AWARD NUMBER: W81XWH-18-2-0033

TITLE: Objective Assessment of Auditory Pathway Integrity and Functional Hearing Abilities

PRINCIPAL INVESTIGATOR: Kenneth W. Grant, PhD

CONTRACTING ORGANIZATION: The Geneva Foundation

REPORT DATE: AUGUST 2022

TYPE OF REPORT: ANNUAL REPORT

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE		*Form Approved* *OMB No. 0704-0188*

1. REPORT DATE AUGUST 2022	**2. REPORT TYPE** ANNUAL REPORT	**3. DATES COVERED** 01 Aug 2021 – 31 JUL 2022
4. TITLE AND SUBTITLE Objective Assessment of Auditory Pathway Integrity and Functional Hearing Abilities		**5a. CONTRACT NUMBER**
		5b. GRANT NUMBER W81XWH-18-2-0033
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) Kenneth W. Grant, PhD E-Mail: kenneth.w.grant.civ@mail.mil		**5d. PROJECT NUMBER** 11003
		5e. TASK NUMBER
		5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Walter Reed National Military Medical Center 8901 Wisconsin Ave Bethesda, MD 20889-0001		**8. PERFORMING ORGANIZATION REPORT NUMBER**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012		**10. SPONSOR/MONITOR'S ACRONYM(S)**
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited		
13. SUPPLEMENTARY NOTES		

14. ABSTRACT

In preparation for imminent hair cell regeneration clinical trials, it is essential to develop a systematic approach to assess the degree of functional hearing restoration as the regeneration of hair cells, the reintegration of these cells and their associated neural pathways within the auditory system, and the reorganization of the auditory cortex to newly restored sound inputs progresses over time. Therefore, the purpose of developing a functional assessment battery is to provide multiple opportunities to demonstrate success, from early physical reintegration of the cochlea through the thalamus-cortical pathway (such as tests of outer and inner hair cell, brainstem, and efferent system activity), to simple and more complex sound discrimination, such as frequency, duration, modulation discrimination crucial for understanding speech in noisy environments. To demonstrate the utility of this behavioral and physiological assessment battery, listeners with a wide range of hearing loss from normal hearing to moderate-to-severe hearing loss will be evaluated to establish expected values for different degrees of hearing damage. To validate the repeatability of the proposed assessment battery, a subset of listeners with varying degrees of hearing loss will be tested on two occasions separated by roughly one month. Finally, the extent to which simple and complex pre-attentive discrimination abilities, as well as cochlear reintegration measures, can predict complex speech in noise performance will be evaluated.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified	34	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The U.S. involvement in Iraq and Afghanistan has resulted in unprecedented amounts of noise and blast trauma to the auditory system. This damage may manifest itself in patients complaining of difficulty understanding speech in complex backgrounds while at the same time presenting with normal to near-normal audiometric thresholds. Standard clinical audiometric tests may fail to properly diagnose the true extent of hearing damage, even when hearing thresholds have been permanently elevated, and current rehabilitation strategies may not restore hearing to a functioning status appropriate for military readiness. To address this problem, biotechnology companies are working on techniques to restore hearing through regeneration of cochlear hair cells. This research project seeks to develop and validate an objective battery of tests to track the various stages of cochlear and auditory pathway reintegration and reorganization necessary to restore hearing from an initial state of severe-to-profound hearing impairment to a functional state more appropriate for active-duty service.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Hearing loss, hearing restoration, electroencephalography, speech perception

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Aim 1: Identify objective pre-attentive and unbiased electrophysiological (EEG) measures that differentiate between normal-hearing systems and those with auditory dysfunction and establish expected values of those measures for varying degrees of hearing loss. (Months 1-18)**

- **Major Task 1.1:** Finalize all hires (completed 12/27/2018). Replace Dr. Rebecca Lewis (completed 08/10/2020). Obtain IRB approval (completed 10/14/2018). Program and pilot all test measures. (completed 6/26/2020). (Planned for months 1–6)**
- **Major Task 1.2:** Program, calibrate, and test equipment for middle-ear muscle reflexes (completed 01/12/2021).
- **Major Task 1.3:** Complete training (12/08/2020) and establish data-sharing agreements for use of ANAM (90% completed).
- **Major Task 1.4:** Administer the proposed test battery to three hearing groups with individual hearing thresholds ranging from 1) normal to 2) mild, to 3) moderate-to-severe to compare results that likely represent stages of incremental improvement during the hearing restoration process. (initiated 2/3/2020; 50% completed). (Planned for months 6–18)**

Aim 2: Assess differences between individual's objective test measures between sessions to determine reliability of the test measure. (24% complete). (Planned for months 6–18)**

- o **Major Task 2.1:** Re-administer the proposed test battery to a subset of participants from the three hearing groups at multiple time periods to determine within-subject differences (initiated 1/19/2021). (Planned for months 6-18)**

Aim 3: Evaluate the ability to predict functional measures of speech in noise performance from objective measures of the physical integrity of the auditory system (ongoing). (Planned for months 1–45)

- o **Major Task 3.1:** Determine the minimum number of tests necessary to provide adequate information about the comprehensive functionality of the entire auditory pathway for clinical feasibility (ongoing). (Planned for months 1–45)**

**** Interruptions due to the response to SARS-CoV-2 and laboratory closures caused significant delays in data collection and analyses. Some project milestones have been extended by 9 months to be completed during NCE, while others were extended to account for the suspension of activities during the first three years. Many of the above Aims have been met (all hiring actions, selection of tests, and analyses pipelines). The primary purpose for the second NCE is to test enough subjects per group to run planned statistical analyses. A second NCE request has been approved to extend recruiting efforts to capture all patients coming to the National Military Audiology and Speech Pathology Center (NMASC), WRNMMC, and to account for continued participant hesitancy coming to Walter Reed-Bethesda.**

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Aim 1: Major Tasks 1.1, 1.2, and 1.3 have been met. Continued recruitment and enrollment of participants (Major Task 1.4). As of July 31, 2022, 50 participants have completed the study with additional subjects who are in the enrollment processes or have been contacted for screening and scheduling. We continue to receive subject referrals from the Hearing Conservation Program, through ASC clinicians, and from the TBI Research Opportunities and Outreach for Participation in Research Studies (TROOPS), as well as from ads placed on the Walter Reed Intranet home page. We have also established a new recruitment source using the patient check-in kiosks in the NMASC lobby. Since the new lobby kiosk recruitment system has been fully operational, we have received interest from an average of 30 new individuals per week and 20% of these individuals meet all inclusion criteria, confirmed by our clinical audiologists. Importantly, many of these individuals have some degree of hearing loss, which will greatly assist us in attaining the required numbers of participants in the mild and moderate-to-severe categories. We are confident that this new recruitment method promises to greatly increase our participant enrollment numbers for this study.

Aim 2: Continued to re-administer the test battery to willing participants at approximately one month after completion of the initial sessions to determine reliability of the test measure (Major Task 2.1). As of July 31, 2022, 11 participants have completed all re-testing. Most participants who complete the initial testing sessions continue to express interest in completing re-testing.

Aim 3: At this stage of the study, the available data are insufficient to evaluate the ability of our test measures to predict speech in noise performance or subjective complaints regarding speech communication or sound quality, and to determine which tests are minimally necessary for this purpose. An abstract detailing the initial results was accepted for a poster presentation at the Military Health System Research Symposium (MHSRS). The MHSRS is the Department of Defense's foremost scientific meeting, and is scheduled to meet in mid-September, 2022. The poster we will be presenting is shown in Appendix D. We continue to develop pipelines and scripts for analyzing test data and checking data quality (Major Task 3.1). Descriptive analyses of the currently-available data indicate that our tests are capturing the intended effects across subject groups and the quality of the data we are collecting is good. Appendix B includes a table with tasks, their associated metrics, and the auditory ability or function they are designed to measure. Descriptive plots for several tasks are included in Appendix C that illustrate the target effects for several experimental tasks, differences between participants with normal hearing pure-tone thresholds (NHT) and participants with elevated hearing thresholds (EHT). EHT participants with mild hearing loss (mEHT), and participants with moderate-to-severe hearing loss (sEHT) groups are being recruited, and correlations between different metrics are being explored. As the group sizes continue to grow, more formal statistical analyses will be conducted to determine the effects of hearing threshold elevation on subjective, behavioral, and objective metrics.

Major regulatory activities to date:

- IRB approval was obtained October 14, 2018.
- CRADA between Geneva and Walter Reed was established in January 2019.
- HRPO approval was obtained on January 24, 2019.
- Continuing review for 2019 was approved on September 11, 2019.
- Continuing review for 2020 was approved on August 11, 2020.
- Data sharing agreement with CNRM was established in July 2020 and renewed August 2021
- Continuing review for 2021 was approved on August 11, 2021.
- Continuing review for 2022 was approved on August 16, 2022.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Analysis of EEG recordings to simple and complex auditory stimuli requires both knowledge and experience in order to achieve good quality data. The creation of a physiological assessment battery which is capable of objectively probing multiple levels of auditory processing requires a detailed reading of the literature regarding different processing stages along the auditory pathways, stimulus creation with signal properties that highlight the processing of different stages of auditory processing, and post-processing analysis scripts to extract relevant data from EEG recordings. Each of these important tasks was undertaken by our research audiologist and research neuropsychologist before they were invited to work for start-up companies and left the project. Dr. Ian Phillips was equally tasked when he was hired. Dr. Phillips was already in possession of EEG acquisition and analysis skills for late cortical components typically associated with the processing of language and meaning. The current project offered additional opportunities to acquire skills in traditional audiological evaluation (audiogram, DPOAEs, tympanometry) as well as electrophysiological evaluations of early cochlear and brainstem processing of simple and complex acoustic signals.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

