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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.

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1. INTRODUCTION:

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: .

Hearing loss, hearing restoration, electroencephalography, speech perception

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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)**

- o **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). (Months 1–6)**
- o **Major Task 1.2:** Program, calibrate, and test equipment for middle-ear muscle reflexes (01/12/2021).
- o **Major Task 1.3:** Complete training (12/08/2020) and establish data-sharing agreements for use of ANAM.
- o **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). (Months 6–18)**

Aim 2: Assess differences between individual's objective test measures between sessions to determine reliability of the test measure. (15% complete). (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). (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). (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). (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 requested NCE is to test enough subjects per group to run planned statistical analyses.**

What was accomplished under these goals?

Aim 1: Continued recruitment and enrollment of participants (Major Task 1.4). Currently 26 participants have completed the study with additional subjects contacted for screening or in the enrollment processes. 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.

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). Currently, three participants have completed all re-testing and four additional participants have expressed interest in completing re-testing and are in the process of scheduling.

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. However, we have continued 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. Descriptive plots for several tasks are included in Appendix A that illustrate the target effects for several experimental tasks and differences between normal hearing (NHT), mild hearing loss (mEHT), and moderate/severe hearing loss (msEHT) groups.

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 24th, 2019.
- Continuing review for 2019 was approved on September 11th, 2019.
- Continuing review for 2020 was approved on August 11th, 2020.
- Continuing review for 2021 was approved on August 11th, 2021.
- Data sharing agreement with CNRM was established in July 2020 and renewed August 2021

What opportunities for training and professional development has the project provided?

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. Additional training will be offered (funds permitting) for Dr. Phillips to participate in the 4th edition of the *Frequency-Following Response (FFR) Workshop*, to be held at University of Barcelona (Catalonia-Spain) on June 8–10, 2022.

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

If face-to-face research activities are not suspended again due to COVID-19, recruitment and enrollment for Aims 1–3 will continue during the first three quarters of the NCE year. We will continue to expand recruitment efforts by identifying new sources of potential study participants. 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.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

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?

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?

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?

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:

Nothing to Report

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays 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 no-cost extension (Year 4) to ensure all goals of the research protocol are met.

Changes that had a significant impact on expenditures

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 17th, 2020 until July 6th, 2020. Since recruitment has resumed, we have observed initially a steady flow of interested volunteers. Additional delays in recruitment due to the Delta variant and increased spread of infection in the VA/DC/MD areas are expected.

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

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:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

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.*

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

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?

Name:	Kenneth Grant, Ph.D.
No change.	PI
Contribution to Project:	Dr. Grant proposed the initial plan for this project, submitted the grant application along with Dr. Jenkins, and oversees development of objective data interpretation and generation of reports.
Name:	Ian Phillips, Ph.D.
Project Role:	Research Associate
Contribution to Project:	Dr. Philips is responsible for subject recruitment, data collection and management, data analyses, and generation of reports.
Name:	Sandeep Phatak, Ph.D.
Project Role:.	Consultant
Contribution to Project:	Dr. Phatak is responsible for data management, analyses, and generation of reports.

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

Nothing to Report.

What other organizations were involved as partners?

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 establishedSeptember 2019

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Appendix: Preliminary Data

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 for each participant's worse ear. 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/severe elevated hearing thresholds group (msEHT). Pure tone threshold averages by participant group from 0.25–16 kHz for participants' worse ear are plotted below in Figure 1. This plot shows hearing thresholds for all participants who have completed the first of two testing sessions (N = 26; *n* = 15 NHT controls, *n* = 6 mEHT, and *n* = 5 msEHT participants). Figure 1 shows separation between NHT, mEHT, and msEHT groups, most prominent between 3 and 8 kHz, which are important frequencies for speech perception.

