AUDITORY RESPONSES IN NORMAL-HEARING, NOISE-EXPOSED EARS

By

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ABSTRACT

Recent investigations in animal ears have described temporary noise-induced hearing loss with permanent deafferentation for up to 50% of auditory nerve fibers in the high-frequency region of the cochlea (Kujawa and Liberman, 2009; Lin et al., 2011, Furman et al., 2013). Although thresholds remained normal, evidence of the deafferentation was apparent in reduced wave I auditory brainstem response (ABR) amplitudes for high-level stimuli. It is unknown if the same phenomenon exists in the human ear.

The goal of this research project was to characterize cochlear and auditory nerve function in human ears with normal behavioral thresholds that are regularly and voluntarily exposed to high levels of noise. Data were collected from 30 normal-hearing subjects with different voluntary noise-exposure backgrounds. Auditory function was assessed across a range of stimulus levels via the ABR and distortion-product otoacoustic emissions (DPOAEs). ABRs were collected in response to 1 and 4 kHz tone bursts and a click stimulus. DPOAEs were assessed at 1, 2 and 4 kHz. Significantly smaller amplitudes were seen in wave I of the ABR in response to high-level (e.g., 70 to 90 dB nHL) click and 4 kHz tone bursts in ears with greater noise-exposure backgrounds. There were no statistically significant differences in supra-threshold DPOAE level across ears with different noise-exposure histories.

These findings are consistent with data from previous work completed in animals where the reduction in high-level wave I ABR responses was a result of deafferentation of high-threshold/low-spontaneous rate auditory nerve fibers. These data suggest a similar mechanism may be operating in human ears following exposure to high sound levels. Furthermore, data from the present study suggest noise-induced auditory damage in normal-hearing ears is only apparent when examining supra-threshold ABR responses.

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Dedication

To my husband, Benton, and my daughter, Freda. Every day brings new and wonderful adventures.

For Kenai

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INTRODUCTION

Exposure to excessive noise is known to be injurious to hearing and the detrimental effects of noise on the auditory system have been well established (e.g., Spoendlin, 1971; Saunders et al., 1985; Bohne and Harding, 2000; Nordmann et al., 2000; Kujawa and Liberman, 2009). The underlying cause of noise-induced hearing loss (NIHL) is not clear (Bohne and Harding, 2000; Nordmann et al., 2000), but likely includes both mechanical and metabolic processes (Saunders et al., 1985). Despite extensive investigation, an imperfect association exists between the amount of acoustic exposure, the resulting anatomical damage, and the effect on auditory function. While it is generally accepted that excessive noise exposure is dangerous to the ear, what constitutes "excessive" remains unclear; the two government organizations (Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH)) responsible for defining permissible noise exposure limits do not agree.

NIHL is a prevalent problem in our nation where roughly 15 percent of Americans 20 to 69 years of age (approximately 26 million individuals) experience hearing loss most likely caused by exposure to loud sound (NIDCD, 2001). Clinical protocols for assessing NIHL have traditionally relied on the evaluation of behavioral thresholds where the hallmark of NIHL is a high frequency 3-6 kHz notching audiometric pattern. Other auditory symptoms associated with exposure to loud sound include difficulty hearing in noise, tinnitus, and/or hyperacusis (Simpson, 1999; Ward et al., 2003b; Musiek and Baran, 2007). It is widely accepted that permanent thresholds shifts (PTS) following noise exposure are a result of permanent damage to the auditory structures. An assumption underlying the concept of a temporary threshold shift (TTS) is that following full recovery of threshold(s), no residual anatomical damage is present and the temporary decrease in hearing has been essentially harmless (Humes et al., 2005; Kujawa and Liberman, 2009). However, recent data challenge the view that temporary NIHL results in no permanent damage to the auditory structures.

Recent investigations in mice (Kujawa and Liberman, 2009) and guinea pigs (Lin et al., 2011; Furman et al., 2013) suggest noise exposures are more dangerous than previously believed. Additionally, these data suggest current clinical testing protocols are insensitive to detecting evidence of early auditory damage. These studies induced a temporary NIHL (up to a 40 dB loss) in animal ears. Following threshold recovery, auditory function was assessed via auditory brainstem responses (ABRs) and distortion-product otoacoustic emissions (DPOAEs). Additionally, evidence of anatomical damage was evaluated by examining the outer hair cells (OHCs), the inner hair cells (IHCs) and their nerve terminal connections (i.e., synaptic ribbons), and spiral ganglion cells. Results demonstrated an abrupt, permanent loss of up to 50% of afferent nerve terminal connections between inner hair cells (IHC) and auditory nerve fibers in the frequency region of maximum threshold shift. This acute loss subsequently led to degeneration in spiral ganglion cells over time. Despite substantial deafferentation, ABR wave I thresholds demonstrated full recovery to pre-exposure levels within 10 to 14 days following noise exposure. Therefore, ABR wave I threshold measures failed to provide evidence of the permanent damage to the auditory structures.

The first wave of the ABR has been shown to be generated by the spiral ganglion cells in the auditory nerve (Melcher and Kiang, 1996) and is contingent upon a sufficient population of afferent synapses from the IHCs. Threshold responses, which are relatively insensitive to large changes in the auditory nerve fiber population (Earl and Chertoff, 2010), are dependent upon synchronous firing of neuronal fibers but are determined by a criterion response only slightly above the noise floor. Therefore, in recent findings from noise-exposed animals (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013), the remaining undamaged IHC afferent connections proved sufficient to preserve the threshold response, even in the presence of a substantial loss of IHC synapses. Although wave I threshold returned to normal, evidence of the loss of IHC afferent connections was seen when examining the ABR wave I response at supra-threshold levels. At high stimulus levels (> 40 dB SPL), the ABR wave I revealed decreased amplitude in the noise-exposed animals relative to control ears. In contrast to threshold, ABR

amplitude is influenced by the number and type of auditory nerve fibers contributing to the response. Furman et al. (2013) reported specific loss of auditory nerve fibers with low spontaneous rates and high thresholds, suggesting that NIHL selectively damages auditory nerve fibers that contribute to high-level amplitude responses. Therefore, supra-threshold responses demonstrated better sensitivity at revealing auditory damage than threshold responses. In contrast to the damage seen in the IHC afferent connections, the outer hair cells (OHCs) appeared undamaged upon anatomical assessment. Since the OHCs are responsible for the generation of DPOAEs, it is not surprising there were no differences in threshold or supra-threshold DPOAE responses in noise-exposed animal ears compared to controls.

These investigations (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013) present a different pattern of auditory damage that contradicts the assumption that no permanent damage occurs with TTS. Additionally, these data suggest the use of supra-threshold stimuli may provide evidence of early-onset noise-induced auditory damage that is not yet evident in behavioral thresholds. This is of clinical importance because the current gold standard for NIHL assessment is monitoring behavioral thresholds. These data are also provocative because high-threshold, low-spontaneous rate auditory nerve fibers are important for hearing in noisy environments, partially due to their resistance to masking in background noise (Costalupes et al., 1984; Lopez-Poveda and Barrios, 2013). Individuals with damage to these fibers might report difficulty hearing in noise, even in the presence of normal behavioral thresholds. Difficulty hearing in noise, tinnitus, and hyperacusis have all been reported in noise-exposed human ears with normal behavioral thresholds (Sanchez et al., 2005; Muhr and Rosenhall, 2010). Based on the work of Kujawa and colleagues, it appears possible to have normal behavioral thresholds in the absence of "normal" auditory function.

Attempts to develop assessment protocols that identify early evidence of noise damage or that identify individuals at high risk for developing NIHL are not unprecedented. Otoacoustic emissions (OAEs), evoked-potential responses, and self-report questionnaires have been investigated in the context of NIHL assessment in the human ear.

While the investigations summarized above (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013) did not find any evidence of OHC damage following TTS, other reports have noted OHC damage following exposure to loud sound (e.g., Spoendlin, 1971; Robertson and Johnstone, 1980; Saunders et al., 1985; Nordmann et al., 2000). OAEs are a byproduct of active cochlear processes in the cochlea and are dependent on OHC function. OAEs have been measured in noise-exposed populations and results have suggested OAE level might be useful in determining if an ear is at risk for or shows early evidence of NIHL (Attias et al., 2001; Lapsley Miller et al., 2006; Lapsley Miller and Marshall, 2007; Marshall et al., 2009). However, a clear interpretable relationship has not been identified. This could be due, at least in part, to the absence of permanent OHC damage following TTS. Another factor contributing to the lack of success with OAE measurement in noise-exposed ears could be the variability in the OAE response that is often seen across individuals, both normal and impaired. This makes it difficult to specify an OAE level that might be indicative of early NIHL. Several researchers have proposed the use of optimized stimulus parameters that have been shown to result in more robust emissions in normal-hearing ears (Neely et al., 2005; Johnson et al., 2006; Kirby et al., 2011). The use of alternate stimulus calibration methods (Scheperle et al., 2008, 2011) could help reduce variability, especially when completing repeat testing in individual ears over time. Forward pressure level (FPL) calibration has been shown to avoid the effects of standing waves in the ear canal, which can be problematic at high frequencies and can lead to calibration errors. If the goal is to detect early evidence of damage caused by noise exposure, it might be possible to more easily visualize differences if the emission response is maximized by utilizing optimal stimulus parameters and if a more stable calibration approach such as FPL calibration is utilized.

There is some evidence of reduced wave I amplitude in human ears not related to changes in behavioral threshold in aging ears (Konrad-Martin et al., 2012) and in normal-hearing ears with tinnitus (Schaette and McAlpine, 2011). A valid concern of ABR wave I assessment is that it can be difficult to visualize at low stimulus levels. Enhancement of wave I can be achieved by using a slower presentation

rate and an ear canal or tympanic membrane electrode (Ferguson and Ferraro, 1989; Schwartz et al., 1994; Hall, 2007b; Gaddam and Ferraro, 2008). Variability is commonly seen in ABR response amplitude, even in normal-hearing ears (Schwartz et al., 1994). In light of the recent animal data relative to wave I amplitude, it is possible some variability could be due to differences in noise exposure background. However, further investigation of ABR responses, particularly wave I, in normal-hearing, noise-exposed human ears is warranted.

Self-report questionnaires have been used to determine if an individual is at risk for developing NIHL based on the type and duration of noise exposures reported. The majority of these efforts are focused on quantifying occupational noise exposures (Neitzel et al., 2004a; Neitzel et al., 2004b; Reeb-Whitaker et al., 2004). A questionnaire was developed that was able to provide an estimate of the annual overall noise exposure by assessing daily and episodic noise exposures (Neitzel et al., 2004b). The questionnaire was expanded by Megerson (2010) to include questions pertaining to music, impact (e.g., firearms), and occupational noise exposures as well as specific queries regarding the duration of each exposure (in hours). The Megerson questionnaire yields a $L_{Aeq8760h}$ value, which provides an annual estimate of the sound pressure level in dB using an A-weighted frequency response with a 3-dB exchange rate over 8760 hours (365 days per year x 24 hours per day). While self-report questionnaires are imperfect in nature by being subject to recall bias, they can be helpful in quantifying how much noise exposure an individual has incurred.

In summary, recent evidence suggests exposure to loud sound is considerably more dangerous than previously believed and that current assessment protocols are insensitive to detecting evidence of early noise-induced auditory damage (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). However, as these studies were completed in the mouse and guinea pig ear, further investigation is needed prior to generalizing findings to the human ear. If a similar pattern of anatomical damage and auditory function is present in the human cochlea, it might be necessary to alter clinical NIHL assessment protocols.

The goal of this research project is to characterize cochlear and auditory nerve function in ears with normal behavioral thresholds that are regularly and voluntarily exposed to high levels of noise. Auditory function was evaluated using ABR and DPOAE testing across a range of stimulation levels in normal-hearing ears with different noise exposure backgrounds (as assessed by a questionnaire). Information gleaned from understanding this relationship could be used to ascertain if the human ear follows a pattern similar to the noise-exposed animals previously discussed. Additionally, data from the present study could be used to identify an assessment approach for early detection of noise-induced auditory damage, potentially allowing for procedures to be initiated that prevent or mitigate further auditory impairment.

It is hypothesized that, in normal hearing subjects, high-level ABR wave I amplitude will decrease as the level of noise exposure background increases. It is also hypothesized that supra-threshold DPOAE level will not differ across ears with varying amounts of noise exposure background. Finally, it is hypothesized that DPOAE and ABR thresholds will not differ across ears with varying noise exposure backgrounds.

MATERIALS AND METHODS

All testing was conducted in the Auditory Research Lab in the Hearing and Speech Department at the University of Kansas Medical Center in Kansas City, Kansas, under the direction of Dr. Tiffany A. Johnson. All subject recruitment, audiological testing and data collection was completed by Greta C. Stamper. Approval for the study was granted through the Human Subjects Committee (HSC). Refer to Appendix C for the informed consent document approved by the HSC.

Subjects

A total of 37 subjects consented to participate in this study. Subjects were primarily recruited from local colleges and universities via broadcast email or word of mouth. To meet study inclusion criteria, subjects were required to have a normal otoscopic examination, normal middle-ear function, and normal hearing.

Individuals who participate in music programs were heavily recruited in order to enroll subjects with a range of different noise-exposure backgrounds. Musicians have been identified as a population frequently exposed *voluntarily* to high levels of noise (Chasin, 1996; O'Brien et al., 2008; Zhao et al., 2010; Cook-Cunningham et al., 2012). Noise exposure levels of approximately 30 different orchestral instruments have been reported to range from 76 to 96 dBA (O'Brien et al., 2008), reaching levels that can exceed NIOSH recommendations. Additionally, hearing loss (both temporary and permanent), tinnitus, and hyperacusis have also been reported to be closely associated with music exposures common to musicians (for a review, see Zhao et al., 2010).

Of the 37 subjects consented, two were recruited for pilot data purposes, three voluntarily withdrew due to scheduling conflicts, one was excluded due to the presence of 4 kHz air-bone gaps, and one subject was not enrolled due to the target number of subjects being achieved. This resulted in a total

of 30 subjects (20 females, 10 males) providing data for analyses. Subjects ranged in age from 19 to 28 years old with an average of 22.8 years old.

Subject Sample Size

A power analysis (SAS) indicated a total of 30 subjects were necessary to achieve a power of approximately 80%. For a test of correlation between two normal variables using Fisher's z statistic with a significance level of 0.05 in the upper tail, a sample size of 30 was necessary to detect a correlation of 0.4. The actual power was 72.4%. To detect a correlation of 0.5, a sample size of 30 resulted in a power of 89.6%.

Testing Procedures

Data were collected in two testing sessions. The first testing session (approximately 1 hour) consisted of consenting procedures, audiometric evaluation, and a detailed case history regarding noise exposure background. The second session (approximately 4 hours) consisted of DPOAE and ABR testing. Between the two testing sessions, subjects were required to complete a 16-hour noise dosimeter monitoring task. Both testing sessions occurred within two weeks of each other with at least one day between sessions.