An abstract detailing the initial results was accepted for a poster presentation at the Military Health System Research Symposium (MHSRS). The MHSRS is the Department of Defense's foremost scientific meeting, and is scheduled to meet in mid-September, 2022. A poster presentation was created (Appendix D) and received publication clearance August 26, 2022. The poster will be presented on September 14, 2022.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Recruitment and enrollment for Aims 1–3 will continue during the first three quarters of the second NCE year. Participant enrollment has increased significantly with the implementation of new recruitment efforts via the NMASC lobby kiosks and the waning threat of COVID-19. During the last quarter, we have experienced an increase in data collection delays and cancellations due to COVID-19. However, we are confident that going forward, these continuing delays will not significantly impact our ability to enroll the number of study participants needed to conduct the planned analyses. Development of data analysis scripts will also continue to reduce analysis times once data collection is completed. Lastly, the data sharing agreement with the US Army Office of The Surgeon General (OTSG) / Medical Command (MEDCOM) for ANAM testing will be established. This DSA does not affect data collection efforts. New analysis scripts will be created to facilitate analyses of ANAM data.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Although progress has been delayed due to SARS-CoV-2, we expect to establish objective electrophysiological biomarkers for auditory system processing in adult Service Members with normal, mild, and moderate-to-severe hearing impairment.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Objective, state independent metrics have several advantages over traditional behavioral measures of auditory function in that they target specific stages of auditory processing from cochlea through midbrain and early cortical response to simple and complex acoustic signals. These measures are ideal for tracking progress over time following efforts to restore missing or damaged cochlear hair cells.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Current use of EEG and other electrophysiological measurement systems are not suitable for clinical evaluation due to expense both in time and money. Future portable and dry EEG solutions are currently being developed. We have made contact with potential industry partners who are currently working on EEG solutions that can collect data continuously over long periods of time (8–24 hours), essential for determining the time course for auditory system structural and functional recovery following hair-cell regeneration.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Individuals with severe-to-profound hearing impairment have very few options available to them regarding hearing restoration. Hearing aids offer some, but not enough, benefit to allow for successful processing of speech. Cochlear implants offer great potential to restore speech processing in quiet, but are still not able to fully restore speech perception when there is competing noise or multiple speakers in the environment. Furthermore, the cost of implants may be prohibitive as a rehabilitation strategy for many adults with hearing loss. Hearing restoration that seeks to "regrow" damaged or missing cochlear hair cells offer the promise of improved perception of speech and non-speech auditory input by restoring auditory processing to a more normal state. Results from this project bring academic and industry attention to the challenges of cochlear hair-cell regeneration and describe restoration milestones as hearing function recovers from severe impairment levels to normal.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Participant enrollment began February 2020. However, due the COVID-19 pandemic, face-to-face research activities were suspended from March 17th, 2020 to July 6th, 2020. Recruitment is once again underway but subject to periodic slow-downs due to COVID-19 and participant reluctance to come to Walter Reed. Dr. Grant and Dr. Phillips have continued to establish new participant recruitment sources to mitigate anticipated slow-downs.

Despite the unexpected interruption, we have experienced a steady flow of interested volunteers for study participation since the return of face-to-face activities. Additional delays in subject testing are ongoing and somewhat unpredictable due to COVID-19 and variant hesitancy. We are using several different recruiting techniques to increase the number of potential study participants that we are enrolling each month. We do not anticipate long-term issues in recruitment/enrollment given the expressed interest of potential volunteers since face-to-face research activities resumed. We requested a second no-cost extension (Year 5) to ensure all goals of the research protocol are met.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Personnel turnovers and delays in programming equipment have contributed to slower expenditures than originally predicted; however, the biggest impact on expenditures has been the suspension of face-to-face research activities due to the COVID-19 pandemic. As a result, recruitment and enrollment of participants was suspended from March 17, 2020 until July 6, 2020. Since recruitment has resumed, we have observed initially a steady flow of interested volunteers.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution *committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if the presentation produced a manuscript.*

Poster presentation to MHSRS 2022 Conference (Appendix D) - to be presented on 14 September 2022. The poster has been approved for dissemination on August 26, 2022.

- **Website(s) or other Internet site(s)**
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques that were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*

- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Data analysis pipelines have been created and utilized to efficiently update reports separately for each proposed metric (e.g. ASSR, MMN).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

<u>Example:</u>

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Kenneth Grant, Ph.D.
No change.	
Name:	Ian Phillips, Ph.D.
No change.	
Name:	Sandeep Phatak, Ph.D.
No change.	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name:	The Center for Neuroscience and Regenerative Medicine (CNRM) / Uniformed Services University of the Health Sciences (USUHS)
Location of Organization:	Bethesda, MD
Partner's contribution to the project:	In-Kind Support. Under this collaboration, the project makes use of the CNRM recruitment database (data sharing agreement established July 2020)
Organization Name:	US Army Office of The Surgeon General (OTSG) / Medical Command (MEDCOM)
Location of Organization:	San Antonio, TX

Partner's contribution to the project:	In-Kind Support. Data sharing agreement in progress for cognitive assessment data (ANAM) on borrowed equipment.
Organization Name:	Dartmouth College
Location of Organization:	Hanover, NH
Partner's contribution to the project:	In-Kind Support. Loaner agreement established to borrow equipment (CRADA modification established September 2019

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Appendix A: References

Abdala, C., & Visser-Dumont, L. (2001). Distortion product otoacoustic emissions: A tool for hearing assessment and scientific study. The Volta Review, 103(4), 281–302.

Brungart, D. S., Sheffield, B. M., & Kubli, L. R. (2014). Development of a test battery for evaluating speech perception in complex listening environments. The Journal of the Acoustical Society of America, 136(2), 777–790. https://doi.org/10.1121/1.4887440

Gatehouse, S., & Noble, W. (2004). The Speech, Spatial and Qualities of Hearing Scale (SSQ). International Journal of Audiology, 43(2), 85–99. https://doi.org/10.1080/14992020400050014

Grant, K. W., Kubli, L. R., Phatak, S. A., Galloza, H., & Brungart, D. S. (2021). Estimated prevalence of functional hearing difficulties in blast-exposed service members with normal to near–normal-hearing thresholds. Ear and Hearing, 42(6), 1615–1626. https://doi.org/10.1097/AUD.0000000000001067

Monson, B. B., Hunter, E. J., Lotto, A. J., & Story, B. H. (2014). The perceptual significance of high-frequency energy in the human voice. *Frontiers in Psychology, 0*. https://doi.org/10.3389/fpsyg.2014.00587

Appendix B: Overview of Experimental Tasks

Table 1 lists the experimental tasks used in this study, along with the specific metrics used to quantify the performance in each task and the auditory ability/function that those metrics are broadly considered to measure.

Table 1. Summary of experimental tasks.

Task	Details & Metrics	Ability / Function
[Audiogram] Pure tone thresholds	Standardized clinical test. Air conduction thresholds [dB HL] of pure tone in both ears.	Audibility
[DPOAE] Distortion-product otoacoustic emission in quiet and in noise	Standardized clinical test. Amplitude [dB SPL] of the strongest distortion-product tone component (2F1-F2 where F1 and F2 are frequencies of the two primary tones) transmitted back to the ear canal.	Cochlear nonlinearity (outer hair cell health)
[ABR] Auditory brainstem response	Standardized clinical test. Peak amplitude and latency of waves I, III, and V in scalp electrical potential elicited by click stimulus.	Inner hair cell (IHC) integrity and synaptic communication between IHC and afferent auditory fibers of the VIIIth nerve
[ASSR] Auditory steady-state response	Amplitude of modulation components assigned to each of 5 simultaneous tone-carrier frequencies (500, 1000, 2000, 4000, 8000 Hz) each modulated at a different modulation frequency (MF) around 40 Hz.	Integrity along the basilar membrane to detect modulation components and higher tracking of modulation components
[IPD] Interaural phase difference ASSR	Mean amplitude of the modulation rate that a biphasic tone presentation (same signal in both ears) switches to an antiphasic tone presentation phase difference across ears.	Binaural detection of phase inversion across ears

Task	Details & Metrics	Ability / Function
[MEMR] Middle ear reflex	Normalized difference in click stimuli spectral average in the ear canal with and without contralateral elicitor.	Middle ear health, Efferent auditory system
[MMN] Mismatch negativity	Mean amplitude and peak latency of scalp electrical potential elicited by frequency, modulation depth, duration, and gap deviants compared to standard stimulus.	Pre-attentive auditory feature discrimination
[QSIN] Quick Speech-In-Noise Test (Brungart et al., 2014)	50% recognition SNR (dB) in standard condition (STD) and in time-compressed, reverberant speech condition (TCR; binaural presentation).	Speech-in-noise understanding
[SSQ6] Shortened version of the Speech, Spatial and Qualities of Hearing Scale (Grant et al., 2021)	Rating on a scale of 0 to 10 for self-perceived performance on six aspects of hearing.	Self-perception of hearing abilities

Appendix C: Preliminary Data

The following subsections outline preliminary descriptive results for the experimental tasks used in this study. As expected, group means across tasks show trends of smaller amplitude (MMN, DPOAE), longer latency (MMN, ABR), or fewer responses (ASSR, MMN) for individuals with elevated hearing thresholds. Inspecting distributions between groups, however, reveals differences in task sensitivity to elevated hearing thresholds.

1.1 Audiometry

Pure-tone audiometry was used to assign participants into three hearing groups based on air-conduction thresholds between 0.25–8 kHz and to identify the worse ear for each participant. Participants with all thresholds equal to or better than 20 dB HL were assigned to the normal hearing thresholds control group (NHT). Participants with thresholds between 25–40 dB HL at one or more frequencies and no threshold worse than 40 dB HL or participants with thresholds greater than 40 dB HL at one frequency and no more than 40 dB HL at all other frequencies were assigned to the mild elevated hearing thresholds group (mEHT). Participants with thresholds between 45–90 dB HL for two or more frequencies and no more than one threshold worse than 90 dB HL at any frequency or participants with thresholds greater than 90 dB HL at one frequency, between 45–90 dB HL at one frequency, and equal to or better than 40 dB HL at all other frequencies were assigned to the moderate-to-severe elevated hearing thresholds group (sEHT). Pure tone threshold averages by participant group from 0.25–12.5 kHz for participants' worse ear are plotted below in Figure 1A. This plot shows hearing thresholds for all participants who have completed the first of two testing sessions (*n* = 26 NHT controls, *n* = 17 mEHT, and *n* = 13 sEHT participants). Figure 1A shows separation between NHT, mEHT, and sEHT groups, most prominent between 3 and 8 kHz, which are important frequencies for speech perception (Monson et al., 2014). Group mean pure tone average (PTA) thresholds over 3, 4, 6, and 8 kHz for the same data are shown in Figure 1B.

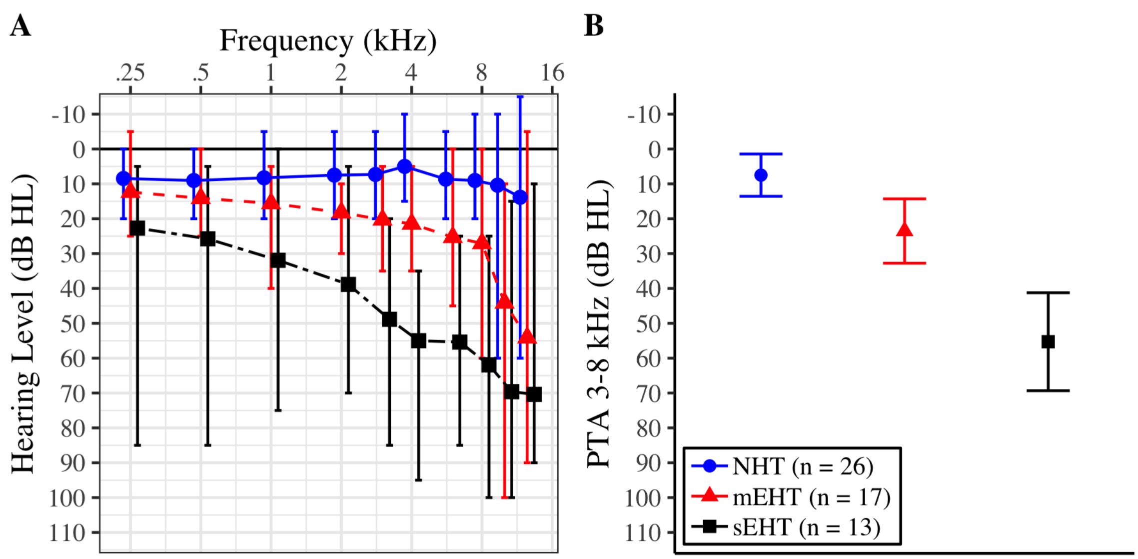


Figure 1. (A) Pure tone air-conduction thresholds at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12.5 kHz for participants' worse ear, averaged by participant group. Error bars show the range of thresholds in each group at each test frequency. (B) Group mean pure tone average (PTA) thresholds over 3, 4, 6, and 8 kHz for participants' worse ear. Error bars show ±1 standard deviation from the mean.