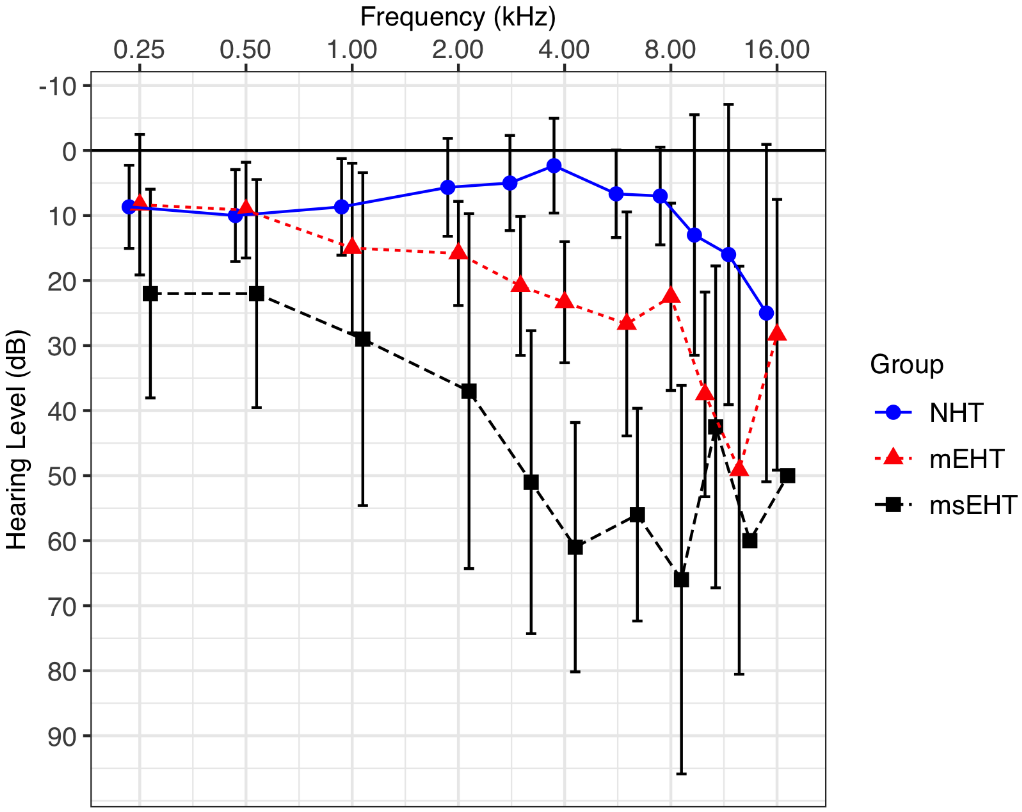

Figure 1. Pure tone threshold averages at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12.5, and 16 kHz for participants' worse ear only, averaged by participant group (*n* = 15 NHT, *n* = 6 mEHT, *n* = 5 msEHT). Error bars show ±1 standard deviation from the mean.

1.2 Questionnaire/SSQ

Questionnaire results: Questionnaire and survey data were analyzed for *n* = 15 NHT, *n* = 5 mEHT, and *n* = 5 msEHT participants. Figure 2 shows that participants with elevated hearing thresholds (mEHT and msEHT) have a higher percentage of tinnitus, blast exposure and hearing aid use. The numbers, however, are too small at this point to draw definite conclusions about the effects of these comorbid factors. Both EHT groups also showed relatively higher age and longer duration of service, which were highly correlated with each other ($r = 0.88$, $p < .001$). 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.

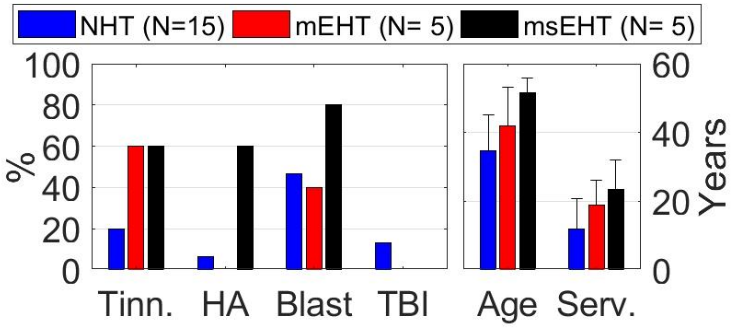

Figure 2. The left panel shows the percentage of participants in each group with a history of tinnitus (Tinn.), hearing aid use (HA), blast exposure (Blast), and traumatic brain injury (TBI). The right panel shows the mean (bar height) and one standard deviation (error bars) of participant age and duration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

SSQ survey results: The six SSQ items shown in Table 1 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 similar levels of complaints across groups when averaged across the six questions.

Table 1. 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 and Noble, 2004. *Int J Audiol*;43(2): 85–99).

#	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.

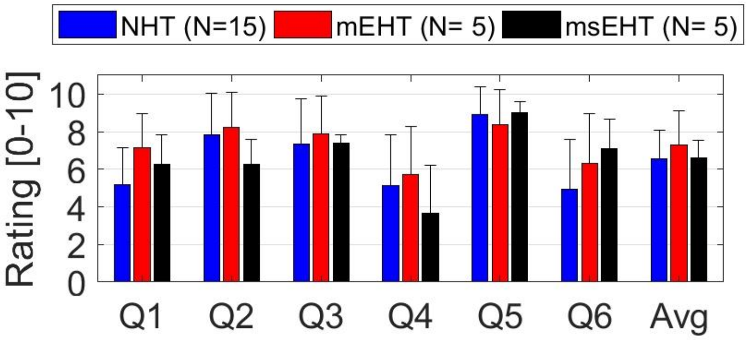

Figure 3. Mean (bar height) and 1 standard deviation (errorbar) within each group for the six SSQ questions ratings (Q1–Q6), as well as for the average SSQ score (Avg). The rating for each question was on a 0 to 10 scale. After adjusting end-point labels for questions 4 and 5, 0 and 10 representing the 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* = 15 NHT, *n* = 5 mEHT, and *n* = 5 msEHT participants. Figure 4 shows elevated thresholds for the TCR condition compared to the Std condition across groups. As expected, the EHT groups showed elevated QSIN thresholds 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. Statistical significance of this difference was not tested due to small sample size.