Audiometric Evaluation

Normal hearing was defined as thresholds ≤ 20 dB HL (re: ANSI, 2004) for the octave and interoctave frequencies from 0.25 to 8.0 kHz. Hearing sensitivity was assessed using insert earphones with conventional behavioral audiometric procedures in 5-dB step sizes. Subjects were required to have no threshold differences > 15 dB between adjacent test frequencies or air-bone gaps ≥15 dB at any test frequency. Middle-ear function was assessed using a standard clinical tympanometer with a 226-Hz probe tone. Normal middle-ear function was defined as follows: static acoustic admittance of 0.3 to 1.7 mmhos and tympanometric peak pressure between -100 and +50 daPa (Margolis and Hunter, 1999). Audiometry

was completed at the first testing session. Otoscopy and tympanometry were completed, and required to be normal, at the beginning of each testing session.

Pure-tone behavioral thresholds and middle-ear function were assessed in both ears of each subject; however, only one ear was selected as the test ear. If the test ear could not be selected based on tympanometric or audiometric results, the test ear was selected as the ear that had the greatest amount of noise exposure. If a test ear could still not be selected, it was chosen at random.

Assessment of Noise-Exposure Background

Two self-report metrics were used to assess noise-exposure background. First, a detailed case history was obtained from each subject. Specific questions included 1) Have you ever been exposed to loud sounds that made your ears "ring" or "buzz"? 2) Have you ever been exposed to loud sounds that made your hearing seem muffled for a while? and 3) Have you ever been exposed to loud sounds that made your ears hurt, feel "full" or bother you in any other way? Second, subjects completed a self-report questionnaire developed by Megerson (2010) to further quantify noise-exposure background. See Appendix B for further detail on the questionnaire and its computation. This noise exposure questionnaire (NEQ) assesses specific known high-noise situations (e.g., music, occupational, power tools, etc.) by querying the frequency and duration of an individual's exposure to loud sound(s) over the past year. The NEQ yields a value that is an estimate of the annual amount of noise exposure in $L_{Aeq8760h}$. Here, "L" represents sound pressure level in dB, "A" represents use of an A-weighted frequency response, "eq" represents a 3-dB exchange rate for calculation of the time/level relationship, and "8760h" represents the total duration of the noise exposure in hours over one year (365 days per year x 24 hours per day).

Each subject completed noise dosimeter monitoring using an Etymotic Research personal noise dosimeter (ER-200D). The purpose of the noise dosimeter was to provide an objective measurement of subject noise exposure that was not susceptible to recall bias. Subjects were trained on how to use the dosimeter and instructed to record sound exposure in a continuous 16-hour block of time during a day

between their two testing sessions. Subjects were further instructed to choose a day that was representative of their typical exposure to loud sound. The ER-200D is calibrated using the NIOSH 100% daily dose equaling an 8-hour exposure to a continuous 85 dB (A) noise with a 3-dB exchange rate. The dosimeter obtains daily dose values every 220 milliseconds and these are averaged over 3.75 minute intervals. The data obtained from the dosimeter include (1) run length, (2) final dose percentage, (3) overall L_{eq} (A-weighted continuous equivalent sound level), and (4) dose and L_{eq} values for each 3.75 minute time block. These measurements were examined for when noise levels exceeded the recommended NIOSH daily dose and used to evaluate the approximate level and duration of the noise exposures encountered.

Auditory Response Data Collection

DPOAE and ABR responses were collected while the subjects were seated comfortably in a reclining chair housed in a sound-treated room. Subjects were encouraged to relax quietly or sleep during data collection. DPOAEs were assessed prior to ABRs to avoid potential temporary reduction in emission level caused by the stimuli used in electrophysiology measures (Mhatre et al., 2010).

DPOAE Protocol

All DPOAE data were collected using custom-designed software (EMAV, Neely and Liu, 1993) that controls a 24-bit soundcard (CardDeluxe, Digital Audio Labs) housed in a PC. An ER-10C (Etymotic Research) probe microphone was used to calibrate, present and record emissions. Calibration was completed using the forward pressure level (FPL) technique outlined by Scheperle et al. (2008, 2011), which estimates the Thévenin-equivalent acoustic properties of the probe microphone (i.e., the source) and allows for isolation of the incident from the reflected components of the calibration signal. Prior to each subject's testing session, a wideband chirp stimulus was presented to five brass tubes with known acoustic impedance. The pressure response in each tube was measured and used to estimate source

impedance and pressure. Source impedance and pressure are needed to estimate load impedance, which is necessary to convert SPL to FPL.

DPOAEs were recorded as level functions in response to pairs of primary tones (f_1, f_2; $f_1 < f_2$) for f_2 frequencies of 1, 2 and 4 kHz. The level of f_2 (L_2) ranged from 0 to 80 dB SPL in 5 dB steps. The level of f_1 (L_1) and the f_2/f_1 ratio was determined based on stimulus parameters from Kirby et al. (2011), where $L_1 = 80 + 0.1 \times log_2\left(\frac{64}{f_2}\right) \times (L_2 - 80)$ and $f_2/f_1 = 1.22 + log_2\left(\frac{9.6}{f_2}\right) \times (\frac{L_2}{415})^2$. These stimulus parameters, when used in conjunction with FPL calibration, were shown to result in increases in test performance when compared to more traditional stimulus parameters (Kirby et al., 2011). Response samples of 0.25-seconds were alternately stored in one of two buffers. The emission level, L_d, was estimated as the level in the $2f_1$-f_2 frequency bin after summing the two buffers. The noise floor, N_d, was estimated from the level in the $2f_1$-f_2 frequency bin as well as the level in the five bins on each side of the $2f_1$-f_2 frequency by subtracting the two buffers.

Measurement-based stopping rules were employed so that data collection ceased for any condition when (1) the noise floor was ≤ -25 dB SPL, (2) the signal-to-noise ratio (SNR) exceeded 60 dB, or (3) 32 seconds of artifact-free averaging time had elapsed. These conditions were chosen so data collection never terminated on SNR criteria, but either reached a noise floor of ≤ -25 dB SPL or 32 seconds of averaging time. For higher f_2 frequencies (2 and 4 kHz), data collection primarily ceased on the noise floor criterion while at the lowest f_2 frequency (1 kHz), it ceased on the averaging time criterion.

DPOAE threshold was defined as the lowest L_2 producing an SNR of ≥ 3 dB. To ensure a single noise spike did not influence threshold determination, subsequent L_2's were required to have an SNR of < 3 dB. Supra-threshold DPOAE data were defined as the dB SPL (i.e., L_d) in the $2f_1$-f_2 frequency bin for each recording condition.

ABR Protocol

ABR testing was performed using Tucker-Davis Technologies (TDT) System 3 (Tucker-Davis Technologies, Inc., Miami, FL). TDT software SigGenRP was used to create the acoustic stimuli and BioSigRP was used to record and analyze ABR responses. Hardware components consisted of an RX6 multifunction processor, RA16 Medusa Base System, PA5 programmable attenuator, and HB7 headphone driver. Stimuli were presented via E-A-R-TONE 3A insert earphones and responses were collected using a RA4PA 4-channel Medusa preamplifier and a RA4LI 4-channel headstage connected to the Medusa base station by a fiber optic cable. A two-channel response was recorded. For both channels, an electrode montage with the negative (inverting) electrode on the high forehead (F_z) and a ground electrode on the contralateral mastoid was used. For the positive (non-inverting) electrode sites, one channel was a tympanic membrane electrode (commercially available from Sanibel Supply, Eden Prairie, MN) and the other channel was a surface electrode placed on the ipsilateral mastoid. This allowed one channel to serve as a response that maximizes visualization of ABR wave I and the other channel to serve as a comparison to a typical ABR collected in the clinic. Prior to analysis, all waveforms were inverted to allow for the typical vertex positive orientation.

ABRs were collected in response to Blackman-gated 1 and 4 kHz tone bursts as well as to 100 µsec clicks. Temporal characteristics of the 1 and 4 kHz tones were based on those from Gorga et al. (1993a), which were designed as a compromise between equal logarithmic energy spread and equal ability to elicit rapid onset responses at low frequencies. The temporal characteristics (with no plateau) were as follows: 1 kHz, 2.0 msec rise/fall and 4 kHz, 1 msec rise/fall. All stimuli were presented with alternating polarity at a rate of 11.3 per second, band-pass filtered (0.1 to 3 kHz) and amplified (20 times). The use of a battery powered preamplifier and a fiber optic cable allowed for the use of less amplification than is typically seen in ABR recordings (a gain of 20 versus 100,000 times).

To calibrate the ABR stimuli, detection thresholds for these signals were measured in a group of 10 normal-hearing individuals. The detection threshold for the brief-duration ABR stimuli were used to specify the stimulus levels in dB nHL. The following describes the relationship between 0 dB nHL and dB ppeSPL: 100μsec clicks, 31 dB ppe SPL=0 dB nHL; 1 kHz tone burst, 19 dB ppe SPL=0 dB nHL; 4 kHz tone burst, 21 dB ppe SPL=0 dB nHL.

Amplitude growth functions using descending 10-dB steps were collected for stimulus levels ranging from 90 dB nHL to 10 dB below threshold for ABR responses to click stimuli. Due to time constraints, ABR responses to 4 kHz tone bursts were collected for stimulus levels beginning at 90 dB nHL to 10 dB below threshold for many subjects and only at 90 and 80 dB nHL for others. Only high-level 1 kHz tone burst ABR responses were collected (90 and 80 dB nHL). At each stimulus level, two replications of 2000 stimulus repetitions were collected. Occasionally, a third replication of 2000 stimulus repetitions was collected, particularly when the response was near threshold. ABR recordings were analyzed within a 20 msec epoch and visual monitoring of the raw EEG was used to avoid contamination of the response by excessive myogenic activity.

Following ABR recording, the two replications were averaged and the averaged waveform was used for analysis. Averaged ABR waveforms were analyzed by two judges, Greta Stamper and Dr. Tiffany Johnson. Both judges reviewed the data together and were in agreement for all waveforms. This procedure was completed separately for waveforms obtained with a tympanic membrane and a mastoid recording site. ABR threshold was defined as the lowest level at which an identifiable peak and trough could be visually detected. ABR amplitude was defined as the voltage difference between the identified peak and the following trough (see example waveforms in Fig. 5).

Data Analysis

Simple linear regression was used to characterize relationships between DPOAE and ABR threshold and supra-threshold data and noise exposure background. In order for linear regression to be an appropriate statistical analysis approach, four assumptions must be met. The first assumption is that a linear relationship between the dependent and independent variables exists. This assumption was verified by visually inspecting scatterplots of DPOAE and ABR data as a function of noise exposure background. Second, individual samples are required to be uncorrelated or display independence from each other. No individual subject influenced another subject's data; the subjects were enrolled at random. Thirdly, homoscedasticity or equal variance is required across all values of the independent variable (i.e., noise exposure background or NEQ value). This assumption was assessed by visually inspecting the scatterplots of the DPOAE and ABR data as a function of noise exposure background and verifying that the spread of the data was uniform. Lastly, normality of the error distribution is required. To determine this, a normal probability plot of the residuals was inspected and was required to fall along a diagonal line.

While the data presented here did not violate any underlying assumptions of linear regression analysis, there were several unusual or potentially influential observations (i.e., outliers) identified in the data. While all data points were valid observations, it was necessary to identify if the exclusion of a potentially influential observation changed the conclusions of the data analysis. To do this, studentized residuals were obtained for each linear regression analysis. The magnitude of the residuals was inspected to see if large values existed (greater than 2 or less than -2). Data analyses were re-run without the inclusion of the potentially influential observation. Excluding these potentially influential data observations did not change the study conclusions and therefore no observations were removed from the data set.

For stimulus conditions where a statistically significant linear relationship was indicated, multiple linear regression was used to determine if behavioral threshold influenced the data. The assumptions of multiple linear regression are the same as simple linear regression with the addition of one more assumption. In multiple linear regression, the two (or more) independent variables are required to not be correlated with each other (collinearity). To determine if collinearity existed, the Variance Inflation Factor (VIF) was inspected and required to be close to 1. This assumption, along with the other four previously mentioned, were all met for conditions where multiple linear regression techniques were employed.

RESULTS

The goal of this study was to explore the relationship between cochlear and auditory nerve function in normal-hearing ears with varying amounts of voluntary noise exposure background. DPOAE and ABR thresholds and supra-threshold DPOAE levels and ABR amplitudes were used to evaluate auditory function. These measures were compared to the amount of voluntary noise exposure background.

NEQ and Dosimeter Readings

A histogram displaying the range of NEQ values obtained by the 30 subjects in this study is shown in Fig. 1. The NEQ has a theoretical range of 64 to 95.5. In the present study, NEQ values ranged from 67 to 84. While there were no subjects enrolled with NEQs close to the upper theoretical range, it is unlikely that an individual scoring a 95 on the NEQ would have normal hearing. Figure 1 demonstrates that the NEQ values in the present study span a wide range and indicates variation in noise exposure background across the enrolled subjects.

All subjects were asked to complete a 16-hour noise dosimeter monitoring task as an objective measure of their noise exposure prior to their second testing appointment. However, two subjects forgot to complete the noise dosimeter monitoring task. The ER200-D noise dosimeter provides an overall L_{eq} (an A-weighted continuous equivalent sound level) for the 16-hour recording. Individual NEQ values are plotted as a function of the dosimeter L_{eq} in Fig. 2. Linear regression analysis revealed a statistically significant positive linear relationship between the L_{eq} and the NEQ (p-value=0.003). While noise dosimeter monitoring is a more objective method to quantify noise exposure, several subjects who reported participation in high-noise episodic or seasonal activities (e.g., football marching band, basketball pep band, etc.) were not actively partaking in the reported activity during the study period. Therefore, the noise dosimeter was not able to capture a representative sample of the reported noise exposure(s). Consequently, the L_{eq} recorded by the noise dosimeter might not accurately reflect the reported noise exposure of these individuals. In contrast, the NEQ queried a multitude of noise exposures

encountered over the past 12 months (see Appendix B). Due to nature of the NEQ format and the ability to address multiple types of noise exposures, a more complete estimate of individuals' noise exposure background was possible. Therefore, the NEQ value was used for all additional data analyses to quantify individual noise exposure background.

DPOAE Data

DPOAEs were assessed in each subject for f_2's of 1, 2, and 4 kHz with L_2 ranging from 80 to 0 dB SPL. DPOAE threshold was defined as the lowest L_2 (in dB SPL) producing an SNR of $\geq$ 3 dB. These data are shown in Fig. 3. Here, DPOAE threshold is plotted as a function of NEQ for 1 kHz (top panel), 2 kHz (middle panel), and 4 kHz (bottom panel). Linear regression analysis did not reveal any statistically significant relationships at 1 kHz (p-value=0.612), 2 kHz (p-value=0.093) or 4 kHz (p-value=0.544) between DPOAE threshold and self-reported noise exposure. These findings suggest that the amount of noise exposure background does not influence the DPOAE threshold.

Supra-threshold DPOAE level (L_d) is plotted as a function of NEQ in Fig. 4. Data are provided for L_2's of 80 dB SPL (top row), 70 dB SPL (second row), 60 dB SPL (third row) and 50 dB SPL (bottom row) for each of the f_2's assessed (1 kHz, first column; 2 kHz, middle column; 4 kHz, last column). Data for these four L_2's and all other L_2's assessed are presented in Table 1. Linear regression was used to explore the relationship between DPOAE supra-threshold response and noise exposure background. No significant relationship was revealed for any L_2 at any f_2 for supra-threshold DPOAE responses.

The data from DPOAEs presented here support the study hypothesis that DPOAE thresholds do not differ across ears with varying noise exposure background and that supra-threshold DPOAE level does not change as the level of noise exposure increases. These data suggest that responses arising from the OHCs do not differ as a function of noise exposure background, at least for the noise exposures reported by the subjects tested here.

