert earphones and subjects verbally repeat back the words they hear. This information will be used to aid in the interpretation of the experimental data.

Immittance audiometry. Immittance audiometry will be used to examine middle ear function and to rule out conductive or retrocochlear pathology. Immittance audiometry will also be conducted immediately prior to TEOAE testing (described below) to ensure normal middle ear function.

Experimental Procedures

The following experimental procedures will be conducted:

TEOAE Testing: The basic task of the participants is similar to TEOAE procedures used clinically to evaluate hearing function objectively. Testing involves listening to sounds presented through earphones while seated comfortably in a sound-treated booth, and remaining alert but quiet in order to successfully measure responses from the cochlea and brainstem. Excessive body movement, swallowing, coughing, talking, and chewing creates acoustic and electric noise that can obscure recordings of TEOAEs, so it is imperative that participants remain as still as they can during the measurements. The experimental measurements differ from clinical measurements primarily in the types of sounds presented, the data analysis, and the use of an attention task to keep participants alert and awake. Specially constructed stimuli intended to stimulate the MOC system will be generated digitally on a computer, and played out to the listener using high-quality digital-to-analog converters, attenuators, filters, and other laboratory equipment. These sounds involve amplitude-modulated tones, click trains, and white noise. All stimuli will be presented at moderate volumes that are well below sound levels considered hazardous by OSHA and NIOSH standards. TEOAE measurements consist of waveforms, which are changes in sound amplitude across time. MOC function will be quantified as the change in waveform amplitude with versus without white noise presented to the opposite ear, where a larger change indicates stronger MOC activity. Repeated measurements will be obtained (both within a study visit and across study visits) to determine the change in MOC activity across time. Immittance audiometry will be obtained immediately prior to TEOAE testing at each visit to ensure that middle ear function is normal (successful measurement of TEOAEs requires normal middle ear function).

Word/Sentence Testing: Testing involves listening to words and sentences presented through earphones while seated in the sound-treated booth. Speech stimuli will be presented in the presence of background noise. Participants make a response about the word(s) they heard. For word testing, participants press a button on a touch screen monitor corresponding to the words that they heard. Their responses are automatically recorded by custom software. For sentence testing, participants verbally repeat back the words they hear in each sentence. The experimenter enters the number of correct responses into the computer. The experimental measurements differ from clinical measurements primarily in the types of sounds presented and the data analysis. Sounds will be presented at safe and comfortable levels. Performance will be quantified as the number of words correct and also the characteristics of the stimuli (e.g., the levels of the speech and background noise). Repeated measurements will be obtained (both within a study visit and across study visits) to determine the change in speech perception ability across time.

Auditory Training (Experimental group only): Listeners will be seated comfortably in the sound booth at a workstation with a computer screen, keyboard, and mouse. Sounds will be presented to the participants through insert earphones. Sounds for the testing and training will be presented at calibrated levels from the computer. Participants will make their responses concerning what they heard by mouse click or keyboard entry. At the end of each

session, the response data will be stored on the local computer. No patient identifiable information will be included on the data files. Performance will be quantified as the number of correct responses and also the characteristics of the stimuli (e.g., the levels of the speech and background noise). The auditory training program consists of a curriculum of word and sentence presentations in various noise levels, and performance on repeated measurements are tracked throughout the subject's participation in the program.

Order of Procedures

At the beginning of the initial study visit, a study team member will first explain the nature of the study and obtain the volunteer's consent. The consent form will be explained and then it will be given to the participant to read. The participant will be encouraged to ask any questions he or she might have, and the team member will provide answers. After it is clear that the participant understands the nature of the study, the team member will emphasize that the participant is under no obligation to participate and will offer to answer questions about the study at any time during the participant's participation. If the participant agrees to participate in the study, he or she will be asked to sign the consent form, and a description of privacy information to be collected and how such information will be used (for Veterans, the HIPAA form will be used; for non-Veterans, the VA Notice of Privacy Practices form will be used). A copy of the consent form and relevant privacy form will be given to the participant along with a copy of the California Experimental Research Subject's Bill of Rights.

Next, the volunteer will undergo routine audiological screening (standard-of-care procedures) as described above to verify their hearing eligibility. If their audiological results are not appropriate for the study, they will be dismissed and will receive a payment of \$10/hour of participation as compensation for participating in this initial session, and our thanks. If the volunteer is suitable for the experiment, the experimental procedures will begin.