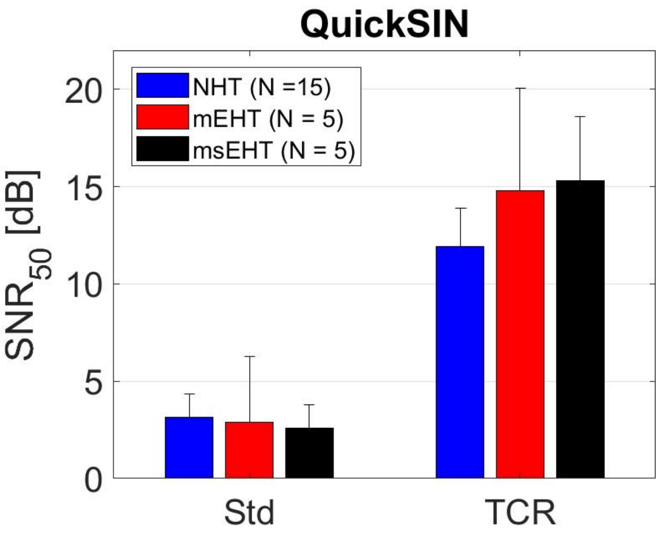

Figure 4. QuickSIN SNR50 mean (bar height) and one standard deviation (errorbar) for each group in standard (Std) and time-compressed, reverberation (TCR) conditions.

1.4 Distortion Product Otoacoustic Emissions (DPOAE)

Distortion product otoacoustic emissions (DPOAE) reflect the health of the outer hair cells (Abdala and 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. 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 for *n* = 15 NHT, *n* = 6 mEHT, and *n* = 5 msEHT participants indicate that this measure is sensitive to differences between hearing groups in our target population (Figure 5). Participants in the NHT group show responses across test frequencies that are at least 6 dB above the noise floor for stimuli presented with and without contralateral suppression. In contrast, participants in the mEHT group show similar DPOAEs to NHT participants at lower frequencies but reduced DPOAEs at higher frequencies, and participants in the msEHT group show reduced DPOAEs at all measured frequencies above 600 Hz. The NHT group had slightly reduced DPOAE amplitudes between 1 to 4 kHz. Both mEHT and msEHT groups showed further reduction in DPOAE amplitudes in that frequency range, with DPOAE almost absent between 2 to 3 kHz (i.e., reduced to the level of ambient noise) for the msEHT group. These preliminary descriptive results suggest that our DPOAE measure can detect differences in outer hair cell function between individuals in our target population.

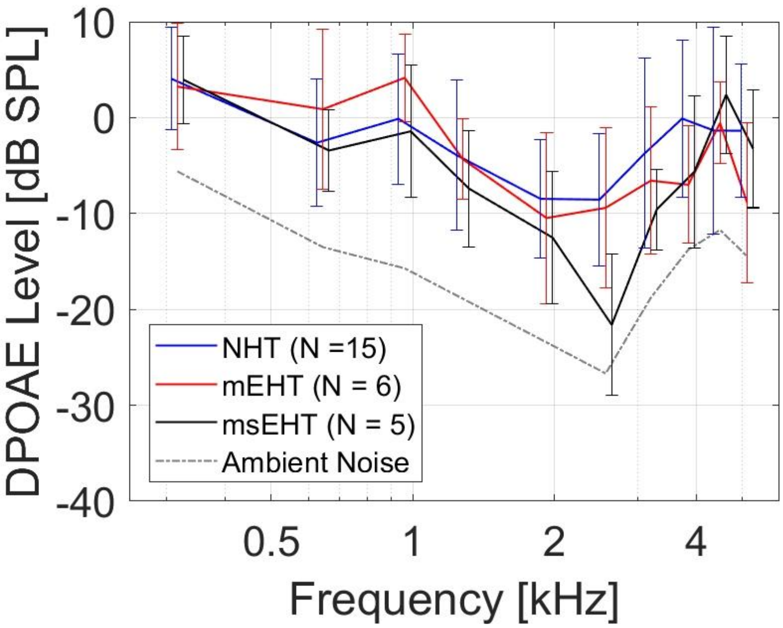

Figure 5. Mean distortion product otoacoustic emission (DPOAE) amplitudes (i.e., DPgram) for NHT, mEHT, and msEHT groups are plotted as a function of f2. Error bars represent ±1 standard deviation from the mean. Dashed lines indicate the average ambient noise floor, which is consistent across the three groups. Responses for both EHT groups are equivalent to the NHT group up to about 1000 Hz, at which point the DPOAE amplitudes decrease. The largest difference across groups appears between 2–4 kHz, which are critical frequency regions for speech perception.