ABR Data

A 2-channel ABR recording was obtained from all subjects at each stimulus condition. One channel utilized a tympanic membrane electrode to enhance visualization of wave I and the other channel utilized a mastoid electrode to serve as comparison to a typical ABR collected clinically. Figure 5 shows example ABR waveforms from one subject collected in response to a click stimulus at 90 dB nHL. Individual waveforms are shown in the top panel and averaged waveforms are shown in the bottom panel. The tracings shown in blue were collected using a tympanic membrane electrode and the tracings in red were collected using a mastoid electrode. At each level, two repetitions were obtained. During analysis, the two repetitions were averaged and the peaks and troughs of wave I and V were picked on the averaged waveform. In Fig. 5, the amplitude of ABR wave I obtained with a tympanic membrane electrode (blue tracing) is larger than wave I amplitude obtained with a mastoid electrode (red tracing). This figure highlights the ability of a tympanic membrane electrode to increase visualization of wave I.

Table 2 provides the latencies and amplitudes of the ABR responses obtained in the present study. Means and standard deviations (SD) of waves I and V are provided for ABR responses obtained at 90 and 80 dB nHL in response to 1 and 4 kHz tone bursts and click stimuli. Waveform morphology in response to a 1 kHz tone burst is less defined when compared to responses to 4 kHz tone bursts or click stimuli. Therefore, in a few subjects, a clear wave I could not be identified, even at the highest level assessed (90 dB nHL) when utilizing a mastoid electrode. Therefore, at 1 kHz, not all 30 subjects provided usable data; the number of subjects (n) contributing data at each level is indicated in Table 2. The latencies and amplitudes of the ABR responses from the present study reported in Table 2 are in agreement with ABR data available in the literature for normal-hearing ears (e.g., Hall, 2007b; Konrad-Martin et al., 2012). The mean latencies and SDs of waves I and V are approximately the same between both electrode recording sites. This finding was seen across all three stimulus conditions. In contrast, larger wave I amplitudes were seen with the use of a tympanic membrane electrode when compared to a mastoid recording site. Additionally, the SDs of wave I amplitude obtained with a mastoid electrode were approximately half of

the SDs obtained with a tympanic membrane electrode. These results were expected as the use of a tympanic membrane electrode has been shown to increase visualization of wave I (Ferraro and Ferguson, 1989). For wave V amplitude, the mastoid recording electrode resulted in slightly larger mean amplitude and SDs when compared to amplitudes recorded with a tympanic membrane electrode.

Click-evoked ABR threshold data are shown in Fig. 6. Here, ABR thresholds in dB nHL are plotted as a function of the NEQ for wave I (top row) and wave V (bottom row). ABR recordings obtained using a mastoid electrode are shown in the first column and recordings obtained using a tympanic membrane electrode are shown in the second column. For thresholds obtained using a tympanic membrane recording site, there were no differences in the wave I threshold (p-value=0.126) or wave V threshold (p-value=0.483) as a function of noise exposure background. Similarly, when using a mastoid recording electrode, no statistically significant difference was seen in wave V thresholds (p-value=0.617) as a function of noise exposure background. However, a statistically significant difference was present in wave I threshold (p-value=0.028) for ABR recordings obtained using a mastoid electrode placement. Here, higher ABR wave I thresholds were seen in ears with greater amounts of self-reported noise exposure background.

Supra-threshold ABR wave I amplitude is displayed as a function of noise exposure background in Figs. 7 through 12. Figures 7 and 8 display wave I amplitude in response to 1 kHz tone bursts presented at 90 and 80 dB nHL utilizing a mastoid (Fig. 7) and tympanic membrane electrode (Fig. 8). Figures 9 and 10 display wave I amplitude in response to 4 kHz tone bursts presented at 90 to 60 dB nHL utilizing a mastoid (Fig. 9) and tympanic membrane electrode (Fig. 10). Figures 11 and 12 display wave I amplitude in response to click stimuli presented at 90 to 60 dB nHL utilizing a mastoid (Fig. 11) and tympanic membrane electrode (Fig. 12). ABR wave I results for all stimulation levels assessed across the three stimulus conditions and for both electrode sites can be seen in Table 3. Linear regression was completed on wave I amplitude as a function of self-reported noise exposure background; the resulting p-

values, r^2, and the number of subjects (n) providing data for each stimulus condition is shown. Statistically significant findings are denoted by an asterisk (*)

in Table 3. Statistical analysis was not performed if data were available from less than 15 (half) of the subjects in the study; in these instances, only the number of subjects providing data is displayed.

For data collected using a mastoid electrode (Figs. 9 and 11), high-level ABR wave I amplitude significantly decreased with increases in noise exposure background for ABR responses to 4 kHz tone bursts (90 dB nHL, p-value=0.013; 80 dB nHL, p-value=0.023; 70 dB nHL, p-value=0.040) and click stimuli (90 dB nHL, p-value=0.011; 80 dB nHL, p-value=0.006; 70 dB nHL, p-value=0.022). As the stimulus level decreased to 60 dB nHL and lower, these relationships were no longer statistically significant at the 0.05 level of significance (Table 3). For ABR responses to 1 kHz tone bursts with a mastoid recording electrode (Fig. 7), wave I amplitude was significantly smaller in ears with greater amounts of noise exposure background when assessed at 80 dB nHL (p-value=0.020) but was not significantly correlated to noise exposure background at 90 dB nHL (p-value=0.235).

For ABR wave I data collected using a tympanic membrane electrode (Figs. 8, 10 and 12), high-level amplitude was not significantly related to noise exposure background at the α=0.05 level of significance. However, there was a trend of smaller wave I amplitudes with greater amounts of noise exposure background in ABR responses to 4 kHz tone bursts (p-values approached 0.05) (Fig. 10) and click stimuli (p-values approached 0.05) (Fig. 12) at high stimulation levels (i.e., 90 to 70 dB nHL). This trend was not present in ABR wave I amplitude collected with a tympanic membrane electrode in response to 1 kHz tone bursts (Fig. 8).

In summary, for ABR responses collected using a mastoid recording site, high-level ABR wave I amplitude significantly decreased with increases in noise exposure background for ABR responses to 4 kHz tone bursts and click stimuli. This relationship disappeared at lower stimulation levels. For ABRs collected using a tympanic membrane recording site, a similar trend of smaller wave I amplitude with

greater amounts of noise exposure background was seen, but these relationships were not statistically significant at the α=0.05 level of significance.

Supra-threshold ABR wave V amplitude as a function of noise exposure background is plotted in Figs. 13 through 18 and shown in Table 4 following the conventions used in Figs. 7 through 12 and Table 3.

For data collected using a mastoid electrode, ABR wave V amplitude was not significantly correlated with noise exposure background for ABR responses to 1 kHz tone bursts (Fig. 13) or to 4 kHz tone bursts (Fig. 15) at any stimulus level. Furthermore, high-level wave V amplitude was not significantly correlated with noise exposure background for ABR responses collected using a mastoid electrode to click stimuli (Fig. 17); however, at very low-level click-evoked ABR responses (10 dB nHL) a statistically significant relationship was revealed between wave V amplitude and noise exposure background. Here, an inverse relationship was seen relative to earlier findings where larger wave V amplitudes were seen in subjects with greater amounts of noise exposure background (p-value=0.048, Pearson's r=0.425) (Table 4).

For data collected using a tympanic membrane electrode, ABR wave V amplitude was not significantly correlated with noise exposure background for high-level responses to 1 kHz tone bursts (Fig. 14), 4 kHz tone bursts (Fig. 16), or to click stimuli (Fig. 18). For low-level responses, a statistically significant relationship was found in wave V amplitude in response to 4 kHz tone bursts at 50 dB nHL (p-value=0.046, Pearson's r=0.395) and to click stimuli at 10 dB nHL (p-value=0.048, Pearson's r=0.424) (Table 4). As was the case for the one significant relationship in the mastoid recording channel, larger wave V amplitudes were present in subjects with greater amounts of noise exposure background. The findings presented in Figs. 13 through 18 and Table 4 do not suggest a systematic relationship between high-level wave V amplitude and noise exposure background for ABR responses measured using a mastoid or a tympanic membrane electrode. At low levels, a few statistically significant relationships

were revealed; however, it should be cautioned that not all 30 subjects provided data for ABR responses at low levels where these significant findings were revealed.

To summarize the findings of ABR assessment, click-evoked ABR wave I threshold data revealed a statistically significant relationship of greater wave I thresholds with increasing amounts of noise exposure background for ABR responses collected using a mastoid electrode. Click-evoked ABR wave I thresholds collected using a tympanic membrane electrode and wave V thresholds collected using either a tympanic membrane or mastoid electrode did not reveal any significant relationship between threshold and noise exposure background. In contrast to threshold responses, supra-threshold wave I amplitudes obtained using a mastoid recording electrode were significantly smaller in subjects reporting greater amounts of noise exposure background for ABR responses to 4 kHz tone bursts and click stimuli. This relationship was statistically significant at high stimulation levels and disappeared at lower stimulation levels (e.g., less than 70 dB nHL). The same trends were present for several responses obtained with a tympanic membrane electrode, but these relationships were not significant at the α=0.05 level of significance. Furthermore, a relationship between wave V amplitude and noise exposure background was not consistently seen in supra-threshold ABR responses to 1 kHz tone bursts, 4 kHz tone bursts, and click stimuli. The ABR data presented here are in agreement with the study hypotheses and with data from Kujawa and Liberman (2009), Lin et al. (2011), and Furman et al. (2013).

The choice of recording electrode (tympanic membrane versus mastoid) influenced the ability to detect a significant difference in ABR wave I amplitude as a function of noise exposure background. While the use of a tympanic membrane electrode led to larger wave I amplitudes and lower wave I thresholds when compared to responses collected with a mastoid electrode, statistically significant differences were not seen at high-level wave I amplitude as a function of NEQ due to increased variability in ABR responses collected with a tympanic membrane electrode. Due to these differences, the remaining data analyses were performed on ABR responses obtained with the mastoid recording site.

Influence of Behavioral Threshold on ABR Level

While all study participants had normal hearing, normal hearing was defined in the present study as behavioral threshold responses ≤ 20 dB HL. Using this definition, normal hearing can encompass up to a 30 dB range. Variation in behavioral threshold within the normal-hearing range has the potential to influence auditory responses (e.g., ABR amplitude). While a relationship between supra-threshold ABR amplitude and noise exposure background was found in the present study, the effect, if any, of variation in behavioral threshold on this relationship is unknown. To evaluate the influence of behavioral threshold on supra-threshold responses, a stepwise multiple linear regression analysis using a significance level of 0.05 was completed using behavioral threshold and NEQ value as independent variables. This analysis was conducted on ABR supra-threshold amplitude for stimulus conditions where a significant relationship was revealed between ABR amplitude and noise exposure background (see Tables 3 and 4). As behavioral thresholds were not available for click stimuli, the mean of behavioral thresholds from 2 through 4 kHz was used a substitute for click threshold.

The results of the multiple linear regression analyses are shown in Table 5. A total of ten analyses were completed. Results indicated a significant relationship between behavioral threshold and wave V amplitude for ABR responses to 4 kHz tone bursts at 50 dB nHL (p-value=0.029). This indicates that the statistically significant relationship revealed between wave V amplitude and noise exposure background at this stimulus condition was influenced by variation in behavioral threshold. In other words, behavioral threshold was a confounding variable at this stimulus condition. For ABR wave I responses collected using a mastoid recording electrode at 90, 80, and 70 dB nHL, behavioral thresholds were not statistically related to the supra-threshold amplitude for ABR responses to 1 kHz tone bursts, 4 kHz tone bursts or click stimuli. Similarly, for ABR wave V responses collected in response to click stimuli using a tympanic membrane or mastoid electrode at 10 dB nHL, behavioral thresholds were not significantly correlated with the supra-threshold amplitude. These results indicate that behavioral threshold did not influence the ABR amplitude and was not a confounding factor for these stimulus conditions.

In summary, behavioral threshold was a confounding factor in only one of the ten statistically significant relationships revealed between supra-threshold ABR amplitude and noise exposure background as indicated in Tables 3 and 4. This occurred at an ABR stimulation level of 50 dB nHL for wave V amplitude in response to 4 kHz tone bursts when measured with a tympanic membrane electrode.

Accompanying Auditory Symptoms

The auditory response data presented in previous sections used the NEQ value to quantify the amount of noise exposure background. While the NEQ is a helpful measure to quantify the amount of noise exposure an individual has encountered, the questionnaire is focused on assessing noise exposure endured in the past 12 months; noise exposures encountered prior to 12 months are not taken into account. To more comprehensively evaluate noise exposure history, subjects were also asked if they have ever experienced three auditory symptoms commonly reported following exposure to loud sound. These auditory symptoms included tinnitus, TTS and hyperacusis (see Methods section for more details). Subjects were grouped into one of four possible categories based on their reported experience with each of these symptoms. These categories are as follows:

1) No report of auditory symptoms (n=7)
2) Report of one auditory symptom (n=13)
3) Report of two auditory symptoms (n=6)
4) Report of three auditory symptoms (n=4)

Supra-threshold ABR data collected with a mastoid electrode in response to 4 kHz tone bursts and to click stimuli at 90 dB nHL were plotted as a function of the number of reported symptoms. Figures 19 and 20 display these results for wave I (Fig. 19) and wave V ABR amplitude (Fig. 20). Here, mean amplitude is displayed with ± 2 standard error of the mean. Due to the small number of individuals in each category, statistical analyses were not completed. However, the data were inspected for any systematic trends.

High-level ABR wave I and wave V amplitude in response to 4 kHz tone bursts and click stimuli does not appear to be strongly correlated with the number of reported auditory symptoms. While mean wave I amplitude is smaller in subjects who report experiencing all three auditory symptoms when compared to experiencing no auditory symptoms (Fig. 19), there is a large amount of variability in the data and therefore no clear relationship can be determined. Similarly, Fig. 20 reveals a large amount of variability in wave V amplitude across the different number of auditory symptom categories.

In summary, when the existence of reported auditory symptoms commonly associated with noise exposure is used to assess noise exposure background, there are no systematic trends in supra-threshold ABR amplitude as a function of noise exposure. These results suggests the use of the NEQ to quantify noise exposure background is a better metric for investigating the influence of noise exposure on ABR amplitude, at least for the stimulus conditions assessed here.

DISCUSSION

The objective of this research project was to characterize cochlear and auditory nerve function in human subjects with normal behavioral thresholds that are regularly and voluntarily exposed to high levels of noise. Three hypotheses were presented: 1) supra-threshold ABR wave I amplitude will be smaller in subjects with greater amounts of noise exposure background, 2) supra-threshold DPOAE level will not differ across subjects with varying amounts of noise exposure background, and 3) ABR and DPOAE thresholds will not differ across subjects with varying noise exposure backgrounds. Each of these hypotheses will be discussed separately, along with additional observations. Furthermore, the findings of the current study pertaining to implications for future research and clinical application will be discussed.