1.2 Questionnaire/SSQ

Questionnaire results: Questionnaire and survey data were analyzed for *n* = 26 NHT, *n* = 16 mEHT, and *n* = 13 sEHT participants. Figure 2 shows that participants with elevated hearing thresholds (mEHT and sEHT) have a higher percentage of tinnitus, blast exposure and hearing aid use. Although there was also an increase in the percentage of TBI with elevated hearing loss, the numbers are too small at this point to draw definite conclusions about TBI. Both EHT groups also showed relatively higher age and longer duration of service, which were highly correlated with each other ($r = .82$, $p < .001$). This is consistent with literature that suggests that the noise-exposure with aging and with service may be a contributing factor for the elevation in hearing thresholds.

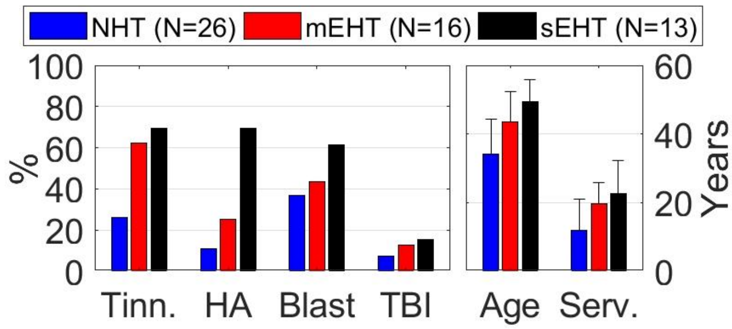


Figure 2. The left panel shows the percentage of participants in each group with a history of tinnitus (Tinn.), hearing aid use (HA), blast exposure (Blast), and traumatic brain injury (TBI). The right panel shows the mean (bar height) and one standard deviation (error bars) of participant age and duration of service (Serv.) within each group.

SSQ survey results: The six SSQ items shown in Table 2 were administered as part of the larger survey. Average ratings for the six SSQ questions, as well as the average rating across all six questions (Avg), for the three groups are shown in Figure 3. Low ratings represent greater difficulty hearing or a greater sense of sound being distorted. Results show a trend of increase in perceived hearing difficulties (i.e., lower rating) with increase in hearing thresholds. Although this decrease in the rating is less, on average, than that reported by some previous studies for the same elevation in hearing thresholds, some of the individual questions that deal with listening in the presence of background noise (Q2 and Q3) show relatively more increase in the perceived difficulty.

Table 2. Individual questions and labels for the two extreme ratings of 0 and 10 that were displayed on the screen for the 6-question abbreviated version of the SSQ questionnaire (Grant et al., 2021). For analyses, the ratings for questions 4 and 5 were reversed so that a higher rating always represented better performance. Numbers in parentheses are sentence numbers based on the original SSQ_{49} (Gatehouse & Noble, 2004).

#	Question	Rating 0	Rating 10
1 (S14)	You are talking to someone on the telephone and someone next to you starts talking. Can you follow what is being said by both speakers?	Not At All	Perfectly
2 (S12)	You are in a group and the conversation switches from one person to another. Can you easily follow the conversation without missing the start of what each new speaker is saying?	Not At All	Perfectly
3 (S5)	You are talking to one person. There is continuous background noise, such as a fan or running water. Can you follow what the person says?	Not At All	Perfectly
4 (Q14)*	Do you have to concentrate very much when listening to someone or something?	No need to concentrate	Hard
5 (Q11)*	Do everyday sounds that you hear seem to have an artificial or unnatural quality?	Natural	Unnatural
6 (Q18)	Can you easily ignore other sounds when trying to listen to something?	Not easily ignored	Easily ignored

* End point labels are reversed compared to original survey questions.

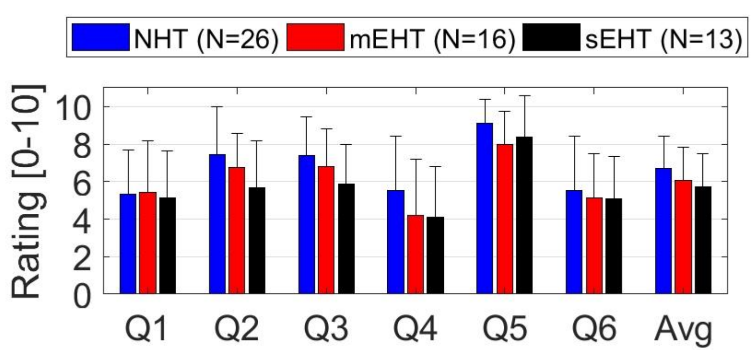


Figure 3. Mean (bar height) and 1 standard deviation (errorbar) within each group for the six SSQ questions ratings (Q1–Q6), as well as for the average SSQ score (Avg). The rating for each question was on a 0 to 10 scale. After adjusting end-point labels for questions 4 and 5, 0 and 10 representing the worst and the best perceived performance, respectively.

1.3 QuickSIN (Standard and Modified)

The Quick Speech in Noise test (QSIN) thresholds (speech-to-noise ratio for 50% correct key words in sentences (SNR50)) for the standard condition (Std) and for the time-compressed, reverberation condition (TCR) were analyzed for n = 26 NHT, n = 16 mEHT, and n = 12 sEHT participants. Figure 4 shows an increase in SNR50 with increasing hearing loss (i.e., the sEHT group performed worse than the mEHT group, which performed worse than the NHT group). As expected, this degradation was greater for both EHT groups in the TCR condition, which, because of its greater task requirements, has been shown to be more sensitive to speech-in-noise deficits due to hearing impairment. All subjects do worse in the TCR condition, but differences across groups are expected to be exaggerated.

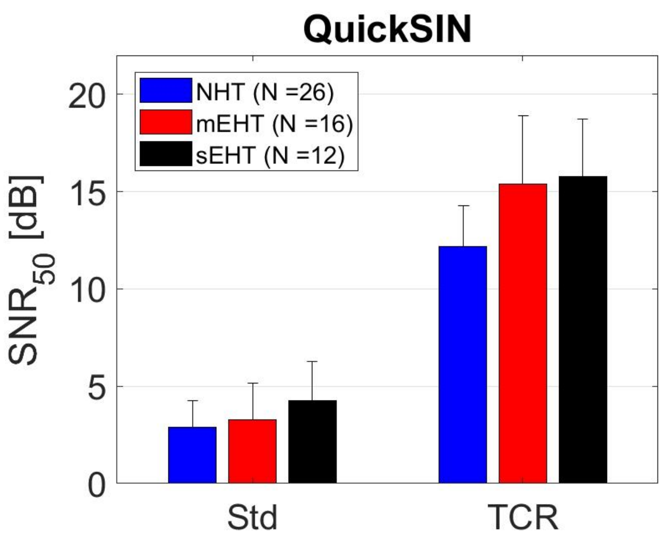


Figure 4. QuickSIN SNR50 mean (bar height) and one standard deviation (errorbar) for each group in standard (Std) and time-compressed, reverberant speech (TCR) conditions.

1.4 Distortion Product Otoacoustic Emissions (DPOAE)

Distortion product otoacoustic emissions (DPOAE) reflect the health of the outer hair cells (Abdala & Visser-Dumont, 2001). When two pure tones at frequencies f1 and f2 are presented simultaneously, the non-linear processing of a healthy cochlea results in the generation of multiple additional tones (i.e., DPOAE) that propagate back to the outer ear and can be recorded. The strongest of these distortion products is at the frequency 2f1-f2 and a plot of the amplitude of that tone, as a function of the frequency of f2, is called a DPgram. The range of frequencies tested were from 500–8000 Hz, with a f2:f1 ratio of 1.22 sweeping in 1/6th-octave increments with intensity levels at 65/55 dB SPL for f1 and f2, respectively. Each frequency was tested with and without contralateral suppression. This standard clinical test was administered using the CREARE Hearing Assessment (CHA) system with DPOAE recorded for each participant's worse ear as determined by audiometric thresholds averaged over 0.5, 1, and 2 kHz.

Preliminary DPOAE results without contralateral suppression for n = 26 NHT, n = 17 mEHT, and n = 13 sEHT participants indicate that this measure is sensitive to differences between hearing groups in our target population, which is reflected in higher mean signal-to-noise ratio (SNR; DPOAE minus noise amplitude at each f2) over f2s between 3–8 kHz for participants with better audiometric thresholds (Figure 5A). These preliminary descriptive results suggest that our DPOAE measure can detect differences in outer hair cell function between our target groups. However, inspection of the cumulative distribution for the same average SNRs (Figure 5B) reveals a large overlap between sEHT and mEHT and between mEHT and NHT that suggests DPOAE SNR may not track shifts from sEHT to mEHT or from mEHT to NHT for most individuals. Only about 30% mEHT have larger averaged SNRs than roughly the top 10% of sEHT, with roughly 20% of mEHT averaged SNRs above the maximum averaged SNR for sEHT (about 15 dB). Similarly, only about 30% NHT have larger averaged SNRs than roughly the top 10% mEHT. There is less overlap between NHT and sEHT (about 55% NHT have larger averaged SNRs than the top 10% of sEHT, with about 40% of NHT averaged SNRs above the maximum average SNR for sEHT), which suggests a higher probability that restoring audiometric thresholds from sEHT to NHT will result in DPOAE SNR shifting outside of the sEHT distribution.