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 as. 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 = 11 NHT, n = 5 mEHT, and n = 5 msEHT participants indicate a difference between the msEHT versus the NHT and mEHT groups in the expected direction. Figure 6 shows the average significance level of the F-ratio test across carrier frequencies and groups calculated for increasing numbers of EEG sweeps included in the average. For the NHT and mEHT groups, beginning with two EEG sweeps included in the average, the addition of each successive EEG sweep to the average improves the significance level of the F-ratio test (i.e., the significance level approaches the p = .05 criterion). In contrast, the significance level for the msEHT group does not begin to improve until after five to seven sweeps are included in the average and it remains much higher than the p = .05 criterion when all 18 sweeps are averaged. This pattern suggests that our ASSR task is successfully capturing differences in basilar membrane function and envelope modulation tracking in our study population.

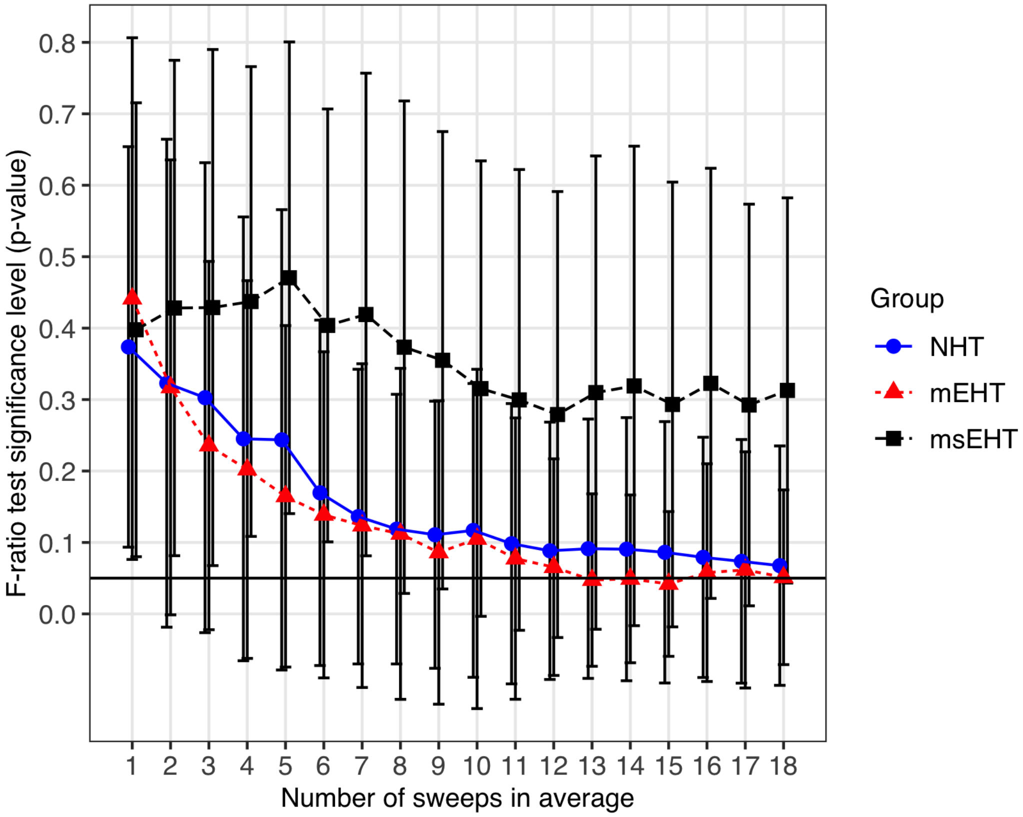

Figure 6. Average F-ratio test significance level for auditory steady state responses (ASSR) obtained for 0.5, 1, 2, 4, and 8 KHz carrier frequencies (CF) as a function of the number of EEG sweeps included in the by-participant average on which the F-ratio test is performed. Error bars show ±1 standard deviation. The horizontal line shows the .05 significance level. This plot includes *n* = 11 NHT, *n* = 5 mEHT, and *n* = 5 msEHT participants.

1.6 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* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants show a robust MMN elicited over frontal midline scalp regions during 100–200 ms following stimulus onset (Figure 7). 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 (AF3, AF4, F3, Fz, F4, FC1, FC2; Figure 8) also show the expected ERP components in each group (N1, P2, N2, P3a; labelled in Figure 8A for NHT participants and duration deviants). The MMN peak latency and mean amplitude during the 40 ms surrounding the peak latency across deviant types are plotted in Figure 9 and Figure 10. These plots indicate trends in the expected direction: NHT participants show a numerically larger amplitude (more negative) and shorter peak latency MMN compared to mEHT participants, who in turn show a numerically larger amplitude and shorter peak latency MMN compared to msEHT participants.