Supra-Threshold ABR Wave I Amplitude

Results of the present study support the hypothesis that supra-threshold ABR wave I amplitude is smaller in normal-hearing subjects with greater amounts of noise exposure background when compared to normal-hearing subjects with lesser amounts of noise exposure background. This relationship was statistically significant for ABR responses measured with a mastoid recording electrode in response to 4 kHz tone bursts and click stimuli at 90 to 70 dB nHL (Figs. 9 and 11) and in response to 1 kHz tone bursts at 80 dB nHL (Fig. 7). Linear regression analyses indicated approximately 15 to 24% of the variance in wave I amplitude can be explained by noise exposure background as assessed by the NEQ at these stimulus conditions. This finding is in agreement with data from mice and guinea pig ears where smaller wave I amplitudes were seen at high stimulation levels in noise-exposed animal ears when compared to control ears (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013).

In data from Kujawa and colleagues, assessment of anatomical damage following noise exposure resulting in TTS revealed substantial deafferentation of the IHCs (up to 50%); this finding was present even after hearing thresholds had returned to normal. The loss of connection between the IHCs and the auditory nerve fibers caused by noise exposure was shown to specifically result in a loss of auditory nerve

fibers with low spontaneous rates and high thresholds, fibers that are responsive at high stimulation levels (Furman et al., 2013). Kujawa and colleagues attributed the findings of decreased supra-threshold wave I amplitude as a reflection of the permanent deafferentation of the IHCs and selective loss of auditory nerve fibers with low spontaneous rates. For practical reasons, anatomical damage cannot be assessed in the human ears tested in the present study. However, the results presented here suggest exposure to loud sound might cause a similar pattern of auditory damage in noise-exposed, human ears as the damage pattern seen in animal ears. The finding of decreasing ABR wave I supra-threshold amplitude in subjects with increasing amounts of noise exposure seen in the present study could be a consequence of deafferentation of the IHCs following regular, voluntary exposure to loud sound.

A statistically significant relationship of decreasing wave I amplitude with increasing noise exposure background was only seen at high stimulation levels (e.g., $\geq$ 70 dB nHL). This relationship disappeared as the stimulation level decreased to 60 dB nHL and lower. Similar to the findings presented in the previous paragraph, the results from the present study are in agreement with investigations in animal ears where no evidence of a relationship between wave I amplitude and noise exposure background was seen at low and moderate stimulation levels (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). Threshold responses are dependent upon synchronous firing of auditory nerve fibers, but are determined by a criterion response only slightly above the noise floor. Therefore, responses at threshold are relatively insensitive to large changes in the auditory nerve fiber population (Schuknecht and Woellner, 1953; Earl and Chertoff, 2010). Furthermore, auditory nerve fibers with high spontaneous rates have low thresholds and therefore contribute to the ABR response at low stimulation levels. A selective loss of low-spontaneous rate (high-threshold) auditory nerve fibers would not be expected to lead to a decrease in wave I amplitude at low to moderate stimulation levels (Liberman, 1978; Schmiedt et al., 1996). The data presented here from normal-hearing, noise-exposed human ears are in agreement with this idea. Support for this is evidenced by the lack of a relationship between wave I amplitude and noise exposure background at low and moderate stimulation levels.

Supra-Threshold DPOAE Level

DPOAE results support the second study hypothesis that supra-threshold DPOAE level does not differ across subjects with different amounts of noise exposure background. This outcome was observed for DPOAE responses collected at f_2's of 1, 2, and 4 kHz for L_2's from 80 to 0 dB SPL (Fig. 4 and Table 1). These findings are in agreement with investigations of DPOAE level in animal ears following recovery from TTS (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013).

Kujawa and colleagues completed anatomical assessment following noise exposure resulting in TTS in mice and guinea pig ears. No evidence of permanent noise-induced anatomical damage to the OHCs, the auditory structures responsible for the generation of DPOAEs, was found in animal ears following complete recovery of TTS. While a lack of OHC damage following noise exposure resulting in TTS is in agreement with some reports (Liberman and Mulroy, 1982; Robertson et al., 1980), it contradicts other reports that have described noise-induced damage to the OHC including swelling of the OHCs (Liberman and Dodds, 1987) and damage to OHC stereocilia (Dunn et al., 1979; Gao et al., 1992). For the human ears assessed in the present study, it is not feasible to do anatomical assessment of the OHCs. Therefore, the status of the OHCs must be inferred from looking at a functional measure of the OHCs such as DPOAEs. As no difference in DPOAE level was found across the 30 normal-hearing human ears with varying noise exposure backgrounds in the present study, it is postulated that subjects' noise exposure did not result in permanent anatomical damage to the OHCs.

Cross-sectional studies have shown that OAEs are a good assessment approach in noise-exposed individuals who have elevated behavioral thresholds (Attias et al., 2001). Furthermore, numerous studies have demonstrated the effectiveness of OAEs in identifying the presence or absence of hearing loss (Gorga et al., 1993b, 1997; Stover et al., 1996); the cause of hearing loss in these studies included NIHL along with a multitude of other causes. However, in ears that have normal behavioral thresholds, the literature has not strongly supported the use of DPOAEs as a method for detecting earlier evidence of

noise damage than that garnered by behavioral threshold assessment (Lapsley Miller et al., 2006; Marshall et al., 2009; Seixas et al., 2012). The results of the current study are in agreement with studies assessing DPOAE level in the presence of normal behavioral thresholds and do not support the use of DPOAE assessment as an effective method to detect evidence of permanent noise-induced damage to auditory structures before increases in behavioral thresholds are apparent.

While the results of the present study did not reveal any systematic difference in DPOAEs as a function of noise exposure background, data were collected at a single test session and pre-noise exposure DPOAE levels were not available for comparison. In the studies completed in animals, DPOAE level was measured prior to noise exposure, during recovery from active TTS, and after TTS had completely recovered. This resulted in the ability to directly ascertain the influence of TTS on DPOAE level over time in animal ears. In the current study, it is unknown how DPOAE levels in a normal-hearing, noise-exposed ear would compare relative to DPOAE levels obtained from that same ear prior to the onset of noise exposure. Furthermore, in an ear with active temporary hearing loss due to noise exposure, it is likely smaller DPOAE levels would be recorded. However, these comparisons could not be investigated in the present study as no baseline DPOAEs were available for subjects and all subjects denied actively experiencing TTS.

ABR and DPOAE Threshold Responses

The third and final study hypothesis was that ABR and DPOAE threshold would not differ in normal-hearing subjects with varying noise exposure backgrounds. The data from the present study do not fully support this hypothesis. For click-evoked ABRs collected using a mastoid recording electrode, significantly higher wave I thresholds were found in subjects who reported larger amounts of noise exposure background (upper left panel of Fig. 6). Wave V threshold collected using a mastoid recording electrode and waves I and V collected using a tympanic membrane electrode were not different across subjects with varying amounts of noise exposure background (remaining panels in Fig. 6). DPOAE

thresholds at f_2's of 1, 2, and 4 kHz were not influenced by the noise exposure background (Fig. 3). To summarize, click-evoked wave I ABR threshold data collected using a mastoid recording electrode do not support the third study hypothesis and remaining ABR threshold data and DPOAE threshold data do support the third hypothesis in the present study.

As stated in previous sections, ABR threshold responses are dependent upon synchronous firing of auditory nerve fibers and have been shown to be reasonably unaffected by changes in the auditory nerve population contributing to the response. Therefore it was expected that there would be no differences in ABR threshold across subjects with varying noise exposure backgrounds. This finding was present in animal ears following recovery from TTS (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). With the exception of wave I threshold collected using a mastoid recording site, the data from the present data are in agreement with the findings in animal ears. For wave I thresholds collected with a mastoid recording electrode (where higher ABR thresholds were found in ears with more noise exposure), it is important to note that while this stimulus condition was statistically significant, a large amount of variability was present across subjects (Fig. 6, upper left panel). In Fig. 6, for subjects with a high noise exposure background (i.e., an NEQ $\geq$ 80), thresholds ranged from 40 to 70 dB nHL. Similarly, for subjects with a low noise exposure background (i.e., an NEQ $\leq$ 70), thresholds ranged from 10 to 60 dB nHL. Unfortunately, threshold was only obtained to click stimuli; ABR thresholds in response to 1 and 4 kHz tone bursts were not collected due to time constraints. Given the isolated finding of higher click-evoked wave I thresholds collected with a mastoid electrode and the large amount of variability across subjects, more data are necessary to fully understand the relationship of ABR threshold and noise exposure background.

DPOAE threshold, defined in the present study as the lowest L_2 with a SNR of $\geq$3 dB, did not show any relationship to noise exposure background. These results are in agreement with data from animal models following full recovery from TTS (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). As previously discussed, investigations by Kujawa and colleagues did not reveal any

anatomical damage to the OHCs and therefore did not result in any differences in DPOAE threshold between animal ears with TTS and control ears. In the present study, it is likely that no damage at the OHC level is present and therefore, no relationship is seen between DPOAE threshold and noise exposure background.

Influence of ABR Recording Electrode

The ABR findings discussed above were collected with the use of a mastoid recording electrode. In the present study, a 2-channel ABR was obtained: one channel utilized a tympanic membrane electrode and the other utilized a mastoid electrode location. The tympanic membrane electrode was used to enhance visualization of ABR wave I. The use of a tympanic membrane electrode generally resulted in the ability to identify wave I at lower stimulation levels when compared to the use of a mastoid electrode. Evidence of this can be seen in Table 3. Here, for example, click-evoked ABR recordings collected with a tympanic membrane electrode resulted in 12 subjects having an identifiable wave I at 30 dB nHL while only 6 subjects had an identifiable wave I at this stimulus condition for recordings collected with a mastoid electrode. Additionally, ABR recordings obtained with a tympanic membrane electrode resulted in larger mean wave I amplitudes when compared to wave I amplitude collected with a mastoid electrode (Table 2). These findings indicate the use of the tympanic membrane electrode was successful in enhancing visualization of wave I of the ABR.

While mean wave I amplitude was larger for responses collected with a tympanic membrane electrode, standard deviations of these responses were approximately twice the standard deviations for responses obtained with a mastoid electrode. This indicated that amplitude variability with the tympanic membrane electrode was substantially greater when compared to response variability obtained with a mastoid electrode. Increased variability in wave I amplitude across subjects for a tympanic membrane electrode compared to an ear canal or mastoid electrode recording site has been reported in previous investigations and some of this variability could be attributed to the larger amplitude that is recorded

when utilizing a tympanic membrane electrode (Ferraro and Ferguson, 1989). In the present study, the standard deviations of wave I measured with a tympanic membrane electrode were larger than those measured with a mastoid electrode. Furthermore, the coefficient of variation (CV), or the ratio of the standard deviation relative to the mean amplitude (i.e., 100 x [standard deviation/mean amplitude]), was typically larger for wave I responses obtained with a tympanic membrane electrode (Table 6). The CV is a measure of dispersion of the variable(s) relative to a mean value; a larger CV value indicates greater variability. As exhibited in Table 6, the tympanic membrane channel CV was almost always greater than the mastoid channel CV for wave I amplitude (with the exception of recordings to 1 kHz tone bursts at 90 dB nHL). Given the systematic trend (as opposed to a statistically significant relationship at the 0.05 level of significance) of decreasing wave I amplitude with increasing amounts of noise exposure background for ABR responses collected with a tympanic membrane electrode (Table 3), it is possible that slightly smaller variability in ABR recordings could have resulted in these findings being statistically significant. In contrast, no systematic trend was present when examining the CV of wave V amplitude between the two recording electrodes.

While a larger response might lead to increases in variability, other potential sources of variability should also be considered. Obtaining the optimal placement of a tympanic membrane electrode on the ear drum can be more challenging than the placement of a mastoid electrode. One reason for this is the inability to visually see the electrode make contact with the tympanic membrane (unless the ear canal is unusually large or straight). Placement of the tympanic membrane electrode in the present study was verified by asking subjects to report when they felt the electrode make contact with the ear drum and subsequently recording a clear waveform. The measured amplitude of the ABR response can be influenced by the placement of the electrode relative to the site of generation (for wave I, the distal portion of the cochlear nerve). If the electrode position is not consistent across subjects, this has the potential to introduce variability into the data. Alhanada (2012) investigated the influence of tympanic membrane electrode location on the tympanic membrane in electrocochleographic responses, specifically

the summating potential/action potential (SP/AP) amplitude ratio. Results indicated no statistically significant effects of electrode placement on the tympanic membrane. However, while the AP is analogous to wave I of the ABR, results from Alhanada were reported as an amplitude ratio rather than absolute amplitude of the AP. Therefore, it is unknown to what degree, if at all, variation in the location of the electrode placement on the tympanic membrane might affect absolute amplitude. Regardless, it can be considered a potential source of variability in wave I amplitude across subjects.

In the present study, high-level (≥ 70 dB nHL) wave I amplitude collected with a tympanic membrane electrode showed a trend of decreasing wave I amplitude with increasing noise exposure background (Figs. 8, 10, and 12, Table 3). However, these relationships were not statistically significant at the 0.05 level of significance. Given these relationships were statistically significant for ABR responses collected with a mastoid electrode, it is possible that inconsistent placement of the tympanic membrane electrode across subjects introduced too much variability into the response for a statistically significant relationship to be revealed.

ABR Wave V amplitude

ABR wave V amplitude was also measured in the present study. For high-level wave V amplitude, data analyses indicated no relationship with noise exposure background for ABRs collected in response to 1 kHz tone bursts (Figs. 13 and 14), 4 kHz tone bursts (Figs. 15 and 16), and click stimuli (Figs. 17 and 18) when utilizing a mastoid or tympanic membrane electrode (Table 4). This finding is in contrast to the analysis of wave I amplitude where decreasing wave I amplitude was seen with increases in noise exposure background.

Wave V of the ABR is generated at the level of the auditory midbrain (Møller et al., 1995; Hall, 2007a). Since lower wave I amplitudes were seen in subjects with greater amounts of noise exposure background, the data suggest the possible involvement of a mechanism along the auditory pathway between the distal portion of the auditory nerve and the auditory midbrain that might compensate for the

reduced amplitude from the auditory nerve. This idea is in agreement with data from Schaette and McAlpine (2013) where reduced ABR wave I amplitudes were found in normal-hearing ears with tinnitus when compared to normal-hearing ears without tinnitus. Similar to the findings of the present study, their data did not reveal any differences between wave V amplitude between these two groups of normal-hearing ears. The authors suggested the existence of a "homeostatic gain control" mechanism. Support for a possible mechanism can be found in recent data from Mulders and Robertson (2009, 2011). These studies examined spontaneous firing rates of neurons in the central nucleus of the inferior colliculus before and after acoustic trauma in guinea pigs. Their results found evidence of a significant increase in the spontaneous firing rate of inferior colliculus neurons in animal ears exposed to noise when compared to control ears. This hyperactivity was not evident until one week after the acoustic trauma and remained present for up to 12 weeks post-exposure (the longest recovery time investigated). While the data in the present study were not designed to specifically address the existence of a homeostatic mechanism along the auditory pathway, the data presented here do follow a similar pattern in ABR amplitude responses to that described by Schaette and McAlpine. If exposure to loud sound does lead to an increase in the spontaneous firing rates of inferior colliculus neurons, this might explain, at least in part, why differences were seen in wave I amplitude (which is generated in the auditory nerve) but not in wave V amplitude (which is generated at the level of the auditory midbrain) across subjects with different noise exposure backgrounds in the present study. Inspecting the amplitude of wave III (which is generated in the cochlear nucleus) of the subjects tested here could help refute or substantiate this idea as the generation site of wave III is located before the auditory pathway reaches the inferior colliculus.