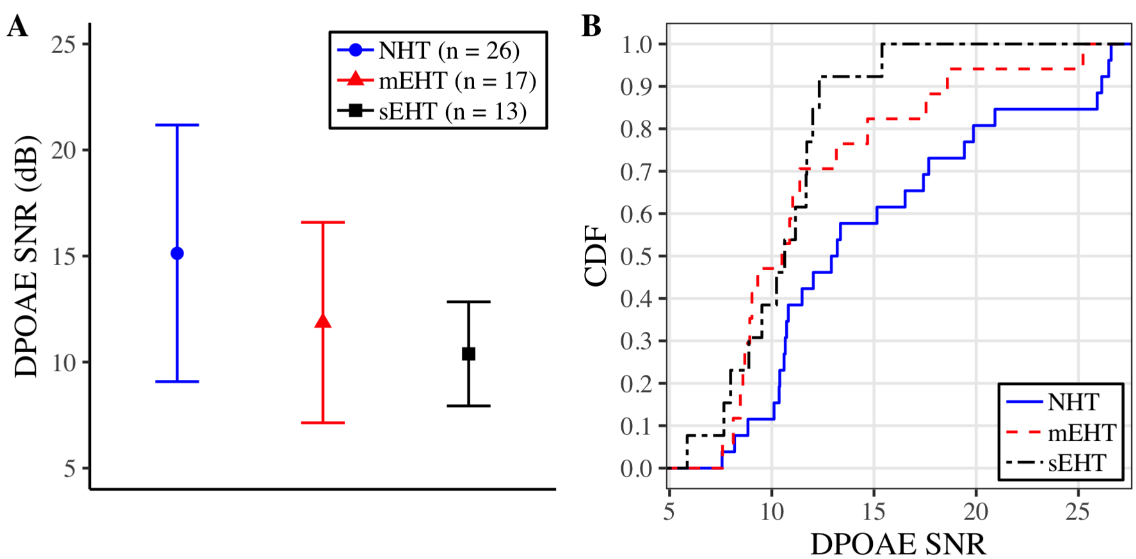


Figure 5. (A) Mean by-subject DPOAE SNR (i.e., DPOAE amplitude minus noise at each f2 frequency) averaged across f2 frequencies 3, 4, 5, 6, 7, and 8 kHz. Error bars represent ±1 standard deviation from the mean. (B) Cumulative distribution function of by-subject average DPOAE SNR across f2 frequencies 3, 4, 5, 6, 7, 8 kHz.

1.5 Auditory Steady-State Response (ASSR)

The auditory steady-state response reflects the health along the basilar membrane and the fidelity of higher-level tracking of stimulus envelope modulations. In this task, participants heard 600 complex auditory stimuli while their electroencephalogram (EEG) was recorded. Each stimulus lasted 500 ms and comprised five carrier frequencies (CFs), with each carrier frequency 100% amplitude modulated at rates between 36–54 Hz. For half of the participants, carrier and modulation frequencies were paired in ascending order; for the other half of participants, the direction of carrier-modulation frequency pairing was reversed. Stimuli were presented at a suprathreshold level (85 dB SPL) to each participant's worse ear. Offline, individual 500 ms EEG epochs beginning at the onset of each stimulus were concatenated into 32-epoch sweeps, which were then averaged in the time domain before being fast-Fourier transformed (FFT) to determine the power for each 1/16 Hz frequency bin. The ASSR at each CF was analyzed at the vertex (Cz) referenced offline to the average mastoids. To determine whether ASSR power at each CF was significantly higher than the background noise (i.e., whether the ASSR was present), the power at each modulation frequency was compared to the power at 120 adjacent frequency bins (60 bins above and below the modulation frequency) with an F-ratio test.

Preliminary descriptive results for n = 21 NHT, n = 14 mEHT, and n = 13 sEHT participants indicate a difference between the sEHT versus the NHT and mEHT groups in the expected direction. The mean number of CFs that elicited an ASSR was higher and less variable for NHT and mEHT participants compared to sEHT (Figure 6A). Inspection of the cumulative distributions of the same data (Figure 6B) reveals a nearly identical distribution for NHT and mEHT, in which four or five CFs elicited an ASSR for about 85% of participants). This contrasts starkly with the sEHT distribution, which shows that ASSRs were elicited by four or five CFs in only about 15% of these participants. In addition, ASSRs were elicited by at least 2 CFs for all NHT or mEHT participants, whereas ASSRs were elicited by zero or one CF for 30% of sEHT participants. This suggests the ASSR will be able to track improvements from sEHT to mEHT or NHT, but may not be sensitive to shifts from mEHT to NHT.

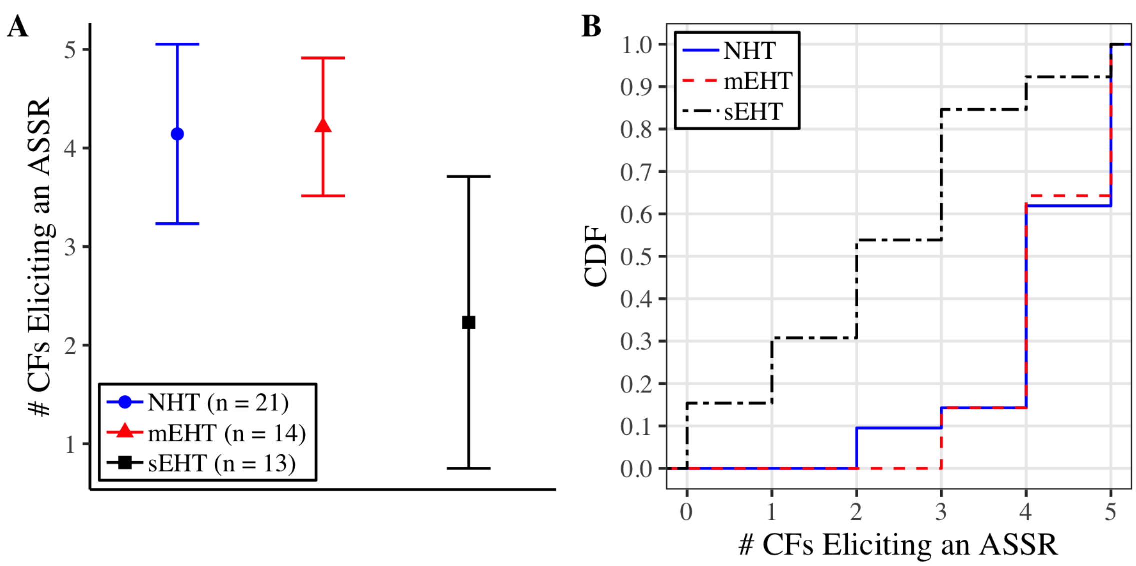


Figure 6. (A) Mean number of CFs that elicited a significant ASSR (out of 5 total CFs). Error bars show ±1 standard deviation. (B) Cumulative distribution of the proportion of participants in each group as a function of the number of CFs that elicited an ASSR.

1.6 Click-Evoked Auditory Brainstem Response (ABR)

The click-evoked auditory brainstem response (ABR) is an electrophysiologic response to transient stimuli that represents synchronous firing of the neurons within the brainstem nuclei along the ascending auditory pathway, and is the most commonly utilized evoked potential clinically. The response comprises 5–7 positive deflecting peaks (waves I–VII), each of which represent neural firing from multiple contributing nuclei within the brainstem. In humans, waves I, III, and V are highly reliable, and are used for both auditory threshold information and neurodiagnostic evaluations. Wave I arises from the activity of the distal portion of the auditory nerve; wave III originates from the cochlear nucleus with contributions from the superior olivary complex; and wave V is generated largely by the contralateral lateral lemniscus (LL) with some contribution from the contralateral inferior colliculus (IC). Differences in ABR wave latencies are noted in varying degrees of sensorineural hearing loss.

ABR wave I, III, and V descriptive results for n = 22 NHT, n = 16 mEHT, and n = 11 sEHT participants show expected differences in peak latency, with greater degree of sensorineural hearing loss corresponding to longer latency peaks, most notably for waves III and V (Figure 7A). These results indicate that the ABR is sensitive to differences in sensorineural hearing loss between our study groups. However, inspection of the cumulative distributions of the same data (Figure 7B–D) reveal that waves I, III, and V are differentially sensitive to degree of sensorineural hearing loss. Wave I latency is unlikely to track shifts from sEHT to mEHT to NHT for most individuals, due to largely overlapping distributions between mEHT and NHT, with only 30% of sEHT showing longer latency than the bottom 5% of mEHT and NHT (i.e., those with the longest latency; Figure 7D). Wave III latency may better track shifts from sEHT to mEHT and NHT given that about 60% of sEHT show longer latency than the bottom 5% of mEHT and NHT and 45% of NHT show shorter latency peaks than shortest sEHT peak (Figure 7C). However, wave III latency may be less likely to track improvements from mEHT to NHT given that the latency distributions largely overlap between these groups. Wave V latency shows the least overlap between groups, suggesting this measure will be good at tracking improvements from sEHT to mEHT to NHT (Figure 7B). About 50% of NHT and 25% mEHT show shorter latencies than the shortest sEHT latency. Roughly 80% of sEHT and 55% of mEHT show longer latencies than the bottom 5% of NHT with the longest latency and about 55% of sEHT show longer latencies than the bottom 10% mEHT with the longest latency.