MMN mean amplitude and peak latency are further separated by deviant type and level (easy vs. hard) in Figure 11 and Figure 12. These more specific measures indicate several promising trends in the MMN that may reflect differences in the precision of short-term sensory memory representations for the deviants among NHT, mEHT, and msEHT groups. Across deviant types, NHT and mEHT groups show the expected trend in which deviants that are harder to discriminate elicit smaller (less negative) MMNs compared to deviants that are easier to discriminate, but the msEHT group shows the opposite pattern for frequency and modulation deviants. In terms of peak latency, the msEHT group also appears to differ from the NHT and mEHT groups for the modulation deviants, which elicit longer latency MMN at both difficulty levels, and the duration deviants, which elicit longer latency MMN only at the hard level. The latency differences for the hard duration deviant is especially interesting because the MMN obtained for deviants and standards that differ in duration alone (especially in the present case when deviants are longer duration) exclude differences in the exogenous N1 component between the standard and deviant, and therefore more accurately represent differences in sensory memory alone. The N1 component reflects sensory processing and its amplitude is influenced by the degree of acoustic change between deviant stimuli compared to standards, contributing to the early part of the MMN in this context. In Figure 8, there appear to be differences in N1 amplitude between groups for the frequency, gap, and modulation deviants, which present an additional electrophysiological variable that may capture group differences in sensory processing. Similarly, there also appear to be differences between groups and deviant types in the magnitude of the endogenous P3a component, which reflects involuntary switching of attention to the deviant stimulus. The P3a elicited by gap deviants is especially prominent among NHT participants (Figure 8), which suggests this group may be more sensitive to the presence of a short silent gap in the stimuli. Together, these preliminary results are promising and continue to suggest that our MMN task is sensitive to individual differences in hearing loss in our study population. However, more data for the two EHT groups are needed before the significance of these trends can be verified statistically.