Don and Eggermont (1978) provide data from click-evoked ABR where a high pass masker was used to mask contributions to the ABR response from the basal end of the cochlea (where high frequencies are encoded). Their results showed that wave V amplitude was unaffected when cochlear contributions from the basal end of the cochlea were masked, although increases in the latency of wave V were seen. In contrast, wave I amplitudes decreased as the masker masked cochlear contributions from

the basal end of the cochlea. The data by Don and Eggermont suggest that wave I is generated mainly by neurons along the cochlear partition with characteristic frequencies greater than 2 kHz while wave V includes contributions from along the entire cochlear partition. Therefore, it can be postulated that if damage to auditory structures is only present in structures responsible for encoding the higher frequencies (i.e., the 3 to 6 kHz region commonly affected by NIHL), it is possible that evidence of this damage could be revealed in smaller wave I amplitudes due to a reduction in the number of neurons contributing to the response. In contrast, if the auditory structures responsible for encoding the lower frequencies (i.e., less than 2 kHz) remains unaffected, wave V amplitude would not be expected to be altered, even when the high frequency neurons are compromised. This idea can help explain, at least in part, why the results of the present study show no influence of noise exposure background on click-evoked wave V amplitude. However, these findings were also present for ABR responses obtained to 4 kHz tone bursts. While it can be postulated that perhaps a similar frequency encoding scheme might exist for high-level wave I and wave V amplitudes obtained in response to 4 kHz tone bursts, further research would be necessary to determine if this was the case.

Three statistically significant relationships between ABR wave V amplitude and noise exposure background were found in the present study (Table 4). These occurred for ABRs collected with a tympanic membrane electrode in response to 4 kHz tone bursts at 50 dB nHL and for ABRs collected with a tympanic membrane and mastoid electrode in response to click stimuli at 10 dB nHL. At each of these three stimulus conditions, larger amplitudes were present in ears with greater amounts of noise exposure background; this is the opposite relationship seen for high-level stimulus conditions.

For ABR responses to 4 kHz tone bursts at 50 dB nHL, behavioral threshold was found to be a confounding factor. In other words, behavioral threshold variation across the normal hearing range influenced the wave V amplitude rather than the amount of noise exposure background. For ABR responses to click stimuli at 10 dB nHL it is possible that poor waveform morphology influenced the ability of the two judges to clearly identify a peak and trough of wave V. At stimulation levels near

threshold, the peaks and troughs of the ABR response are much less defined when compared to responses at high stimulation levels. While the two judges agreed on whether or not there was a waveform present, there were several instances for ABR responses near threshold where considerable ambiguity was present in identifying the exact location of the peak and trough of wave V. In light of this ambiguity and lack of significant findings for the adjacent stimulation levels, caution should be taken in interpreting these results at low stimulation levels.

Quantifying Noise Exposure Background

In the present study, the NEQ was used to assess noise exposure background. While dosimeter measurements were significantly related to NEQ scores (Fig. 2), two subjects did not complete dosimeter monitoring. Furthermore, several subjects were not able to capture representative noise levels of reported activities because the noise dosimeter monitoring occurred over a single 16 hour window that did not include participation in those activities. Therefore, the decision was made to use the NEQ to quantify noise exposure background in the present study.

Additional analyses were undertaken where the number of accompanying auditory symptoms commonly associated with noise exposure (e.g., tinnitus, TTS, and hyperacusis) was used to quantify noise exposure background. The reasoning behind this alternate method to quantify noise exposure was for several reasons. First, the NEQ assesses exposures to loud sound that have occurred during the past 12 months; exposures outside that time period are not addressed. It is possible that some subjects had experienced excessive noise exposure that was not reflected in their NEQ score. By including questions pertaining to subjects' experience with accompanying auditory symptoms that had occurred at any point during their lifetime, it was hopeful that these significant noise events could be accounted for. Second, the animal data presented by Kujawa and colleagues were collected in ears that suffered TTS. While the NEQ assesses the type and duration of exposure to loud sound, the computation of the NEQ value does not take into account whether or not the individual has experienced TTS (see Appendix B for NEQ computation).

Lastly, while a range of NEQ scores were collected during this study, it is unknown at what NEQ value an individual might acquire the auditory damage patterns described by Kujawa and colleagues. Stated another way, it was possible that only a few or no individuals recruited for the current study had experienced noise exposure that resulted in deafferentation of auditory nerve fibers. While a score of 79 on the NEQ has been projected to determine when an individual is at risk for developing hearing loss (Megerson, 2010), longitudinal data is necessary to ascertain how many individuals deemed at risk go on to develop a hearing loss. By using an alternate method to quantify noise exposure, it was possible that a pattern might emerge between subjects that had experienced all three auditory symptoms compared to no auditory symptoms or a smaller number of auditory symptoms.

This alternate approach to quantify noise exposure background did not reveal any clear relationship between ABR responses and the number of auditory symptoms reported. It was, therefore, concluded that the use of the NEQ to quantify noise exposure background was a better metric for investigating the relationships described in the present study. However, this study was powered to detect a correlation between auditory response and noise exposure background as measured along a continuum, like the NEQ. With a larger number of subjects, it is possible that analyses on the type and number of accompanying auditory symptoms reported by subjects might reveal relationships not seen in the present study.

Clinical Implications of the Research Outcomes

The results from the present study suggest that noise exposures that do not result in permanent hearing loss might still lead to permanent damage to auditory structures and evidence of this damage can be seen by inspecting the ABR wave I amplitude. A prevailing view of TTS is that if behavioral thresholds return to normal, the temporary decrease in hearing has been essentially harmless. The results presented here are in agreement with recent data from animal models (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). Together, they suggest this view is flawed and requires revision,

although more research is still needed to understand the relationship between noise exposure and the effect on the human auditory system.

The findings presented here suggest that current NIHL clinical protocols would benefit from the addition of high-level ABR wave I amplitude assessment. While the use of a tympanic membrane electrode allowed wave I to be visible at lower stimulation levels and record larger amplitudes, the use of a mastoid electrode was sufficient to identify differences in high-level (e.g., ≥ 70 dB nHL) wave I amplitude across normal-hearing subjects with varying amounts of noise exposure background. However, additional research is needed in more normal-hearing, noise-exposed ears prior to supra-threshold amplitude assessment being implemented in a clinical practice setting. Although the results of this study indicate a statistically significant relationship between high-level ABR wave I amplitude and noise exposure background, data from the present study also exhibit too much variability to draw clear conclusions from for an individual subject. It is hopeful that additional data collected from a larger number of subjects might provide normative amplitude ranges for determining when an ear is exhibiting abnormally small amplitude responses and possibly indicate noise-induced auditory damage prior to developing permanent changes in behavioral threshold(s).

Future Research

Further research into the relationship of high-level ABR amplitude and noise exposure background is warranted. Results of the present study indicate a statistically significant linear relationship of smaller high-level ABR wave I amplitudes in subjects with greater amounts of self-reported noise exposure background. However, this research project was designed as a pilot study and was only performed on a small number of subjects. Additional data from a larger number of subjects spanning a wider range and variety of noise exposure background are needed to more fully understand the relationship between supra-threshold auditory responses and noise exposure. Subjects recruited for the current study had noise exposure primarily from a musical setting. Collecting data from construction

workers, factory workers, or other types of noise exposure background would be beneficial. Future research studies should include the assessment of speech recognition ability in noise to determine if smaller ABR wave I amplitudes are associated with poorer ability to recognize speech in complex listening environments. Furthermore, future research studies that monitor supra-threshold wave I amplitude in normal-hearing, noise-exposed individuals over time may also provide valuable information.

CONCLUSIONS

The goal of the present study was to characterize cochlear and auditory nerve function in ears with normal behavioral thresholds that are regularly and voluntarily exposed to high levels of noise. Smaller ABR wave I amplitudes were found in normal-hearing human ears with greater amounts of noise exposure background for ABR responses to high level click and 4 kHz tone bursts. These results are consistent with data from previous work completed in animals where the reduction in high-level responses was a result of deafferentation of high-threshold/low-spontaneous rate auditory nerve fibers. The data presented here suggest a similar mechanism may be operating in human ears following exposure to high sound levels and provide evidence that noise exposure may damage high-threshold auditory nerve fibers in humans. Furthermore, the data presented here indicate evidence of this damage is only apparent when examining supra-threshold ABR wave I response amplitude. In contrast, there were no statistically significant differences in supra-threshold DPOAEs across ears with different noise-exposure histories. This was expected, given noise-induced auditory damage findings in animal ears did not extend to OHCs, the generator for the DPOAE response.

The results of the present study warrant further investigation of supra-threshold auditory nerve function, with particular focus on ABR wave I, in normal-hearing ears exposed to high levels of sound. If additional research can identify an assessment approach that indicates early detection of auditory noise damage before behavioral thresholds have been affected, this might allow procedures to be initiated that prevent or mitigate further auditory impairment.

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APPENDIX A

LITERATURE REVIEW

Introduction

The use of high-level (or supra-threshold) ABR amplitude to detect underlying auditory dysfunction in noise-exposed, normal-hearing ears might provide a technique for identifying early evidence of noise damage and allow for procedures to be initiated that prevent or mitigate further impairment. This literature review will first concentrate on research related to the prevalence and regulation of noise-induced hearing loss (NIHL), the effects of noise on the auditory system and the capability of current clinical protocols to detect noise-induced auditory damage. The focus will then shift to provide a review of research utilizing alternate assessment tools, such as otoacoustic emissions (OAEs), the auditory brainstem response (ABR), and self-report questionnaires, to identify the presence of NIHL or to determine if an individual is at risk for developing NIHL. Finally, a summary of several recent studies investigating the use of supra-threshold amplitude measures in noise-exposed animal ears will be presented.

Prevalence and Regulation of NIHL

In the United States, an estimated 10 million workers suffer from permanent NIHL while an additional 30 million are at risk due to daily exposure to hazardous levels of noise (NIOSH, 2001; NIDCD, 2008). When recreational noise exposure is considered, roughly 15 percent of Americans 20 to 69 years of age experience hearing loss that may have been caused by noise exposure encountered during occupational or recreational activities (NIDCD, 2008). It is estimated that $242 million is spent annually on worker's compensation due to hearing loss disability (NIOSH, 2001). The Healthy People 2020 initiative has recognized the negative impact of NIHL by aiming to decrease the number of adolescents and adults displaying a high-frequency hearing loss indicative of noise exposure (USDHHS, 2011). Therefore, NIHL has been identified as an area of great public health concern.

Although NIHL is a prevalent problem facing our nation, it is a preventable cause of hearing loss (Dobie, 2008). Efforts to prevent NIHL by eliminating or reducing exposure to loud noise are well

established in the occupational setting. The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) specify recommended exposure limits (REL) and permissible exposure limits (PEL) for occupational noise exposure (OSHA, 1983; NIOSH, 1998). Levels are based on typical hearing threshold changes, or "shifts," seen after noise exposures. The NIOSH REL is 85 dBA for an 8-hour time-weighted average (TWA) and the OSHA PEL is 90 dBA for an 8-hour TWA; noise exposures at and above these levels are considered hazardous. The REL/PEL also take into account the equal-energy principle, which considers the duration of the exposure and the level of the noise encountered. This principle states that equal amounts of sound energy over time result in equal amounts of hearing damage (Earshen, 2003; Ward et al., 2003a). The NIOSH REL specifies the use of a 3-dB exchange rate criterion, meaning that 8 hours of exposure to 85 dBA is equivalent to 4 hours of exposure to 88 dBA. The more lenient OSHA PEL specifies the use of a 5-dB exchange rate criterion, where 8 hours of exposure to 90 dBA is equivalent to 4 hours of exposure to 95 dBA.

The NIOSH and OSHA guidelines attempt to reduce the negative impact of occupational noise exposure. However, occupational NIHL remains a prevalent problem and exposure to loud sound does not only occur in the workplace. For example, digital portable listening devices have been shown to be capable of producing sound intensities ranging from 97 to 107 dBA, with average levels of 101.5 dBA for earbud style and 97 dBA for supra-aural earphones (Portnuff et al., 2011). Intensity of some common musical instruments include: violin, 77 to 91 dBA; clarinet, 80 to 94 dBA; French horn, 81 to 96 dBA; trombone, 78 to 95 dBA; vocalist, 85 to 100 dBA (O'Brien et al., 2008; Cook-Cunningham et al., 2012). Other commonly encountered sounds include: lawnmower, 90 dB SPL; motorcycle, 95 dB SPL; rock concert, 110 dB SPL; ambulance siren, 120 dB SPL. Therefore, the importance of reducing exposure to loud sound remains high as many noises encountered at work and at home have the potential to be hazardous to the auditory system.

Effects of Noise on the Auditory System

The deleterious effects of excessive noise on the auditory system have been well researched (e.g., Spoendlin, 1971; Saunders et al., 1985; Kujawa and Liberman, 2009). Briefly, excessive noise damages structures in the inner ear and can lead to either a temporary or permanent reduction in hearing.

Many investigators have examined anatomical damage following excessive acoustic exposures. Due to the invasive nature of these studies, animal models are often utilized to identify specific structures within the inner ear that are compromised. The underlying cause of NIHL is not clear, but several hypotheses have been proposed (Bohne and Harding, 2000; Nordmann et al., 2000). These include mechanical damage (Spoendlin, 1971; Saunders et al., 1985), hypoxia (Yamane et al., 1995), excitotoxicity resulting from excessive release of glutamate (Puel et al., 1998; Pujol and Puel, 1999), metabolic exhaustion of involved cells (Lim and Dunn, 1979) and an imbalance in cochlear fluids caused by damage in the reticular lamina (Bohne and Rabbitt, 1983; Bohne and Harding, 2000). Rather than a single cause, it is likely that multiple processes are involved. Additionally, the level and duration of the noise exposure is correlated with the extent of the anatomical damage seen.

At exposures resulting in permanent losses of hearing, anatomical damage tends to be dominated by mechanical destruction. At less intense exposures resulting in temporary changes in hearing, an interaction between mechanical and metabolic processes is more likely present (Saunders et al., 1985). The outer and inner hair cells (OHCs and IHCs) and the afferent auditory nerve fibers are the inner ear structures most commonly examined for noise-induced anatomical damage.

Reports of anatomical assessment after permanent NIHL have revealed disordered or missing hair cell stereocilia of the OHCs and IHCs, missing OHCs and IHCs, bulging of the reticular lamina, afferent nerve fiber rupture, and an increased density of efferent nerve endings (Spoendlin, 1971; Robertson and Johnstone, 1980; Gao et al., 1992). The first row of the OHCs appears to be most susceptible to damage, but with increasing noise levels all three rows may be affected (Saunders et al., 1985). A trend of greater

degrees of mechanical destruction being associated with higher acoustic exposures has emerged, but a direct relationship between exposure level and resulting anatomical damage has not been revealed.

In noise exposures that result in temporary hearing loss, some researchers have noted distorted OHCs and swelling in afferent nerve fiber terminals below the IHCs (Spoendlin, 1971; Puel et al., 1998), while other reports have described no identifiable OHC damage and permanent damage to afferent nerve fibers (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). A buckling in pillar bodies and an uncoupling of OHC stereocilia from the tectorial membrane has also been described (Nordmann et al., 2000).