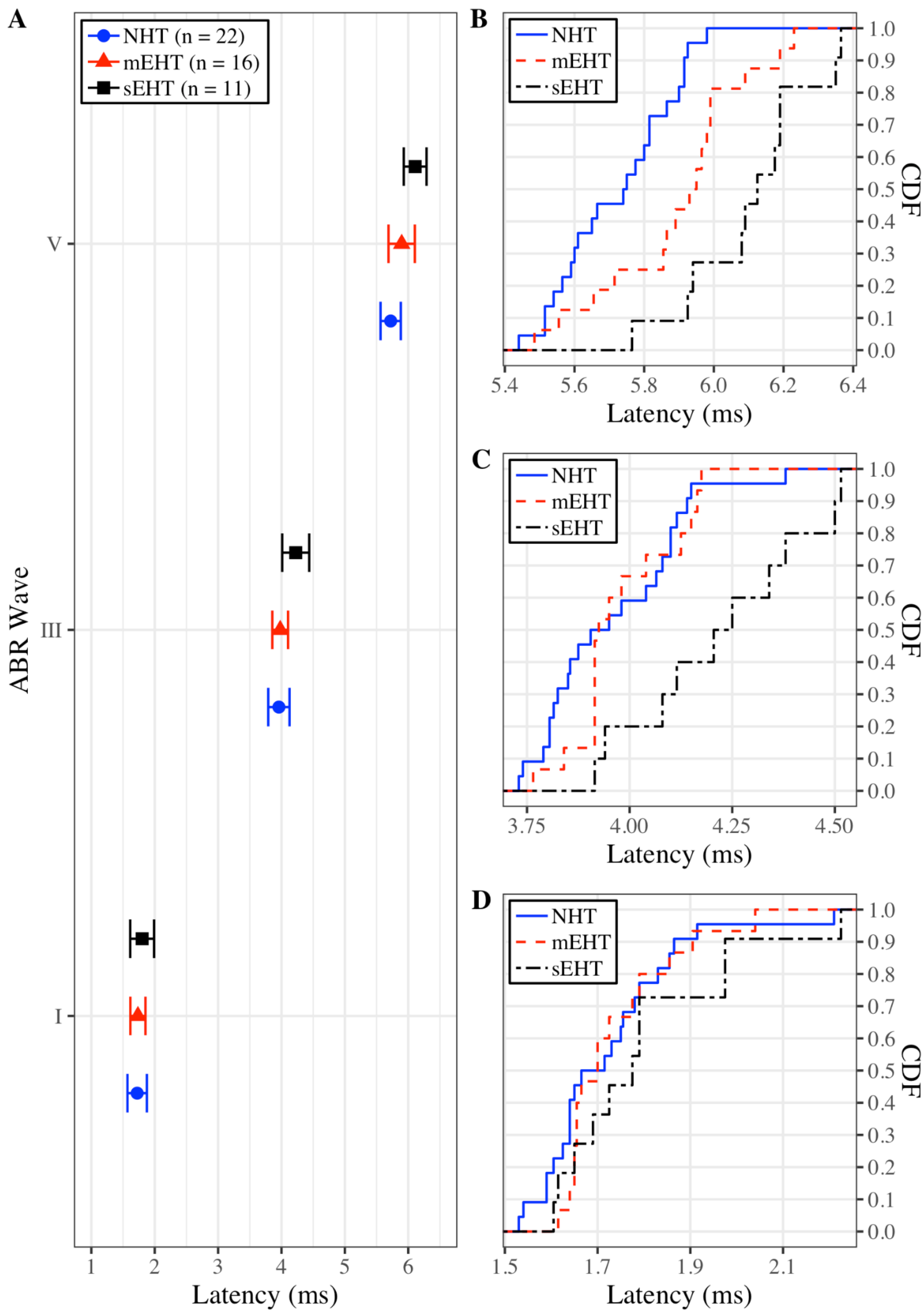


Figure 7: (A) Mean peak latencies of waves I, III, and V. Error bars represent ±1 standard deviation. Cumulative distributions of the proportion of participants in each group as a function of ABR peak latency for (D) wave I, (C) wave III, and (B) wave V.

1.7 Mismatch Negativity (MMN)

The mismatch negativity (MMN) reflects short-term sensory memory representations of acoustic stimuli in auditory cortex. It is obtained by subtracting the event-related potential (ERP) elicited by a frequently occuring standard stimulus from the ERP elicited by an infrequently occurring deviant stimulus that is presented interspersed among the standard stimuli. The MMN is identified in the resulting subtraction wave as a negativity maximal over fronto-central scalp sites that generally peaks between 100–250 ms relative to the first point at which the standard and deviant stimuli acoustically differ. MMN topography is generally stable but its amplitude and peak latency are variable and depend on the degree of acoustic difference between the standard and deviant stimulus. Larger acoustic differences elicit greater MMN amplitude and shorter peak latency, reflecting auditory sensitivity to deviations in different stimulus features. In this task, sensitivity to two deviation levels—larger (easier to discriminate) vs. smaller (harder to discriminate)—in each of four acoustic stimulus features was tested (stimulus duration, fundamental frequency, amplitude modulation depth, and duration of a silent gap presented in the middle of the stimulus).

Mismatch negativity (MMN) descriptive results for the grand mean of n = 21 NHT, n = 12 mEHT, and n = 13 sEHT participants show a robust MMN elicited over frontal midline scalp regions during 100–200 ms following stimulus onset (Figure 8). The smaller amplitude MMN for the duration deviant, visible only during the 150–200 ms window, may be due at least in part to the fact that the duration deviant cannot be detected until 75 ms after stimulus onset, which is the point at which longer duration deviants differ from the standard duration of 75 ms. Time series plots for ERPs elicited over frontal and frontocentral sites (averaged over AF3, AF4, F3, Fz, F4, FC1, FC2) show the expected ERP components (N1, P2, N2, P3a) in each group (Figure 9A) and a negative deflection during the analysis window, which is the MMN (Figure 9B).

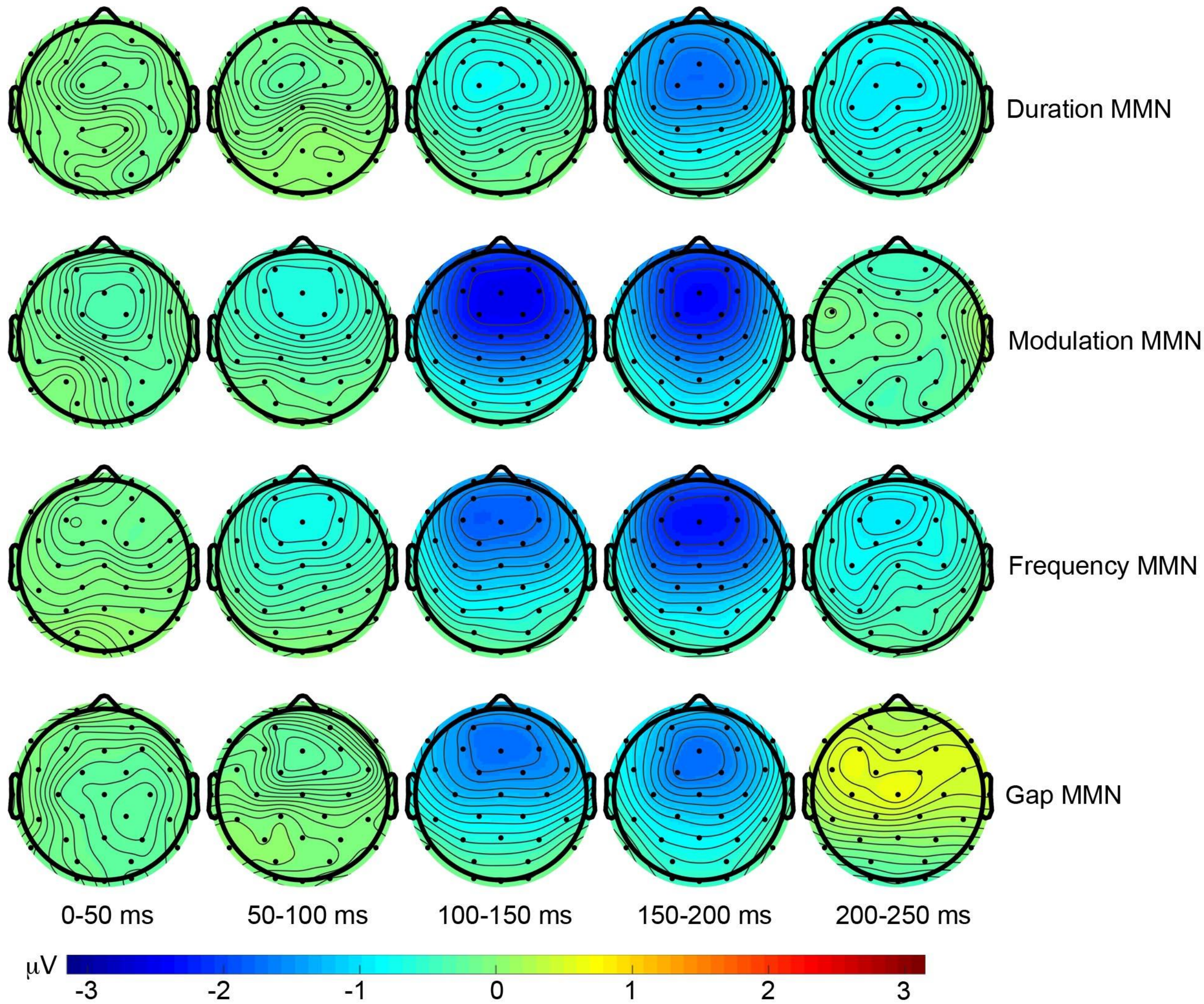


Figure 8. Grand mean topographic plots (looking down on a head with the nose pointed up) illustrating the deviant minus standard mismatch negativity (MMN; prominent dark blue area centered over frontal scalp sites during 100–200 ms windows) elicited by duration, amplitude modulation, frequency, and gap deviants averaged over 50 ms bins relative to stimulus onset (averages collapsed over easy and hard levels of each deviant). This grand mean plot includes n = 21 NHT, n = 12 mEHT, and n = 13 sEHT participants.

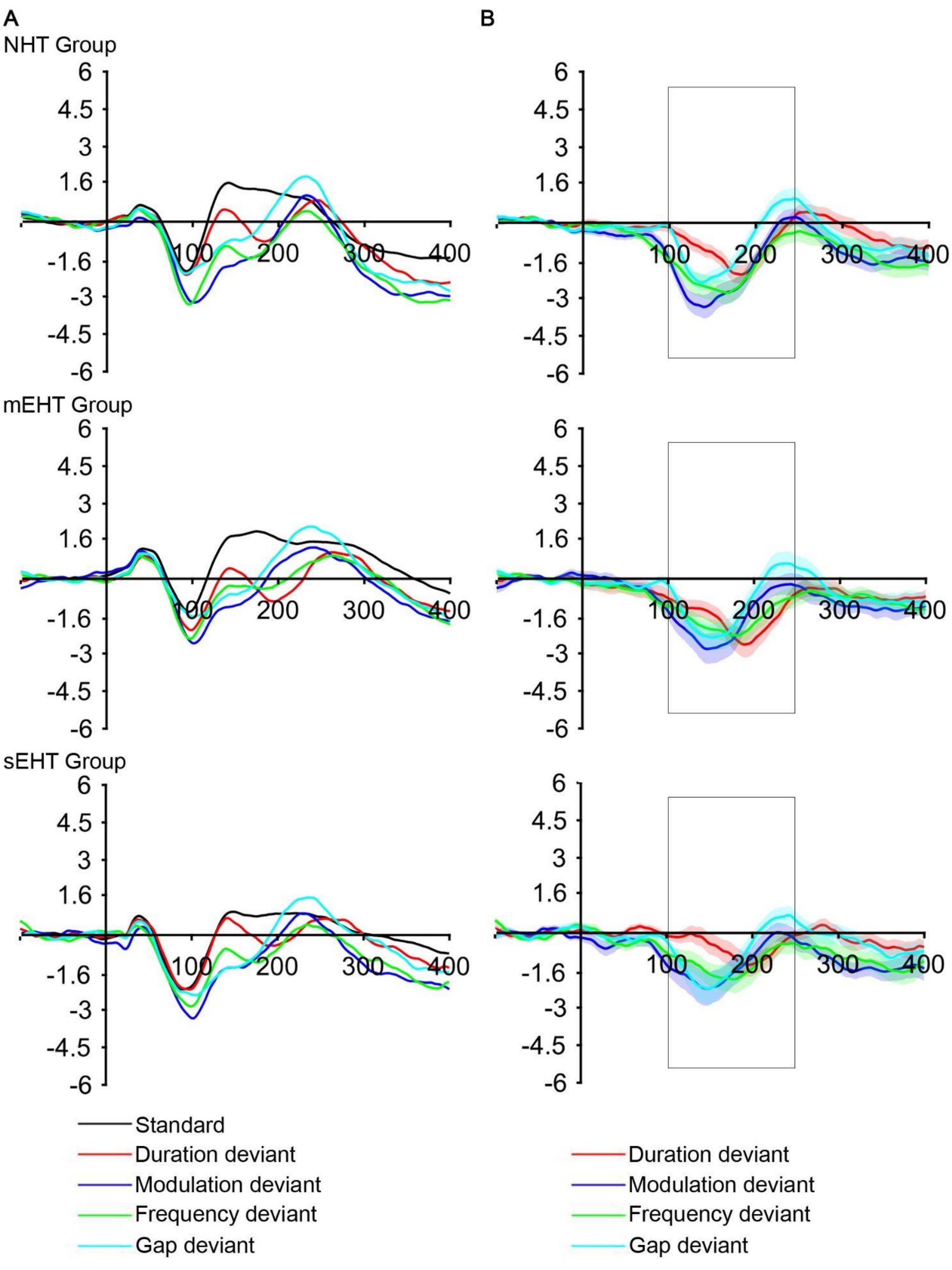


Figure 9. (A) Event-related potential (ERP) plots averaged by group (n = 21 NHT, n = 12 mEHT, and n = 13 sEHT) and stimulus type. Frontal and frontocentral sites where the MMN is strongest (AF3, AF4, F3, Fz, F4, FC1, FC2) are averaged in the time domain

prior to calculating ERPs. (B) Mismatch negativity (MMN) difference waves calculated by subtracting subject-averaged standard waves from deviant waves. Gray rectangles represent the typical time window where the MMN occurs. Shading shows ±1 standard deviation from the mean.