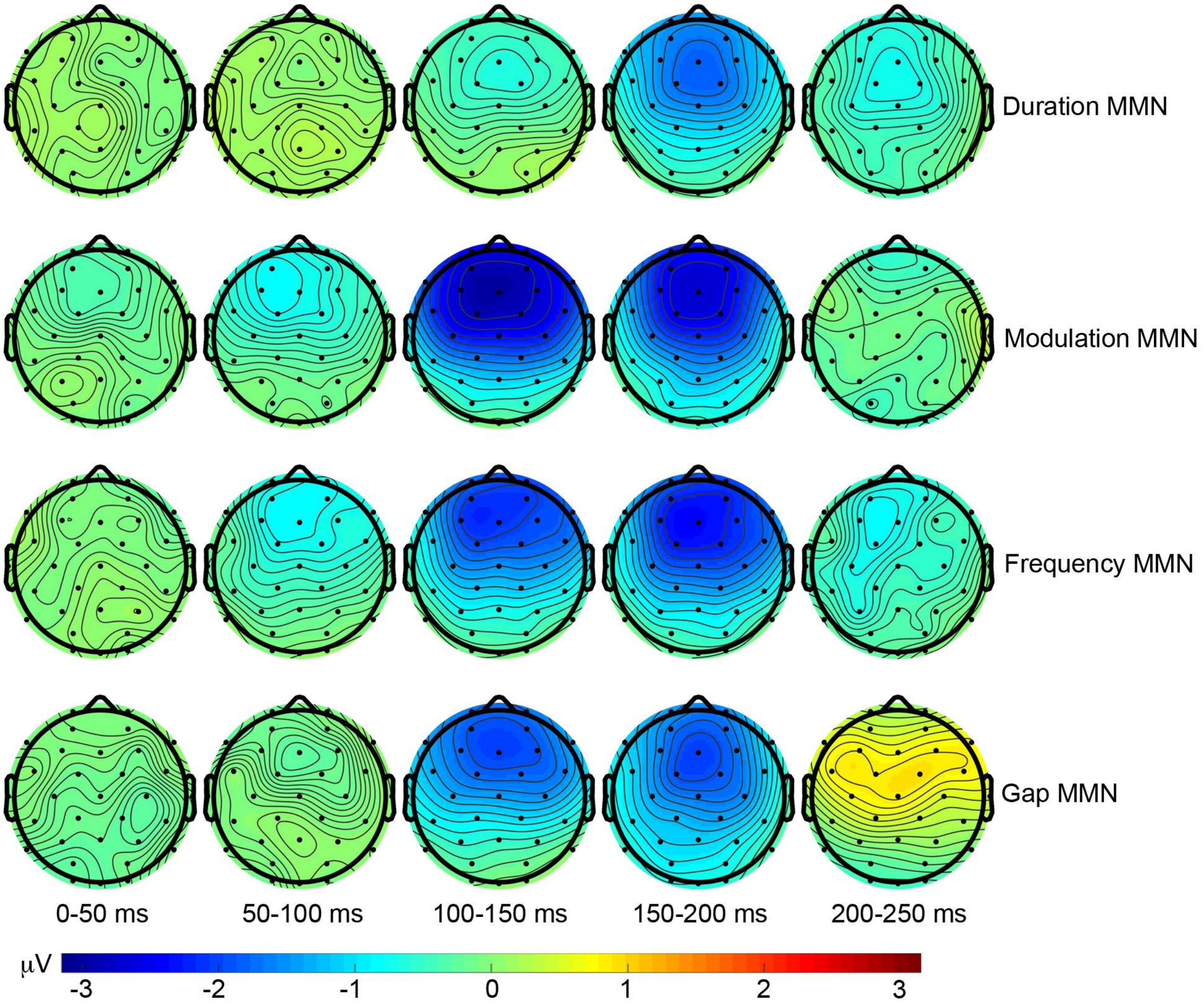

Figure 7. Grand mean topographic plots (looking down on a head with the nose pointed up) illustrating the deviant minus standard mismatch negativity (MMN; prominent dark blue area centered over frontal scalp sites during 100–200 ms windows) elicited by duration, amplitude modulation, frequency, and gap deviants averaged over 50 ms bins relative to stimulus onset. This grand mean plot includes *n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants.