While many reports of noise damage following noise exposure exist, few studies report how anatomical damage correlate with auditory response changes (e.g., thresholds or response behavior at supra-threshold levels). Additionally, even in very controlled studies, variability is seen in the damage noted across ears with identical noise exposures (Cody and Robertson, 1983; Nordmann et al., 2000). Consequently, an imperfect association exists between the amount of acoustic exposure, the resulting anatomical damage, and the effect on auditory function. Furthermore, because the majority of the anatomical studies were performed in animals, it is not clear how analogous anatomical damage patterns to high intensity sound seen in animal ears is to the human ear.

Clinical NIHL Protocols

Current clinical protocols for assessing NIHL have traditionally relied on the evaluation of behavioral thresholds, or the ability to hear soft sounds. The clinical hallmark of a NIHL is a high-frequency notching audiometric pattern with poorest thresholds between 3-6 kHz. The reason for this notching configuration is likely due to how sound is transmitted to the inner ear. Most noise exposures are to broadband sound and the incoming sound is influenced by resonance characteristics of the outer and middle ear. This results in an intensity increase across the 2-7 kHz frequency range, likely contributing to

the 3-6 kHz audiometric notch that is associated with NIHL (Simpson, 1999; Ward et al., 2003b; Musiek and Baran, 2007).

NIHL can be either temporary or permanent. A temporary threshold shift (TTS) recovers to pre-exposure hearing levels generally within 30 days of exposure (Humes et al., 2005) while a permanent threshold shift (PTS) does not recover. TTS and PTS are not mutually exclusive; an individual can experience TTS with residual PTS following noise exposure. To quantify with absolute certainty the amount of threshold shift, a baseline audiogram prior to the onset of noise exposure is necessary. An assumption underlying the concept of a TTS is that following full recovery of threshold(s), no residual anatomical damage is present and the temporary decrease in hearing has been essentially harmless (Humes et al., 2005; Kujawa and Liberman, 2009).

Additional auditory symptoms beyond hearing loss have been reported in noise-exposed ears. These include tinnitus, hyperacusis, and difficulty understanding speech in noise (Davis et al., 1998; Ward et al., 2003b; Sanchez et al., 2005; Muhr and Rosenhall, 2010). When occurring in the presence of PTS, the elevated behavioral thresholds can to at least to some degree explain the presence of these symptoms as permanent damage has occurred to the auditory structures. However, these auditory symptoms have also been reported in noise-exposed ears with normal behavioral thresholds, or ears that have likely experienced TTS (Sanchez et al., 2005; Muhr and Rosenhall, 2010; Schaette and McAlpine, 2011). Recent data from animal models also provide evidence of permanent damage to auditory structures in the presence of only temporary decreases in hearing (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). Based on reports of auditory symptoms in ears with normal hearing and the work of Kujawa and colleagues, it appears possible to have normal behavioral thresholds in the absence of "normal" auditory function. Consequently, it may be important to investigate alternate assessment methods beyond behavioral testing, the current gold standard, for the noise-exposed individual.

Alternate Approaches to NIHL Assessment

Efforts to develop assessment protocols that identify early evidence of noise damage or that identify individuals at high risk for developing NIHL are available in the literature. Otoacoustic emissions (OAEs), evoked-potential responses, and self-report questionnaires have all been investigated in the context of assessing noise damage in the human ear.

Otoacoustic Emissions

OAEs, first described in 1978 by David Kemp, are sounds that are generated by the inner ear in response to acoustic stimuli that can be recorded in the ear canal using a sensitive microphone. They are a byproduct of active cochlear processes in the cochlea, specifically stemming from the OHCs (Kemp, 2002). As some reports have described damage to the OHCs following noise exposure (e.g., Spoendlin, 1971; Robertson and Johnstone, 1980; Saunders et al., 1985; Nordmann et al., 2000), OAEs have emerged as an obvious choice for objective measurement in NIHL assessment (Lapsley Miller and Marshall, 2007).

Some investigators have suggested OAE level might be useful in determining if an ear is at risk for or shows early evidence of NIHL. Two longitudinal studies have measured OAE responses over time in military personnel for impact noise (e.g., aircraft carrier) (Lapsley Miller et al., 2006) and impulse noise (e.g., weapons and artillery) (Marshall et al., 2009). Results indicate average OAE levels in noise-exposed ears decrease over time in the presence of unchanged behavioral thresholds. However, Lapsley Miller et al. (2006) did not report a control group and therefore OAE levels could not be compared to those obtained in non-noise exposed ears. Data from Marshall et al. (2009) were compared to a control group; however, although the control group refrained from noise exposure during the duration of the study, prior noise exposure was not accounted for. Therefore, it is unknown how OAE levels over time in normal-hearing, noise-exposed ears would have compared to normal-hearing ears with relatively low noise exposure backgrounds.

It has also been suggested that low-level or absent OAEs in individual ears may indicate an increased risk for developing NIHL or provide evidence of early noise-induced cochlear damage. While supporting evidence can be found in longitudinal and cross-sectional studies, reports have either not included non-exposed control ears (Lapsley Miller et al., 2006) or have not carefully accounted for audiometric threshold differences across normal-hearing ears (Attias et al., 2001). Therefore, a clear, interpretable relationship between OAEs and noise exposure has not been identified.

One limitation in OAE assessment that could contribute to the lack of success with OAE measurement in noise-exposed ears could be the variability in the OAE response that is often seen across individuals with both normal and impaired hearing. This makes it difficult to specify an OAE level that might be indicative of early NIHL. Several researchers have proposed the use of optimized stimulus parameters for distortion-product OAEs (DPOAEs) that have been shown, on average, to result in more robust emissions in normal-hearing ears (Neely et al., 2005; Johnson et al., 2006; Kirby et al., 2011). These stimulus parameters recommend varying both the primary tone level (L_1, L_2) relationship and the primary tone frequency relationship (f_2/f_1) across both f_2 and L_2. This is in contrast to more traditional parameters where the primary tones are fixed at $L_1 = L_2 + 10$ and where $f_2/f_1 = 1.2$. If the goal is to detect early evidence of damage caused by noise exposure, it might be possible to more easily visualize differences if the emission response is maximized through the use of optimal stimulus parameters. However, the use of optimized stimulus parameters might also lead to more robust DPOAEs in impaired-hearing or noise-exposed ears, thus not improving test performance relative to DPOAEs collected with traditional stimulus parameters (Johnson et al., 2010).

Another factor contributing to the variability seen in OAE responses, especially when completing repeat testing in individual ears over time, is the calibration approach that is used. In standard calibration approaches, the stimulus is calibrated *in situ* in SPL at the plane of the transducer (i.e., the probe). The level at the probe can be substantially different than the stimulus level at the tympanic membrane. These differences arise primarily from ear canal impedance variability and variability in SPL along the length of

the ear canal due to constructive and destructive interference of the incident (forward) and reflected (reverse) components of the acoustic stimulus. This approach can lead to standing wave errors, which can be particularly problematic at high frequencies. When completing repeat testing in individual ears over time, small variations occur in the placement of the transducer in the ear canal. In other words, the probe is not placed in the exact same spot in the ear canal at every testing session. Therefore, the influence of standing wave errors may not be the same at each testing session and this might introduce variability in the measured DPOAE response that is due to calibration error rather than changes in DPOAE level. Forward pressure level (FPL) calibration has been shown to avoid the effects of standing waves by separating the incident wave component (Scheperle et al., 2008, 2011). Therefore, the use of a more stable calibration approach, such as FPL, can be helpful in decreasing some of the variability seen in the OAE response over repeated testing sessions.

In summary, while the use of OAEs in the assessment of NIHL has shown promise, it has yet to be commonly implemented in a clinical setting. Conflicting reports exist that question whether permanent damage to the OHCs, the auditory structure responsible for the generation of the OAE response, occurs following noise exposures resulting in TTS (e.g., Spoendlin, 1971; Robertson and Johnstone, 1980; Saunders et al., 1985; Nordmann et al., 2000; Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). This could, at least in part, provide some explanation as to why OAEs have not been widely successful in NIHL assessment.

Electrophysiological Assessment

The use of evoked-potential responses, such as the ABR, has been investigated in noise-exposed ears. The ABR response is a series of electrical potentials generated in the auditory nerve and brainstem that consists of five to seven peaks and troughs occurring within the first 10 milliseconds following a transient stimulus. The response can be recorded using surface electrodes placed on the skin. Each peak, or wave, of the ABR response is associated with a region or area of neural generation along the auditory

pathway. Waves I and II are generated in the distal and proximal portions of the cochlear nerve, respectively, and wave III is generated within the cochlear nucleus (Møller, 1994). Evidence indicates wave IV is generated in the brainstem by structures close to the midline at the level of the superior olivary complex (Møller et al., 1995) and wave V may be generated by the lateral lemniscus as it enters the inferior colliculus (Møller et al., 1995; Hall, 2007a).

Clinical assessment of the ABR focuses primarily on threshold and latency determination, and the threshold of the ABR is correlated with behavioral thresholds of hearing (Gorga et al., 1993a; Sininger, 1993; Stapells, 2000). Specific focus is typically placed on wave V as this wave persists to lower stimulation levels than all others. Therefore, the majority of research has focused on wave V and how its characteristics relate to behavioral thresholds. The response amplitude may also be examined; however a limitation to using absolute amplitude measures is the inherent variability commonly seen even in normal ears (Schwartz et al., 1994). Therefore, clinical applications tend to concentrate on amplitude ratios between waves (e.g., V/I) or interaural amplitude differences (Hall, 2007b).

Recent data from animal models have shown substantial deafferentation of the IHCs and delayed degeneration of spiral ganglion cells following noise exposure (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013). The first wave of the ABR, also referred to as the compound action potential, has been shown to specifically be generated by the spiral ganglion cells in the auditory nerve (Melcher and Kiang, 1996). The anatomical damage seen in animal ears by Kujawa and colleagues was accompanied by reduced wave I amplitudes in noise-exposed animal ears when compared to control ears. In light of these findings, examination of ABR wave I amplitude could provide important information pertaining to auditory status in humans following noise exposure. However, a valid concern of ABR wave I assessment in humans is that it can be difficult to visualize at low to moderate stimulation levels. Enhancement of wave I can be achieved by adjusting recording parameters. A slower stimulus presentation rate and an electrode montage utilizing either an ear canal or tympanic membrane electrode

(rather than mastoid or earlobe locations) have both been shown to increase visualization of wave I (Ferguson and Ferraro, 1989; Schwartz et al., 1994; Hall, 2007b; Gaddam and Ferraro, 2008).

There have been some investigations examining wave I amplitude in human ears. Konrad-Martin et al. (2012) examined age-related changes (from 26 to 71 years of age) of the ABR in a predominately male Veteran population. Results indicated reduced wave I amplitudes with increasing age, even after adjusting for the effects of behavioral threshold changes associated with hearing loss. While the data from Konrad-Martin et al. focused on the influence of aging on the ABR, the majority of individuals in a Veteran population would likely have been exposed to high levels of noise at some point during their lifespan. It is possible that at least some variation in amplitude could be a result of prior noise exposure. Schaette and McAlpine (2011) examined wave I amplitude in normal-hearing ears with tinnitus. Findings revealed decreased wave I ABR amplitudes in ears with tinnitus relative to control ears. Wave V was also examined but revealed no differences between the tinnitus and the control group. The authors argued for the existence of a "homeostatic" or "central gain" mechanism along the auditory pathway between the generation sites of wave I and V that adjusts the neural response to compensate for reduced output from the auditory nerve fibers. In summary, further investigation of ABR responses, particularly wave I amplitude, in normal-hearing, noise-exposed human ears would be useful.

Self-Report Questionnaires

Self-report questionnaires have been used to identify the type and duration of noise exposures in efforts to determine if an individual is at risk for developing NIHL. The majority of these efforts have been led by the University of Washington Department of Environmental and Occupational Health Sciences study group (Neitzel et al., 2004a; Neitzel et al., 2004b; Reeb-Whitaker et al., 2004). NIOSH and OSHA recommendations are targeted at occupational noise exposures; they assume that some auditory recovery from noise might occur during non-occupational (e.g., non-noisy) activities. Work from the University of Washington study group focused on the development of a questionnaire to help quantify

the amount of noise exposure construction workers encountered outside of a workplace setting. The questionnaire included questions about exposures to noise during "routine" daily activities (e.g., home, travel, shopping, etc.) and "episodic" activities (e.g., power tools, sporting events, etc.). Exposure levels to different activities were shown to be reliably self-reported when compared to dosimeter measurements (Reeb-Whitaker et al., 2004). The questionnaire was able to provide an estimate of annual overall noise exposure encountered during the 6070 hours a year spent outside of a workplace setting (Neitzel et al., 2004b).

The questionnaire by Neitzel et al. (2004b) was modified by Megerson (2010) to be more applicable to the general public by including questions pertaining to music, impact (e.g., firearms, fireworks), and occupational noise exposures. Additionally, specific queries were directed at the duration of each exposure (in hours). The overall annual exposure levels found by Megerson were consistent with other published reports of typical noise exposures. Based on repeated questions pertaining to noise activities, good internal reliability of the questionnaire was demonstrated. The noise exposure questionnaire (NEQ) by Megerson consists of a total of 18 questions directed at daily and episodic noise exposures. The NEQ yields a $L_{Aeq8760h}$ value, which provides an annual estimate of the sound pressure level in dB using an A-weighted frequency response over 8760 hours (365 days per year x 24 hours per day). The NEQ and details on its computation can be found in Appendix B.

While self-report questionnaires can be beneficial in assessing at risk populations, longitudinal studies are necessary in order to assess how many individuals identified as being at risk or not at risk develop a hearing loss. For ethical reasons, it is not reasonable to expose individuals to noise and follow them over time. Therefore, research must be conducted on populations that have voluntary occupational or recreational noise exposures (e.g., construction workers, musicians, etc.). Self-report measures are susceptible to recall bias, where the measure of interest (e.g., noise exposure) is influenced by the ability (or inability) to accurately recollect the event (Coughlin, 1990). Therefore, self-report questionnaires, along with more objective measurements such as noise dosimeter monitoring, can be helpful in

quantifying how much noise exposure an individual has incurred. This information, when incorporated with more objective measures of auditory function, might provide further insight into the effects of noise on the auditory system.

Recent Investigations in Temporary NIHL

Recent investigations in mice (Kujawa and Liberman, 2009) and guinea pigs (Lin et al., 2011; Furman et al., 2013) describe functional auditory status and damage to auditory structures following TTS. These results indicate a different pattern of auditory damage than previously discussed, where TTS is thought to result in no permanent damage to auditory structures. In each of these studies (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013), TTS (up to a 40 dB loss) was induced using high intensity octave-band noise. Physiologic auditory function was determined via ABR and DPOAE measures; responses were measured prior to noise exposure and were repeated 10 to 14 days following recovery of TTS. Additionally, evidence of anatomical damage was evaluated by examining the OHCs, the IHCs and their nerve terminal connections (i.e., synaptic ribbons), and spiral ganglion cells. Anatomical damage was assessed from 24 hours up to 2 years post noise exposure.

All three studies indicated similar findings of an abrupt, permanent loss of up to 50% of afferent nerve terminal connections between IHCs and auditory nerve fibers in the frequency region of maximum threshold shift. This acute deafferentation led to a delayed degeneration in spiral ganglion cells that was evident up to two years after noise exposure. Despite irreversible damage to auditory structures, ABR wave I thresholds demonstrated full recovery to pre-exposure levels. Therefore, ABR wave I threshold measures failed to detect the presence of anatomical damage.