MMN peak latency and mean amplitude for the separate deviant types and levels (easy vs. hard) are plotted in Figure 10A and Figure 11A, respectively. These summary statistics indicate several promising trends in the MMN that may reflect differences among NHT, mEHT, and sEHT groups in the precision of short-term sensory memory representations for the deviants or perhaps slowing of the brain processes involved in acoustic feature discrimination. Peak latencies across the easy deviants follow the expected trends, with longer mean latencies elicited for increased sensorineural hearing loss (Figure 10A). However, this trend is less consistent for the hard deviants. For the hard duration and modulation deviants, shorter mean latencies are observed for mEHT, followed by NHT and then sEHT. For the hard frequency deviant, the shortest mean latency is observed for NHT, followed by sEHT and then mEHT. And for the hard gap deviant, the shortest mean latency is observed for sEHT, followed by NHT and then mEHT.

The differences in latencies between hard and easy deviants is also less consistent than expected. For the modulation deviants, the expected pattern is observed, in which latencies for the hard deviant are longer than latencies for the easy deviant for NHT, mEHT, and sEHT. For the silent gap deviants, this pattern only holds for NHT and mEHT, while the hard gap deviant elicits a shorter mean latency than the easy gap deviant for sEHT. For the frequency deviant, the expected pattern only holds for mEHT, while for NHT and sEHT the hard deviant elicits shorter latencies than the easy deviant. For the duration deviants, shorter latencies are elicited by the hard deviant than for the easy deviant for NHT, mEHT, and sEHT. However, the unexpected pattern across groups for the duration deviants requires further analysis given that the easy duration deviants were longer than the hard duration deviants, which may have influenced peak MMN latencies independent of the level of difficulty for this deviant type.

Collapsing across subject-level MMNs elicited for all deviants, Figure 10B shows the expected pattern in which MMN latency increases with a greater degree of sensorineural hearing loss, with an increase in mean latency of about 7 ms from NHT to mEHT, and 7 ms from mEHT to sEHT. Figure 10C shows the cumulative distribution of latencies represented in Figure 10B and suggests that MMN peak latency may track improvement from sEHT to NHT for many individuals. About 25% of NHT showed MMN latencies shorter than the shortest latency elicited for sEHT and about 30% of sEHT showed longer latencies than the bottom 5% of NHT (i.e., 5% longest latencies). However, latencies for mEHT largely overlap those elicited for NHT and sEHT, suggesting this measure may not reliably track improvements from sEHT to mEHT or mEHT to NHT.

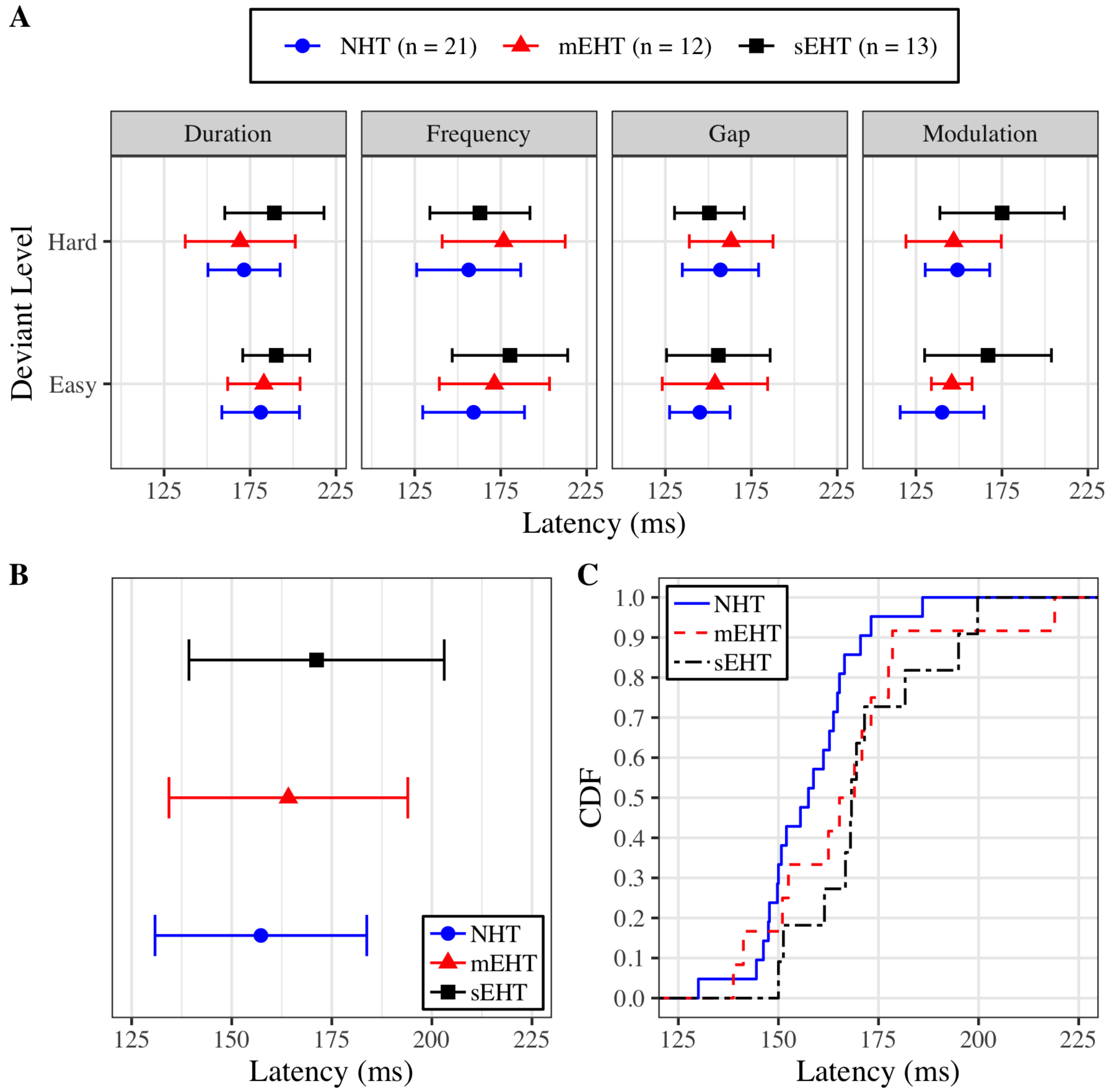


Figure 10. (A) MMN peak latency and ±1 standard deviation over 100–250 ms following stimulus onset averaged by deviant type and level. (B) Grand mean peak latency and ±1 standard deviation averaged over all deviant types and levels. (C) Cumulative distribution of participants as a function of MMN peak latency.

Considering MMN mean amplitudes, all groups show the expected trend across deviants, in which deviants that are harder to discriminate elicit smaller (less negative) MMNs compared to deviants that are easier to discriminate (Figure 11A). However, between-group trends are less consistent across deviant types and levels. The easy duration and frequency deviants are the only stimuli that elicit the expected pattern of smaller amplitude MMN corresponding to greater degree of hearing loss. For all other deviant types and levels, except the silent gap deviants, the expected pattern holds for NHT and sEHT, with NHT showing larger amplitudes. However, in these same cases, amplitudes for mEHT are either the largest (hard duration and easy modulation deviants) or the smallest (hard frequency and hard modulation deviants). The silent gap deviants differ from the others in that sEHT show the largest amplitudes for the easy and hard level, while NHT showed the smallest amplitude for the hard gap deviants and mEHT showed the smallest amplitude for the eas gap deviants.

Collapsing across subject-level MMNs elicited for all deviants, Figure 11B shows the expected pattern in which MMN amplitude decreases with a greater degree of sensorineural hearing loss, with an decrease in mean amplitude of less than 0.1 microvolt from NHT to mEHT, and less than 0.2 microvolt from mEHT to sEHT. Figure 11C shows the cumulative distribution of mean amplitudes represented in Figure 11B. The large degree of overlap in the cumulative distributions between groups suggests that MMN mean amplitude is unlikely to track audiometric threshold improvements.