All participants will undergo otoscopy, immittance testing, TEOAE testing, word testing, and sentence testing at each visit. Participants in the experimental group will also complete the auditory training program, with baseline (pre-training) measures at visit 1, training occurring in visits 2-11, and visit 12 serving as the retention (post-training) measurements. These participants will therefore undergo a total of 15 hours of auditory training spread across 10 visits, plus pre- and post-tests. Pure-tone audiometry will be repeated for all participants at visits 6, 11, and 12 to detect any significant changes in hearing thresholds during the course of a participant's participation (not due to actual participation in the study because all sound levels will be presented at safe volumes). Such changes in audiometric measures are not likely to occur over this relatively short time period. All participants (except those in the Speech group) will be asked to return for a visit twice a week for the first 6 weeks (visits 1-11) and return for the final visit 4 weeks later (visit 12). Each subject will be allowed a maximum of two make-up visits in case a visit needs to be stopped early, resulting in a maximum of 14 study visits.

Personal Information to be Collected

Individuals who make initial contact regarding the study will provide authorized study staff with their first and last name and last 4 of SSN. This information will be stored on the password-protected [REDACTED]. This information will be used to determine participant eligibility (via previous audiograms stored in CPRS, if any exist) and to schedule a study visit in VISTA if the individual is interested in participating. These individuals

will also answer several questions over the phone to study staff, which are related to the inclusion and exclusion criteria.

Personal information to be collected for participants participating in the research study will include first and last name, address, phone number, date of birth, full SSN, and hearing screening results conducted for the current study. This information is necessary to determine eligibility, contact the individual, document informed written consent, access medical records and write progress notes in CPRS, and to process the payment for participation.

This information will be stored on a password-protected document saved on [REDACTED], and only authorized lab members will have access. Participants will be assigned an experimental ID number in sequential order. This document will also serve as the linkage log that links participant names with ID numbers. The signed informed consent document will be stored in the locked filing cabinet, stored separately from any experimental data. In order for LLVARE to process participant payments, participants will fill out an IRS W9 form and a participant payment form. Both forms will contain the participant's first and last name, address, and full SSN. Copies of these forms will be stored in a locked filing cabinet in a locked office within the lab, stored separately from the experimental data. The original copies will be sent to the LLVARE business office via interoffice mail.

Participants expressing an interest in being contacted for future studies will indicate their agreement by initialing the designated part on the informed consent document. For these individuals, their first and last name, date of birth, last 4 of SSN, phone number, and hearing screening results will be saved on a password-protected file on [REDACTED] that will only be accessible to authorized study staff.

Risk to Participants

This is a minimal risk study. The participants will all be healthy adults (other than mild hearing loss in some participants). There are no foreseeable risks involved in these studies beyond those associated with routine audiological practice, such as boredom or fatigue during testing. All sound levels to be used in the studies fall below the Damage Risk Criteria established by OSHA for intensity-duration interaction. If there is a breach of confidentiality, participants' personal information (name, address, date of birth, last 4 of SSN, and hearing ability) may be revealed.

Steps Taken to Minimize Risks and Data Safety Monitoring

Participants will be provided with as many breaks during testing as they or the experimenter feel are helpful to minimize mental fatigue and boredom. Loudness levels of stimuli are carefully controlled, with frequent calibration and monitoring of laboratory equipment. Participant confidentiality will be protected by using only participant codes (three numbers) to label data collection sheets and computer data files. Participant numbers will be assigned sequentially and will not contain identifying information. Neither names nor social security numbers will be included in the participants' data files, although names and contact information will be filed separately so that participants can be contacted for future appointments. Signed consent forms will be stored separately from the experimental data as well. Any written or oral report or publication of the information obtained in this study will not contain the names of participants or identifying information. All data records will be stored on password-protected computers or as hard copy in locked offices or laboratories. Data are stored in the laboratory and/or in the experimenter's office, both of which are kept locked when no one is there.

Participant safety and comfort and data collection will be constantly monitored for each participant by the research team member collecting the data for that participant. Overall data collection will be monitored by the Principal Investigator, Dr. Marjorie R. Leek. Following completion of the study, all data will be maintained in accordance with VHA guidelines.

Benefits of Participating

All individuals will receive an up-to-date hearing screening and a further understanding of their own hearing. Participants in the Experimental group may or may not notice an improved ability to hear sounds in background noise after undergoing auditory training. The knowledge gained from this study may also benefit individuals with hearing-in-noise problems by contributing to improved diagnosis and treatment of hearing-in-noise problems in Veterans and in the civilian population.

Data Analysis

Correlational analyses will be used to determine the correspondence between changes in MOC activity and changes in speech perception during the course of auditory training. Statistical analyses of test-retest reliability from the Control group data will be used to determine what constitutes a statistically significant change in MOC activity and speech perception ability. Repeated measures analyses of variance (both within a study visit and across study visits) will also be performed.