As previously discussed, threshold measures have been shown to be relatively insensitive to large changes in the number of nerve fibers contributing to the response (Earl and Chertoff, 2010). Therefore, in the work by Kujawa and colleagues (Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013), the remaining undamaged IHC afferent connections proved sufficient to preserve the threshold

response, even in the presence of a substantial loss of IHC synapses. Although wave I thresholds returned to normal, evidence of the deafferentation was seen when examining the ABR response at supra-threshold levels. At stimulus levels greater than 40 dB SPL, the ABR wave I revealed decreased amplitudes in the noise-exposed mice and guinea pig ears relative to control ears and these differences became greater with further increases in stimulus level. In contrast to threshold measures, ABR amplitude is influenced by the number and type of auditory nerve fibers contributing to the response. Furman et al. (2013) reported greater amounts of auditory nerve fiber loss in fibers with low spontaneous rates and high thresholds. This suggests that NIHL might selectively damage auditory nerve fibers that contribute to high-level amplitude responses and are important for hearing in noisy environments due to their resistance to masking in background noise (Costalupes et al., 1984; Lopez-Poveda and Barrios, 2013). This selective loss of high-threshold auditory nerve fibers could also contribute to difficulty hearing in noise, tinnitus, and hyperacusis, all auditory symptoms that have been reported in noise-exposed human ears with normal behavioral thresholds (Sanchez et al., 2005; Muhr and Rosenhall, 2010). In summary, in the animal ears discussed above, ABR supra-threshold responses demonstrated better sensitivity at revealing damage to auditory structures than threshold responses.

In contrast to the IHCs, the OHCs appeared undamaged upon anatomical assessment. Since the OHCs are responsible for the generation of the DPOAE response, it is not surprising there were no differences in threshold or supra-threshold OAE responses in noise-exposed animal ears compared to control ears. DPOAEs did show an initial decrease in emission level during active temporary hearing loss. However, as threshold responses recovered, supra-threshold DPOAE levels also returned to pre-exposure levels.

The data from Kujawa and Liberman (2009), Lin et al. (2011), and Furman et al. (2031) present a pattern of damage to auditory structures following noise exposure that contradicts the assumption that no permanent damage occurs with TTS. In other words, these data suggest noise exposures are considerably more dangerous than previously believed. Additionally, their findings advocate for the use of high-level

stimuli when assessing auditory function as it may provide evidence of early-onset noise-induced auditory damage that is not yet evident in behavioral thresholds. However, these studies were completed in animal models and it is unknown how these findings might generalize to the noise-exposed, normal-hearing human ear. If a similar pattern occurs in humans, the assumption that noise exposures resulting in TTS are essentially harmless is inaccurate. Furthermore, current NIHL assessment protocols based on threshold determination may be insensitive to identifying early signs of noise damage and the use of supra-threshold amplitude measures may be a beneficial addition to the clinical assessment of NIHL.

APPENDIX B

NOISE EXPOSURE QUESTIONNAIRE (NEQ) AND COMPUTATION

The noise exposure questionnaire (NEQ) developed by Megerson (2010) was used in this study to quantify subjects' noise exposure background. The questionnaire contains 18 questions and specifically assesses nine categories of noisy activities: power tools, heavy equipment/machinery, commercial sporting/entertainment events, motorized vehicles (e.g., motorcycles, speed boats, etc.), small/private aircraft, musical instrument playing, music listening via personal earphones, music listening via audio speakers, and occupational exposure (summer and school year). The questionnaire, which can be found at the end of this appendix, was transferred from a paper format to an electronic Microsoft Access form for ease of use. Questions 1 through 18 were included in the electronic format; the demographic information included at the beginning of the paper format NEQ was not included. The electronic NEQ took subjects approximately 5-10 minutes to complete. Following completion of the NEQ, results were exported to a Microsoft Excel file for ease of computation.

NEQ Computation

Computation of the NEQ yields a $L_{Aeq8760h}$ value which can be interpreted as an annual estimate of noise exposure. Here, "L" represents sound pressure level in dB, "A" refers to the use of an A-weighted frequency response, "eq" represents a 3 dB exchange rate for calculation of the time/level relationship, and "8760h" represents the total duration of annual noise exposure in hours (365 days per year x 24 hours per day). Several stages exist to calculating the $L_{Aeq8760h}$. To begin, exposure doses (D) were computed for the nine types of noise activities queried by the NEQ. D is defined as:

$$D = \left[\frac{C}{T}\right] \times 100$$

D is the noise dose for an individual subject given a 79 dBA recommended exposure limit for 8760 hours and a 3 dB exchange rate. The 79 dBA exposure limit is based on NIOSH recommended annual limits for noise exposure. A dose of under 100% can be interpreted as not exceeding NIOSH

recommendations and a dose of greater than 100% can be interpreted as exceeding NIOSH recommendations of what is considered a safe listening environment.

In the dose (D) equation, C refers to the actual number of hours per year reported by the subject for the noisy activity. While C is a reflection of the number of hours spent annually in a reported activity, the questionnaire derives this information from a two part question: how often did participation in the noisy activity occur and on average, for how many hours did the exposure last. A numerical value is assigned to each possible categorical response. In the first part of questions 7 through 11 and 14 through 16, five possible responses exist to determine how often a noisy activity occurred. These responses are assigned the following values: daily=200; weekly=50; monthly=12; every few months=1; never=0. In the second part of questions 7 through 11 and 14 through 16, four possible responses exist to determine how long the noisy activity lasted. These responses are assigned the following values: 8 hours or more=8; 4 to 8 hours=6; 1 hour up to 4 hours=3; less than 1 hour=1. To calculate C, the two values are multiplied and this creates a possible range of 0 to 1600 hours per year. For questions relating to occupational noise exposure (questions 17 and 18), the subject is prompted to report on average how many hours a week they worked during the summer (question 17) or the school year (question 18). These responses are multiplied by 10 (10 weeks per year) if it is a summer job and by 40 (40 weeks per year) if it is a school year job.

In the exposure dose (D) equation, T represents the number of hours per year at which the activity is considered hazardous using NIOSH recommended limits for noise exposure. T is defined as:

$$T = \frac{8760}{2^{\left[\frac{L-79}{3}\right]}}$$

Here, L is the continuous equivalent sound level in dB L_{Aeq} derived from scientific literature for that specific noise exposure type (e.g., power tools, small/private aircraft, etc.). The L for each of the nine noisy activities categories are as follows: power tools, 94 dB L_{Aeq}; heavy equipment/machinery, 97 dB L_{Aeq}; commercial sporting/entertainment events, 94 dB L_{Aeq}; motorized vehicles, 98 dB L_{Aeq};

small/private aircraft, 91 dB L_{Aeq}; musical instrument playing, 87 dB L_{Aeq}; music listening via personal earphones, 76 dB L_{Aeq}; music listening via audio speakers, 78 dB L_{Aeq}; occupational exposure, 90 dB L_{Aeq}.

Because the $L_{Aeq8760h}$ is an estimate of the amount of noise exposure encountered in one year, or 8760 hours, the noise level of routine activities not readily associated with high noise environments also needs to be taken into account. These activities refer to time spent at home eating, sleeping, reading, watching television as well as traveling by bus or car, eating at a restaurant, shopping and other similar activities. The duration of the amount of time (C) spent engaging in routine activities is calculated as 8760 hours minus the subject's reported number of hours spent in the nine noisy activity categories assessed by the NEQ (i.e., the remaining hours in a year). The level (L) of routine activities was defined as 64 dB $L_{Aeq8760h}$. This number was obtained from studies completed by Neitzel et al., (2004a, 2004b). This resulted in a noise dose percent that is reflective of time spent in routine activities.

Dose percents can be added arithmetically. Therefore, the dose percent for each of the nine categories of noisy activites were added together, resulting in a dose reflective of the overall amount of time spent annually in noisy environments relative to NIOSH dose requirements. This dose was then added to the dose of time spent in routine activities, resulting in a dose reflective of all exposure to noise within a 12 month period. The overall dose percent, D, is necessary to compute the $L_{Aeq8760h}$ using the following equation:

$$L_{Aeq8760h} = \left[10 \times \log_{10} \frac{D}{100}\right] + 79$$

Sample NEQ Calculation

Activity	Question	Response	C (hours)	L (L_{Aeq})	T (hours)	D (%)
Power tools	7a 7b	Never (0) n/a	0	94	273.75	0.00%
Heavy equipment & machinery	8a 8b	Never (0) n/a	0	97	136.88	0.00%
Commercial sporting & entertainment events	9a 9b	Every few months (1) 1 hour up to 4 hours (3)	3	94	273.75	1.10%
Motorized vehicles	10a 10b	Never (0) n/a	0	98	108.64	0.00%
Small/private aircraft	11a 11b	Never (0) n/a	0	91	547.50	0.00%
Musical instrument playing	14a 14b	Daily (200) 1 hour up to 4 hours (3)	600	87	1379.61	43.49%
Music listening via personal earphones	15a 15b	Every few months (1) Less than 1 hour (1)	1	76	17520	0.01%
Music listening via audio speakers	16a 16b	Monthly (12) 1 hour up to 4 hours (3)	36	78	11036.91	0.33%
Occupational exposure	17 18	Yes (15 hours) Yes (25 hours)	150 1000	90	689.81	166.71%
Routine activities			6970	64	280320	2.47%
					Total Dose	214.10%
					$L_{Aeq8760h}$	**82.31**

The above table shows an example $L_{Aeq8760h}$ calculation of subject 18 from the present study. In this individual, the majority of their noise exposure is attributable to occupational noise exposure (subject 18 was a high school band teacher) (166.71%) and to musical instrument playing (43.49%). The NEQ from Megerson (2010) can be found on the following pages.

Noise Exposure Study

Hearing & Speech Dept.
Susan Cooper Megerson

INSTRUCTIONS:

- ***Please answer the following questions about yourself, your hearing, and any noise you may have been around during the past year. Write an answer in the blank [_____] or check [√] the best answer to each question.***
- ***Be sure to complete all 4 pages.***
- ***This survey is anonymous (you are not identified), it is voluntary, and it does not affect your grades in any way.***

Thank you for your participation!

Today's date: _____

You are: ☐ Male ☐ Female Your age: _____ years

Do you consider yourself Hispanic/Latino? ☐ Yes ☐ No

What race do you consider yourself? *(for this question only, please check all that apply)*

☐ American Indian or Alaska Native
☐ Asian ☐ Native Hawaiian or Pacific Islander
☐ Black or African American ☐ White or Caucasian

Please answer these <u>general</u> questions about your hearing and any loud sounds.
DURING THE PAST YEAR (12 months):

1.	How often were you around or did you shoot firearms such as rifles, pistols, shotguns, etc.? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily
2.	How often were you exposed to loud sounds while working on a <u>paid</u> job? By loud sounds, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily
3.	How often were you exposed to any other types of loud sounds, such as power tools, lawn equipment, or loud music? By loud sounds, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily
4.	How often were you exposed to loud sound that made your ears "ring" or "buzz"? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily
5.	How often were you exposed to loud sound that made your hearing seem muffled for a while? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily
6.	How often were you exposed to loud sound that made your ears hurt, feel "full," or bother you in any other way? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily

Please answer these <u>detailed</u> questions about any loud sounds. **DURING THE PAST YEAR (12 months):**	
7.	Outside of a paid job, how often did you use power tools, chainsaws, or other shop tools? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you used power tools, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you used power tools, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always
8.	Outside of a paid job, how often did you drive heavy equipment or use loud machinery (such as tractors, trucks, or farming or lawn equipment like mowers/leaf blowers)? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you drove/used loud machinery, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you drove/used machinery, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always
9.	How often did you attend car/truck races, commercial/high school sporting events, music concerts/dances or any other events with amplified public announcement (PA)/music systems? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you attended these events, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you attended these events, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always
10.	How often did you ride/operate motorized vehicles such as motorcycles, jet skis, speed boats, snowmobiles, or four-wheelers? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you rode motorized vehicles, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you rode motorized vehicles, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always
11.	How often did you ride in or pilot small aircraft/private airplanes? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you flew airplanes, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you flew airplanes, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always

Please continue answering these <u>detailed</u> questions about any loud sounds. **DURING THE PAST YEAR (12 months):**	
12.	How often were you around or did you shoot firearms such as rifles, pistols, shotguns, etc.? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you were around/shot firearms, on average, how many shots did you fire each time/session? _____ **shotgun/rifle** shots per session _____ **pistol** shots per session If you were around/shot firearms, how often did you wear earplugs or earmuffs while shooting? ☐ Never ☐ Sometimes ☐ Always
13.	How often were you around firecrackers or other fireworks? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you were around fireworks, on average, how many fireworks did you shoot each time/session? _____ firecracker/firework shots per session If you were around/shot fireworks, how often did you wear earplugs or earmuffs during this activity? ☐ Never ☐ Sometimes ☐ Always
14.	How often did you play a musical instrument? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you played, please tell us what musical instrument: _____ If you played a musical instrument, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you played a musical instrument, how often did you wear earplugs or earmuffs while playing? ☐ Never ☐ Sometimes ☐ Always
15.	How often did you listen to music, radio programs, etc. using personal <u>headsets</u> or <u>earphones</u>? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you listened through earphones, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you listened through earphones, what was the typical <u>volume setting</u> (control knob rotation) when listening? ☐ Full/maximum volume ☐ ¾ maximum volume ☐ ½ max. volume ☐ ¼ max. volume
16.	Other than music concerts and headset use (*already covered in questions 9. and 15.*), how often did you listen to music, radio programs, etc. from audio speakers in a car or at home? ☐ Never ☐ Every few months ☐ Monthly ☐ Weekly ☐ Daily If you listened via speakers, on average, how many hours did each time/session last? ☐ 8 hours or more ☐ 4 hours up to 8 hours ☐ 1 hour up to 4 hours ☐ Less than 1 hour If you listened via speakers, what was the typical <u>volume setting</u> (control knob rotation)? ☐ Full/maximum volume ☐ ¾ maximum volume ☐ ½ max. volume ☐ ¼ max. volume

Please continue answering these <u>detailed</u> questions. **NOTE DIFFERENT TIME-FRAMES:**	
17.	**Now think back to this past <u>summer</u>. Over the summer months,** did you work a noisy <u>paid</u> job, such as in construction, farming, a factory, lawn service, carwash, or other indoor or outdoor job working around loud equipment or machinery? By noisy job, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Yes ☐ No *(if no, skip to # 18.)* If yes, please describe this noisy job: _____ If you worked a noisy job, please estimate the number of hours you worked in a typical week: _____ hours worked per typical week this summer If you worked a noisy job this summer, did your employer give you earplugs or earmuffs to wear at work? ☐ Yes ☐ No How often did you wear earplugs or earmuffs when around loud noise at this summer job? ☐ Never ☐ Sometimes ☐ Always Did you receive training on this job about noise and hearing loss? ☐ Yes ☐ No Did you receive a hearing test through this job? ☐ Yes ☐ No Other comments:
18.	**<u>Other than</u> during the summer, over the past year**, did you work one or more noisy <u>paid</u> jobs, such as in construction, farming, a factory, lawn service, carwash, or other indoor or outdoor job working around loud equipment or machinery? By noisy job, we mean sounds so loud that you had to shout or speak in a raised voice to be heard at arm's length. ☐ Yes ☐ No *(if no, you're done with the survey)* If yes, please describe the noisy job(s): _____ If you worked a noisy job, please estimate the number of hours you worked in a typical week: _____ average hours worked per typical week during the school year If you worked a noisy job during the school year, did your employer give you earplugs or earmuffs to wear at work? ☐ Yes ☐ No How often did you wear earplugs or earmuffs when around loud noise at this noisy job(s)? ☐ Never ☐ Sometimes ☐ Always Did you receive training on the job about noise and hearing loss? ☐ Yes ☐ No Did you receive a hearing test through work? ☐ Yes ☐ No Other comments:

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APPENDIX C

RESEARCH CONSENT FORM

RESEARCH CONSENT FORM

AUDITORY RESPONSES IN NORMAL-HEARING, NOISE-EXPOSED EARS

You are being asked to join a research study. You are being asked to take part in this study because you have normal hearing and either have a little or a large amount of exposure to loud sound(s). You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) under the direction of Tiffany Johnson, Ph.D. as the principal investigator, and Greta Stamper, Ph.D. candidate, as a secondary investigator. About 40 people will be in the study at KUMC.