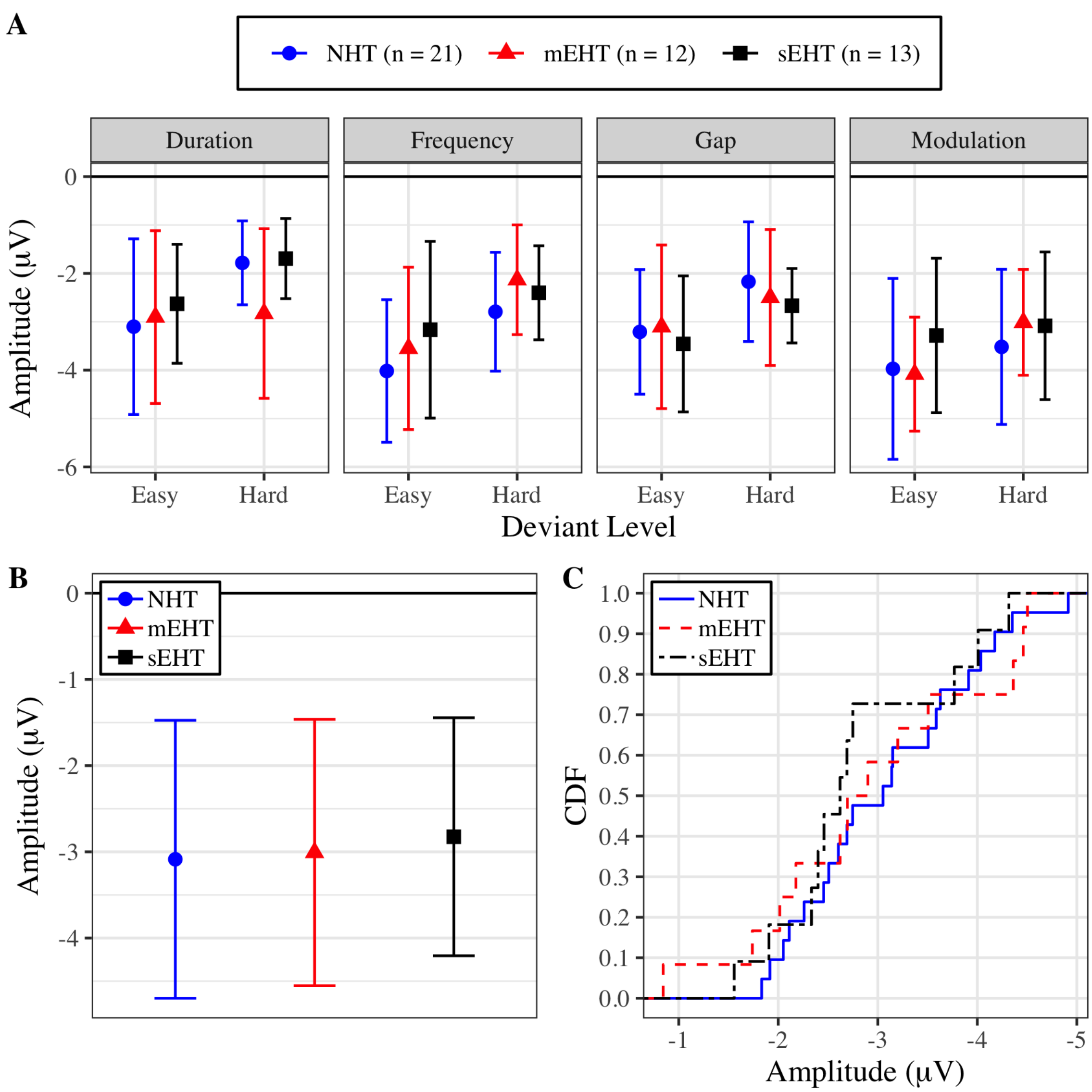


Figure 11. (A) MMN mean amplitude and ±1 standard deviation during the 40 ms window centered on each participant's MMN peak latency averaged by deviant type and

level. (B) Grand mean amplitude and ±1 standard deviation averaged over all deviant types and levels. (C) Cumulative distribution of participants as a function of MMN mean amplitude.

One additional metric from the MMN task that may be useful in tracking improvements in audiometric thresholds is the number of deviants that elicited an MMN within participants. For each deviant type and level, the MMN was determined to be absent if the most negative point of the subtraction wave during the MMN window was positive. Figure 12 shows the cumulative distribution of participants in each group as a function of the number of deviants that elicited an MMN. These cumulative distributions suggest that the number of absent versus present MMNs in this paradigm may track improvements from sEHT to NHT for some individuals. While all eight deviants elicited an MMN for most participants, fewer than eight deviants elicited an MMN in about 30% of sEHT and 25% of mEHT, but only 10% of NHT. Furthermore, at least seven deviants elicited an MMN in all NHT participants, but fewer than seven deviants elicited an MMN in about 23% of sEHT. Importantly, this metric provides complementary information to the latency and amplitude measures discussed above, as deviants that failed to elicit an MMN were excluded from those calculations.

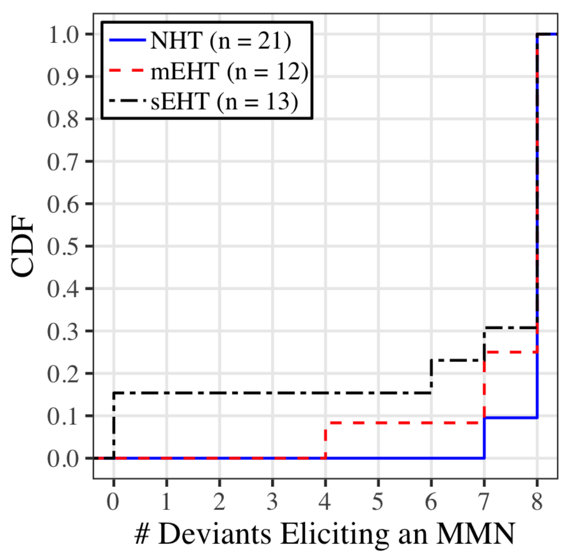


Figure 12. Cumulative distribution of participants in each group as a function of the number of deviants that elicited an MMN.

1.8 Correlations Between Task Measures

Spearman rank correlations between the metrics discussed above are presented in Figure 13. As expected, participant age shows strong positive correlations with PTA over 3–8 kHz (ρ = .60, p < .001) and ABR wave V latency (ρ = .48, p < .001), and a moderate positive correlation with ABR wave III latency (ρ = .37, p < .01). Participants' PTA over 3–8 kHz shows strong negative correlations with DPOAE SNR (ρ = -.40, p < .001) and number of CFs eliciting an ASSR (ρ = -.45, p < .001), strong positive correlation with ABR wave V latency (ρ = .59, p < .001), and moderate positive correlations with ABR wave III latency (ρ = .35, p < .05) and MMN grand mean latency (ρ = .39, p < .01).

DPOAE SNR also shows a moderate negative correlation with ABR wave V latency (ρ = -.38, $p < .01$) and a moderate positive correlation with number of CFs eliciting an ASSR (ρ = .30, $p < .05$). ABR wave III shows strong positive correlations with ABR wave I latency (ρ = .59, $p < .001$) and ABR wave V latency (ρ = .54, $p < .001$), although ABR waves I and V show a weak positive (non-significant) correlation (ρ = .22, $p = .12$). Lastly, the number of CFs eliciting an ASSR shows a strong negative correlation with MMN grand mean latency (ρ = -.42, $p < .01$). These significant correlations indicate that several pairs of test metrics have some shared variance, although the absence of any correlations above ± .60 suggest these measures are also likely to reflect distinct aspects of auditory function.

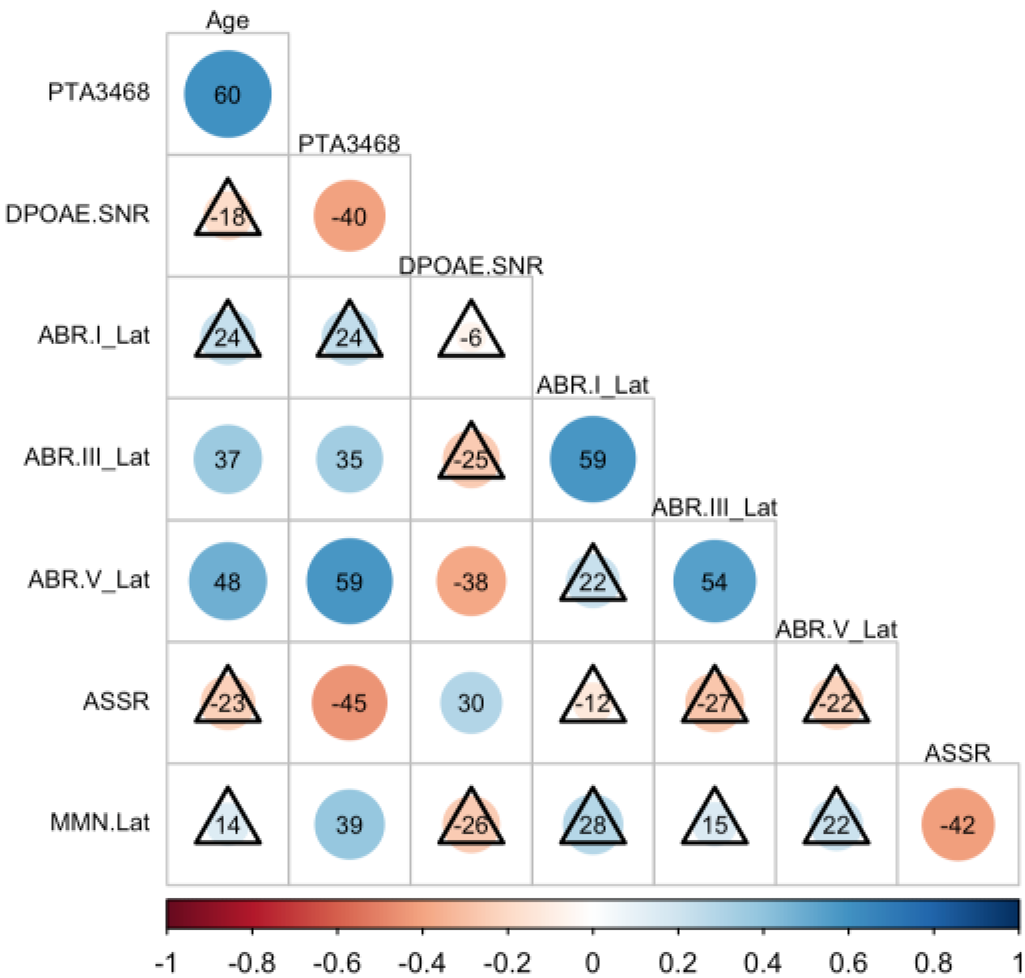


Figure 13. Correlation matrix for metrics described above. Spearman rank correlation strength is given numerically and depicted visually by the size of the underlying circle. Correlation direction is indicated by circle color and a negative sign preceding negative correlation coefficient. Significance of pairwise correlations is not adjusted for multiple comparisons. Correlations that are not significant at $p < .05$ are denoted with triangles.

Appendix D: MHSRS 2022 Poster

Development of an Objective Test Battery to Assess Benefits of Hearing Restoration Therapies

Ian Phillips, Ph.D., Sandeep Phatak, Ph.D., Kimberly A. Jenkins, Au.D., Ken W. Grant, Ph.D.
National Military Audiology & Speech Pathology Center, Walter Reed National Military Medical Center, Bethesda, MD

MHS Military Health System health.mil

Walter Reed National Military Medical Center

INTRODUCTION

- Hearing loss is the second most prevalent service-connected disability.
  - > 1.3 million Veterans compensated as of Sept 2020 (VBA 2020)
  - degrades not only the detection of sound, but also suprathreshold functions such as speech recognition in noise (Plomp, 1978)
- Medical researchers are developing therapies that may reverse sensorineural hearing loss by regenerating damaged auditory hair cells.
  - clinical trials show promise of improving audiometric thresholds but variable success in speech understanding
  - return of various auditory functions and improved speech understanding will likely progress over time as hair cells and auditory pathways reintegrate and reorganize
  - need to track improvements at various stages of the auditory system

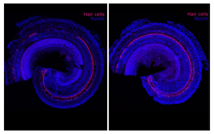


Figure 1. Restoration of cochlear hair cells (pink points, right panel) compared to untreated ear (left panel) in a preclinical model. Image credit: MIT, licensed under CC BY-NC-ND 3.0 (https://news.mit.edu/2022/frequency-therapeutics-hearing-regeneration-0329).