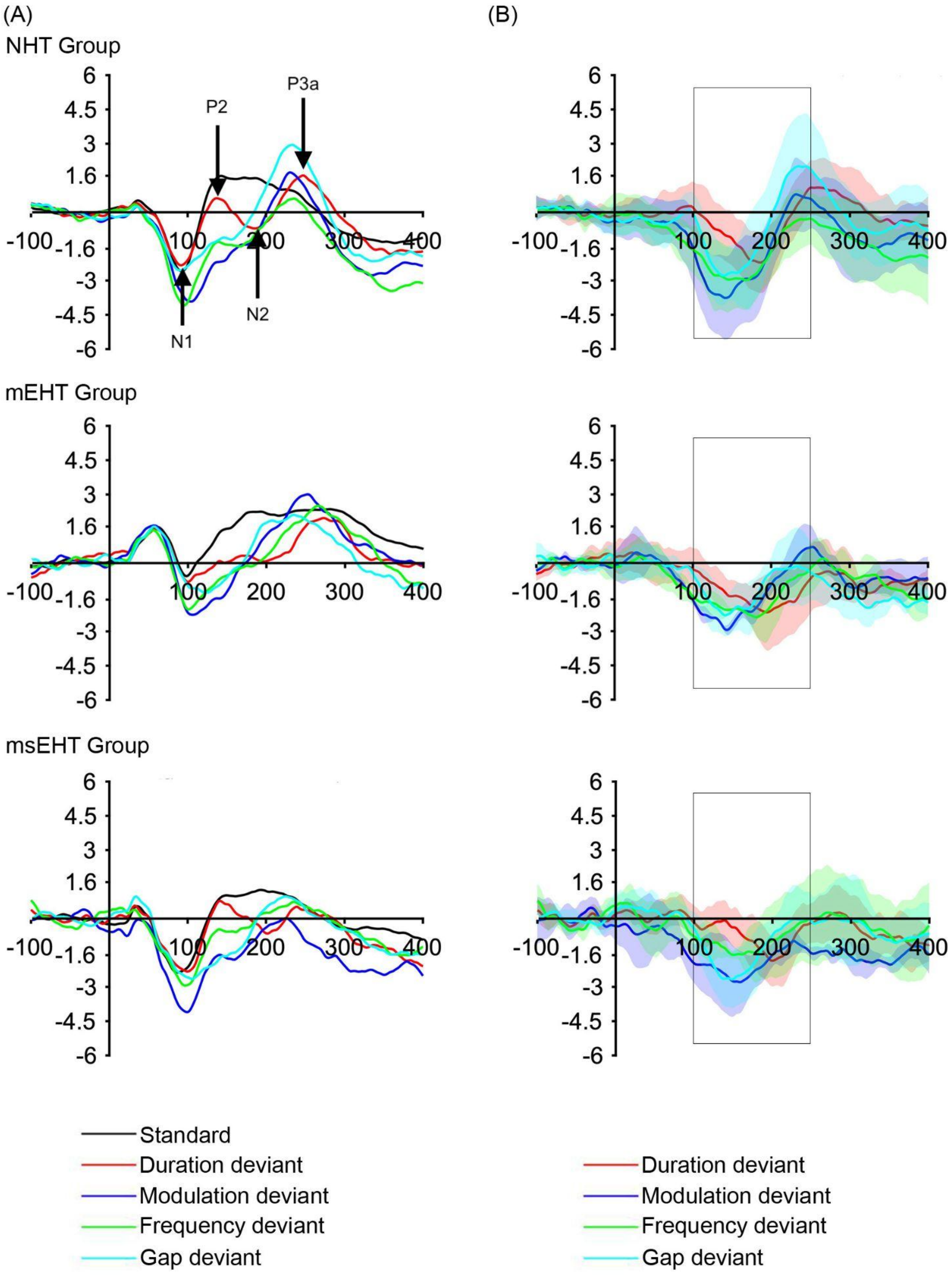

Figure 8. A) Event-related potential (ERP) plots averaged by group (*n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT) and stimulus type. Frontal and frontocentral sites where the MMN is strongest (AF3, AF4, F3, Fz, F4, FC1, FC2) are averaged in the time

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.

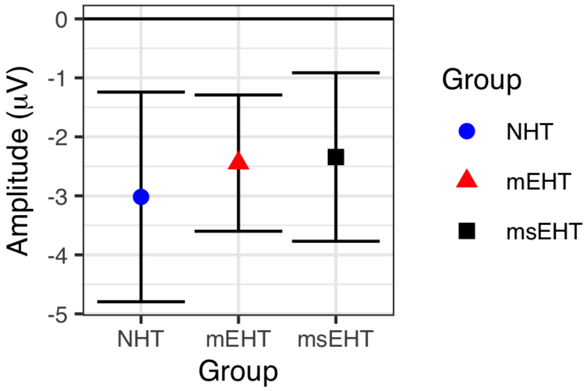

Figure 9. MMN mean amplitude and ±1 standard deviation during the 40 ms window centered on each participant's MMN peak latency averaged over all deviant types and levels for *n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants.

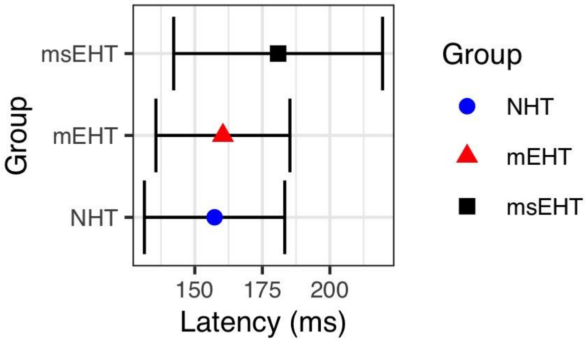

Figure 10. MMN peak latency and ±1 standard deviation over 100-250 ms following stimulus onset averaged over all deviant types and levels for *n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants.