- **Goal: To identify an objective test battery that (1) systematically evaluates the integrity of the physical pathways of the auditory system from the periphery through the central auditory nervous system and (2) assesses the effect of sensorineural hearing loss on (a) fundamental building blocks of auditory function and (b) on more complex functional hearing abilities.**

METHODS

Participants

- Three hearing groups that represent the likely stages of incremental improvement over the remediation period
  - **sEHT**: moderate-to-severe elevated hearing thresholds (n = 13)
  - **mEHT**: mild elevated hearing thresholds (n = 17)
  - **NHT** : normal hearing thresholds (n = 26).

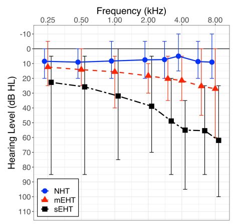


Figure 2. Mean audiometric thresholds for participants' test ear. Error bars = threshold range.

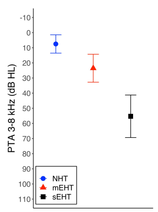


Figure 3. Mean PTA over 3–8 kHz for participants' test ear. Error bars = +/- 1 SD.

Procedures

Unless noted, stimuli in each task were presented monaurally to each participant's test ear (ear with higher/worse pure tone averages (PTA) over 0.5, 1, 2 kHz, or right ear if no difference in PTA) determined via the audiogram.

Task	Details & Metrics	Ability / Function
[Audiogram] Pure tone thresholds	Standardized clinical test. Air conduction thresholds [dB HL] of pure tone in both ears.	Audibility
[DPOAE] Distortion-product otoacoustic emission in quiet and in noise	Standardized clinical test. Amplitude [dB SPL] of the strongest distortion-product tone component (2F1-F2 where F1 and F2 are frequencies of the two primary tones) transmitted back to the ear canal.	Cochlear nonlinearity (outer hair cell health)
[ABR] Auditory brainstem response	Standardized clinical test. Peak amplitude and latency of waves I, III, and V in scalp electrical potential elicited by click stimulus.	Inner hair cell (IHC) integrity and synaptic communication between IHC and afferent auditory fibers of the VIIIth nerve
[ASSR] Auditory steady-state response	Amplitude of modulation components assigned to each of 5 simultaneous tone-carrier frequencies (500, 1000, 2000, 4000, 8000 Hz) each modulated at a different modulation frequency (MF) around 40 Hz.	Integrity along the basilar membrane to detect modulation components and higher tracking of modulation components
[MMN] Mismatch negativity	Mean amplitude and peak latency of scalp electrical potential elicited by frequency, modulation depth, duration, and gap deviants compared to standard stimulus.	Pre-attentive auditory feature discrimination
[QSIN] Quick Speech-In-Noise Test (Brungart et al., 2014)	50% recognition SNR (dB) in standard condition (STD) and in time-compressed, reverberant speech condition (TCR; binaural presentation).	Speech-in-noise understanding
[SSQ6] Shortened version of the Speech, Spatial and Qualities of Hearing Scale (Grant et al., 2021)	Rating on a scale of 0 to 10 for self-perceived performance on six aspects of hearing.	Self-perception of hearing abilities

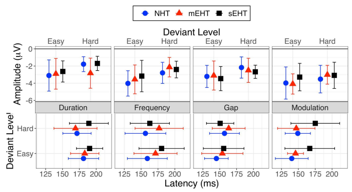


Figure 9. MMN mean amplitude (top panel) and peak latency (bottom panel) by deviant type and difficulty level. Error bars = +/- 1 SD.

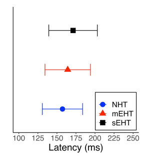


Figure 10. Mean MMN peak latency. Error bars = +/- 1 SD.

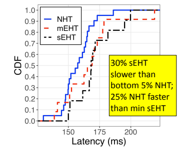
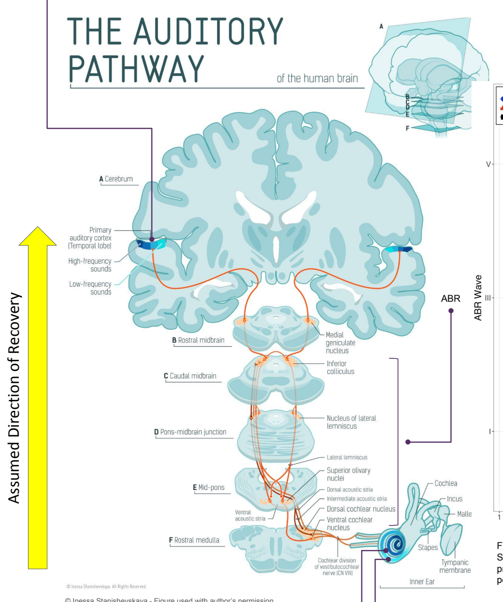


Figure 11. Cumulative distribution of the proportion of participants in each group as a function of MMN peak latency.



© Inessa Stanishevskaya - Figure used with author's permission.

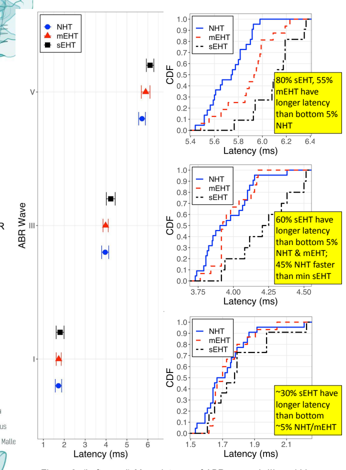


Figure 8. (Left panel) Mean latency of ABR waves I, III, and V. SD = +/- 1 SD. (Right panel) Cumulative distribution of the proportion of participants in each group as a function of ABR peak latency for wave I (bottom), III (middle), and V (top).

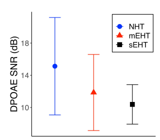


Figure 4. DPOAE mean SNR over F2s between 3–8 kHz. Error bars = +/- 1 SD.

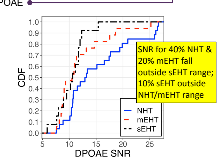


Figure 5. Cumulative distribution of the proportion of participants in each group as a function of DPOAE mean SNR over F2s between 3–8 kHz.

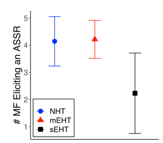


Figure 6. Mean number of MFs that elicited an ASSR (out of 5 total MFs). Error bars = +/- 1 SD.

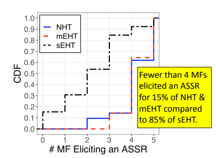


Figure 7. Cumulative distribution of the proportion of participants in each group as a function of number of MFs that elicited an ASSR.

RESULTS

- As expected, group means across tasks shows trends of smaller amplitude (DPOAE, MMN), longer latency (ABR, MMN), or fewer responses (ASSR) for individuals with increasing elevated hearing thresholds.
- Inspecting distributions reveals differences in sensitivity to elevated hearing thresholds between tasks
  - **[DPOAE]** large overlap between **sEHT** & **mEHT** suggest SNR may not track shifts from **sEHT** to **mEHT** for most individuals.
  - **[ASSR]** distributions nearly identical for **NHT** & **mEHT** but little overlap with **sEHT**. Suggests ASSR will be able to track improvements from **sEHT** to **mEHT/NHT**, but not **mEHT** to **NHT**.
  - **[ABR]**
    - **Wave I** unlikely to track shifts from **sEHT** to **mEHT** to **NHT**
    - **Wave III** may track shifts from **sEHT** to **mEHT/NHT**
    - **Wave V** less overlap between groups, likely to track improvements from **sEHT** to **mEHT** to **NHT**
  - **[MMN]** may track improvement from **sEHT** to **NHT** but not from **mEHT** to **NHT** or **sEHT** to **mEHT**
- Above metrics do not correlate strongly with each other or PTA (Fig 14).

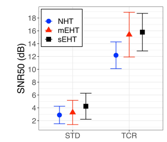


Figure 12. QSIN mean SNR50 for STD and TCR conditions. Error bars = +/- 1 SD.

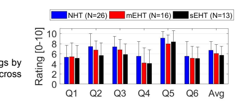


Figure 13. SSQ6 mean ratings by item and for the average across items. Error bars = +/- 1 SD.

- **[QSIN]** **NHT** SNR50 scores for STD and TCR stimuli align with published findings; **mEHT** and **sEHT** TCR scores are more similar than expected (Fig 12)
- **[SSQ6]** SSQ individual item and average scores decrease (more subjective problems) with elevated thresholds; but scores for **NHT** are lower than expected (Fig 13)

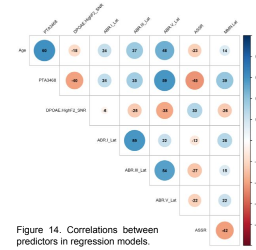


Figure 14. Correlations between predictors in regression models.

Table 1. Summaries for regression models predicting QSIN TCR SNR50 (left-hand side) and SSQ6 average rating (right-hand side). The number of observations differs between models because data were missing for some tasks for different participants.

Regression Models

	QSIN_TCR_SRT50			SSQavg		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	14.10	13.29 – 14.91	**<0.001**	6.44	5.95 – 6.93	**<0.001**
czPTA3468	1.41	0.62 – 2.20	**0.001**	-0.60	-1.14 – -0.07	**0.028**
czMMN FreqHard	1.06	0.24 – 1.87	**0.012**			
czMMN ModEasy				0.62	0.07 – 1.17	**0.028**
Observations	41			39		
R^2	0.377			0.161		

- Including these metrics with PTA accounted for more variance of speech-in-noise understanding and subjective hearing ratings.
  - Each metric was entered with PTA and age (all centered, non-interacting) in two linear regression models: one predicting QSIN TCR SNR 50, a second predicting SSQ6-Average (Table 1).
  - Model fit with backwards stepwise elimination. Retained factors that significantly improved model fit.

CONCLUSION

- The objective metrics tested in this study track degree of sensorineural hearing loss as measured with audiometric thresholds, albeit with varying degrees of sensitivity.
- These metrics provide multiple opportunities to demonstrate hair cell regeneration success beyond improvements in audibility and before improvements in speech understanding may occur.
- Use of objective and pre-attentive auditory and electrophysiological measures may benefit tracking of hearing restoration progress in the future by removing potentially confounding effects inherent to behavioral testing, such as lapses in attention, fatigue, working memory differences, etc.
- Data collection is ongoing. More data will refine conclusions drawn from distributions & permit testing of additional factors in models of speech-in-noise understanding and subjective hearing ratings.