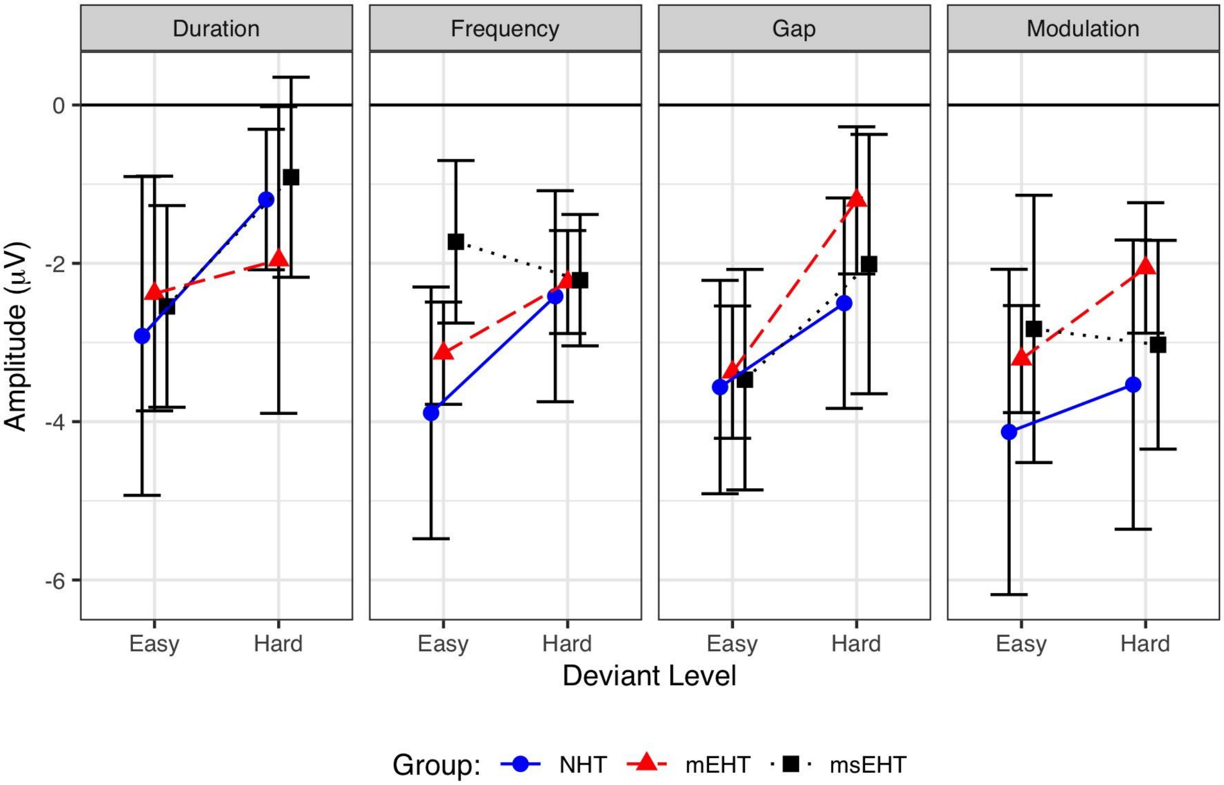

Figure 11. MMN mean amplitude and ±1 standard deviation during the 40 ms window centered on each participant's MMN peak latency averaged by deviant type and level for *n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants.

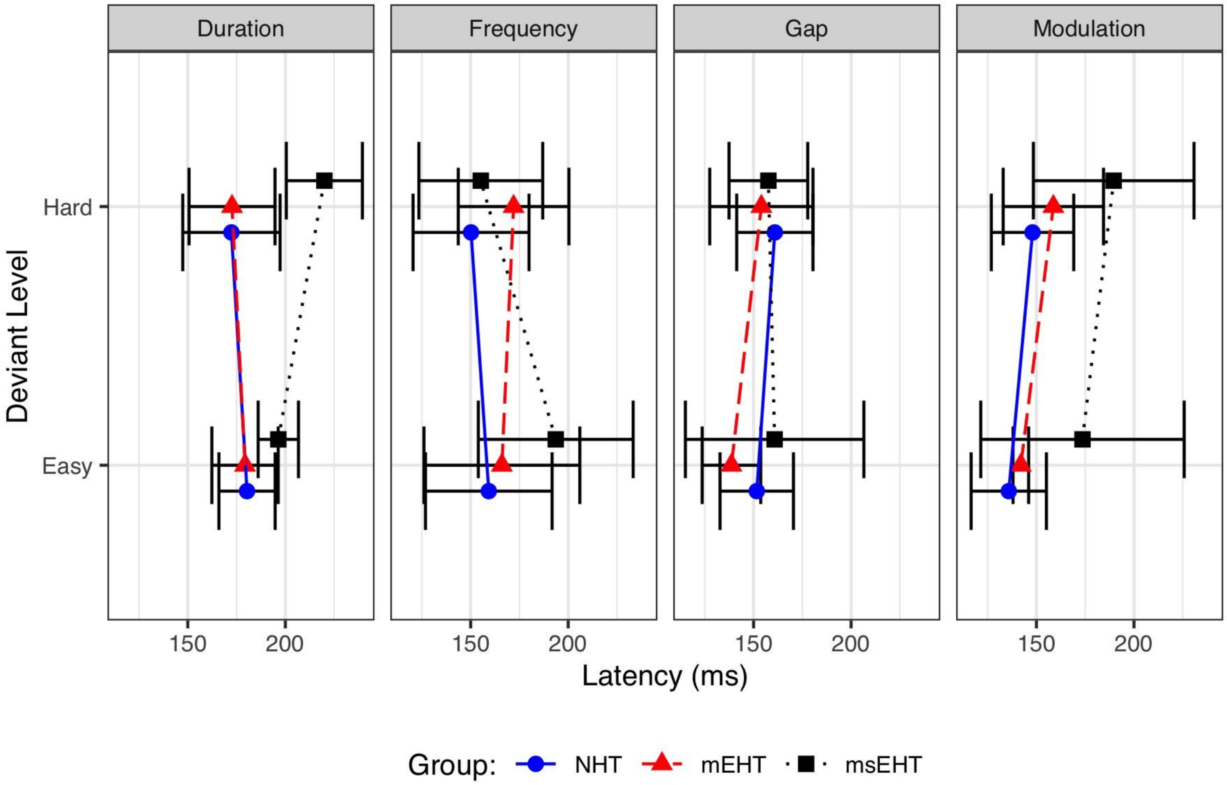

Figure 12. MMN peak latency and ±1 standard deviation over 100-250 ms following stimulus onset averaged by deviant type and level for *n* = 11 NHT, *n* = 3 mEHT, and *n* = 5 msEHT participants.