BACKGROUND

Frequent exposure to loud sound can cause damage to the ear and can lead to a hearing loss. However, recent research has given us new information about how loud sounds affect the ear. New studies have questioned the amount of noise that is harmful and suggest it might be less than previously thought. The new studies also suggest that the techniques we use in the clinical setting to test for damage from loud sounds in the ear might not be sensitive enough to identify early damage.

Two clinical tests will be used to help us determine how well your ears are working: *otoacoustic emissions* and the *auditory brainstem response*.

- *Otoacoustic emissions* are quiet sounds that we record in the ear canal. They are produced by the inner part of the ear in response to sound and can help us to know if a person has normal hearing or hearing loss.

- The *auditory brainstem response* is a measure of the brain's electrical activity as it processes sound. The response is produced by neural activity in the auditory nerve and the brain and can help us know if a person has normal hearing or hearing loss.

Neither of these tests are experimental, but new studies suggest that testing with a broader range of loudness levels during these tests than has previously been used might help identify damage

from loud sounds before a hearing loss develops.

Many individuals are regularly exposed to loud noise through work or leisure activities. This research study will compare test results of individuals who are regularly and voluntarily exposed to loud noise in a musical setting with those who have little exposure to loud noise. Musicians are frequently around loud sounds during performances and practice sessions. We are asking college students to participate in this research and will be testing those who are involved in music programs within their college or university. We will also be testing college students not involved in music programs who have little exposure to loud noise.

PURPOSE

By doing this study, the researchers hope to identify methods of detecting auditory damage from exposure to loud noise before a hearing loss develops.

PROCEDURES

If you are eligible and decide to participate in this study, your participation will last approximately 3.5 to 4 hours, spread over 2 testing sessions.

Your participation will involve different activities across the 2 sessions.

Day 1): During the first test session, your participation will consist of the following activities:

- A standard hearing test. This test tells us how soft a sound you can hear. During this test, we will first look in your ears using a light called an otoscope. You then will be asked to wear headphones and to respond by either pressing a button or by raising your hand when you hear a tone. This test will take 10-15 minutes to complete.

- A standard tympanogram. This tests checks how well your middle ear is working. During this test, a small rubber tip will be placed in your ear canal. You will hear a low-pitched sound and will feel slight pressure changes in your ear canal. This test will take no more than 5 minutes to complete.

Both of these tests are used to verify that you have normal hearing and can participate in the research. If you do not have normal hearing, your participation will be complete at this time. You will be counseled regarding the outcome of your hearing test and will receive information regarding any further testing that is recommended. If you have normal hearing, you will be invited to continue in the research. If you choose to continue, you will undergo additional testing.

- A noise-exposure questionnaire. You will be asked a series of questions related to your involvement in common activities where you may have been exposed to loud sounds. Because loud sounds can damage your hearing, we would like to know how much exposure to loud sounds you've had in the last year. We will evaluate your responses on the questionnaire to see if you have a lot of exposure to loud sounds or if you have only a little. You will take this questionnaire on a computer. You will either take it alone or with the assistance of one of the researchers. This questionnaire will take 5-10 minutes to complete.

- Noise dosimeter monitoring. You will be given a noise dosimeter to take home with you. A noise dosimeter is a small microphone that will monitor the level of sounds around you. You will be given instructions on how to use it and when you need to use it to monitor sounds. This information will help the researchers know how much exposure to loud sounds you have. You will need to bring the noise dosimeter with you when you return for your second appointment.

The total test time for the first day will be approximately 1 hour.

Day 2): You will return within a week or two following your first testing session for your second testing session. You should bring the noise dosimeter with you.

On this day we will again complete the middle-ear test (the tympanogram). After the tympanogram, we will proceed directly to otoacoustic emission testing followed by auditory brainstem response testing.

- Otoacoustic emission testing. For this testing, you will sit quietly in a comfortable recliner. You can read quietly, sleep, or watch a video with the sound turned off. A soft, foam eartip will be placed in your ear canal and you will hear sounds presented through the eartip. The sounds will change in loudness and some will be high pitched, while others are low pitched. The sounds will never get loud enough to hurt or cause harm to your hearing.

The total test time for otoacoustic emissions will be approximately 15-20 minutes.

- Auditory Brainstem Response testing. For this test, you will sit quietly in a comfortable recliner and can read quietly or sleep. Your forehead and the area behind each ear will be gently scrubbed with a gel and stickers called surface electrodes will be placed on the skin. A small, rubber-tipped electrode, called a tymptrode, will be gently placed on the outer surface of your eardrum. A soft, foam eartip will be placed in your ear canal and you will hear sounds presented through the eartip. The sounds will change in loudness and some will be high pitched while others are low pitched. The sounds will never get loud enough to hurt or cause harm to your hearing.

The total test time for auditory brainstem response testing will be approximately 2.5 hours.

You will be offered (and can request) breaks during testing and you should tell us if you feel the sounds are louder than is comfortable for you.

The total test time for the second day will be up to 3 hours.

RISKS

The sounds that will be played to your ear will vary in loudness. You will feel slight pressure in your ear during the testing. If any of the sounds are bothering you, please tell us to turn off the sound.

Your skin needs to be cleaned using a mild abrasive scrub in order to place the electrodes. You should let us know if it is irritating your skin too much. As the electrode is placed on your ear drum, it may be uncomfortable. Please let us know if it is bothering you and we can reposition it.

You may feel restless during the test sessions. We will offer you breaks during each session and you may ask us to take a break at any time.

There may be other risks of the study that are not yet known.

BENEFITS
You will not directly benefit from this study. You will receive a hearing test during the study. Researchers hope that the information from this research study may be useful in improving our ability to identify early damage to the ear caused by loud noise.

ALTERNATIVES
Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center.

COSTS
There is no cost for being in the study.

PAYMENT TO SUBJECTS
You will be paid $60 for your participation in this study if you complete the entire study. If you do not meet inclusion criteria for the study or choose to withdraw before the end of the study, you will be paid $20 for your participation in the study. You will receive payment in the form of a check and will receive it within 30 days after your final study visit.

The KUMC Research Institute will be given your name, address, social security number, and the title of this study to allow them to write checks for your study payments. Study payments are taxable income. A Form 1099 will be sent to you and to the Internal Revenue Service if your payments are $600 or more in a calendar year.

IN THE EVENT OF INJURY
If you have discomfort or other problems during this study, you should immediately contact Dr. Johnson or Dr. Stamper at 913-588-5929. If it is after 5:00 p.m., a holiday or a weekend, you should leave a message at the same number. A member of the research team will decide what type of treatment, if any, is best for you at that time.

INSTITUTIONAL CONTACT
If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Their phone number is 913-588-1240.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION
The researchers will protect your information, as required by law. Absolute confidentiality

cannot be guaranteed because persons outside the study team may need to look at your study records. Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KUMC by Dr. Johnson, members of the research team, the KUMC Research Institute and officials at KUMC who oversee research, including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information will not expire unless you cancel it. Any research information that is placed in your medical record will be kept indefinitely.

The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

QUESTIONS

Before you sign this form, Dr. Tiffany Johnson or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Tiffany Johnson. The mailing address is Tiffany Johnson, Ph.D., University of Kansas Medical Center, 3901 Rainbow Boulevard, Mail Stop 3039, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

CONSENT

Dr. Johnson, or the research team, has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

_____

Print Participant's Name

_____ _____ _____

Signature of Participant Time Date

_____

Print Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

APPENDIX D

FIGURES AND TABLES

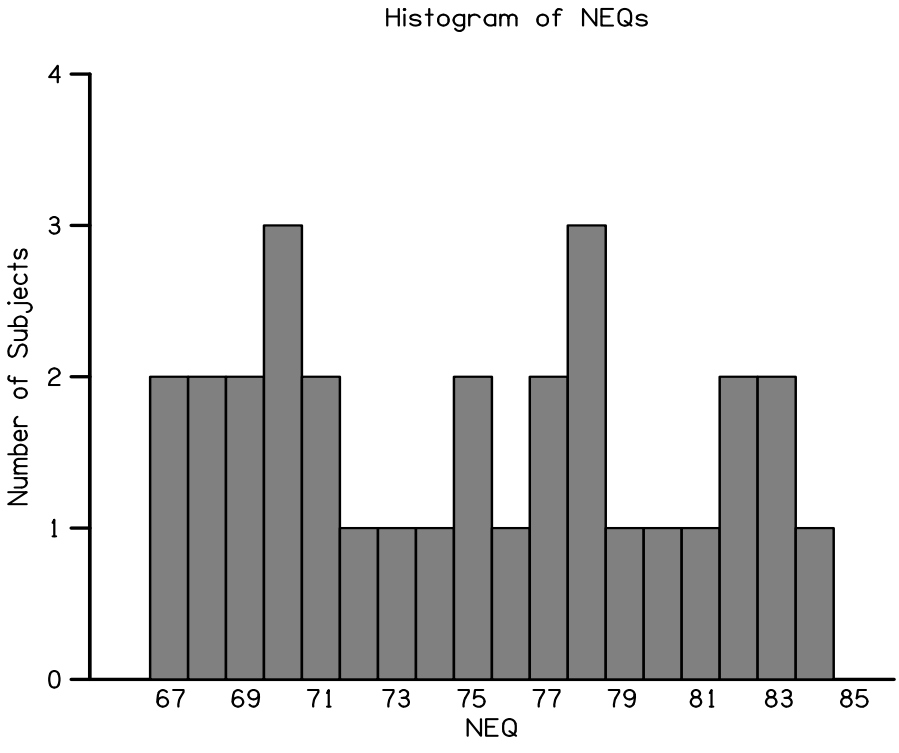

Figure 1: Histogram of Noise Exposure Questionnaire (NEQ) values obtained from study participants (n=30).

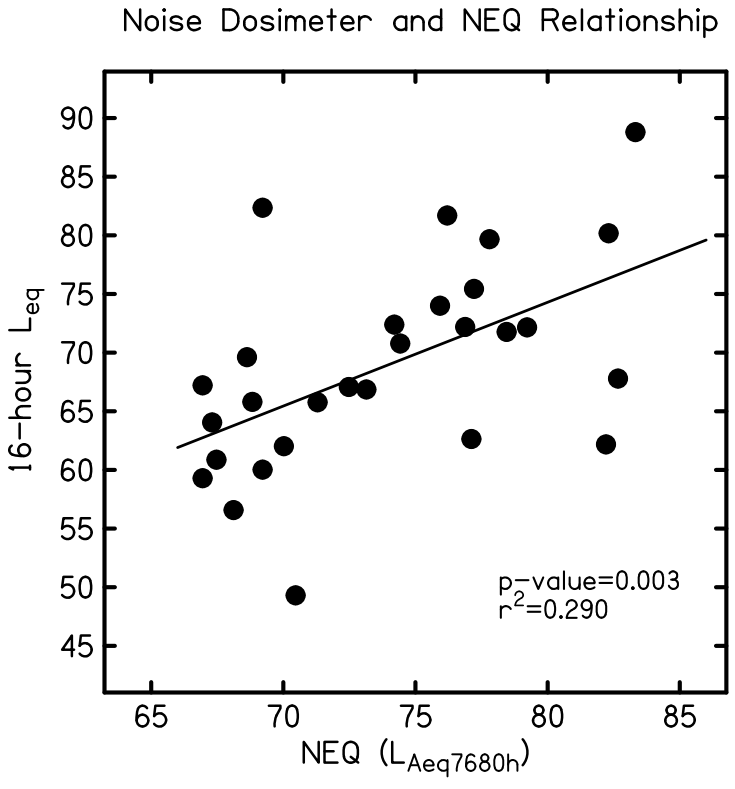

Figure 2: 16-hour noise dosimeter readings (L_{eq}) displayed as a function of the NEQ value (n=28).

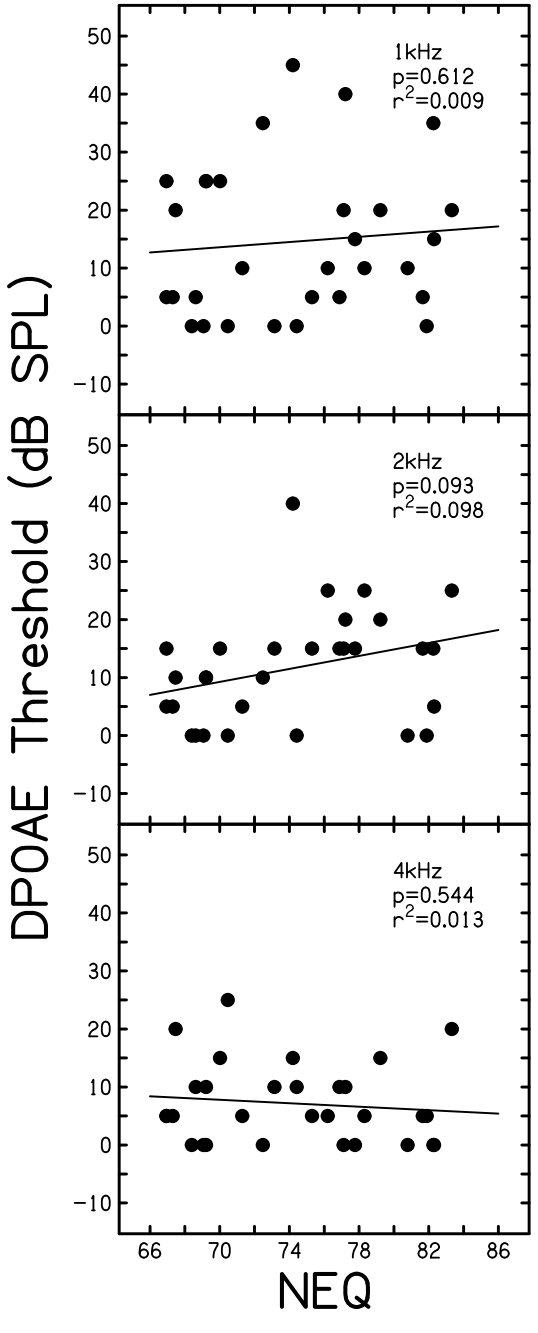

Figure 3: DPOAE threshold for f_2's of 1 kHz (top panel), 2 kHz (middle panel), and 4 kHz (bottom panel) plotted as a function of the NEQ value (n=30 at each f_2). Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed at each f_2 and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

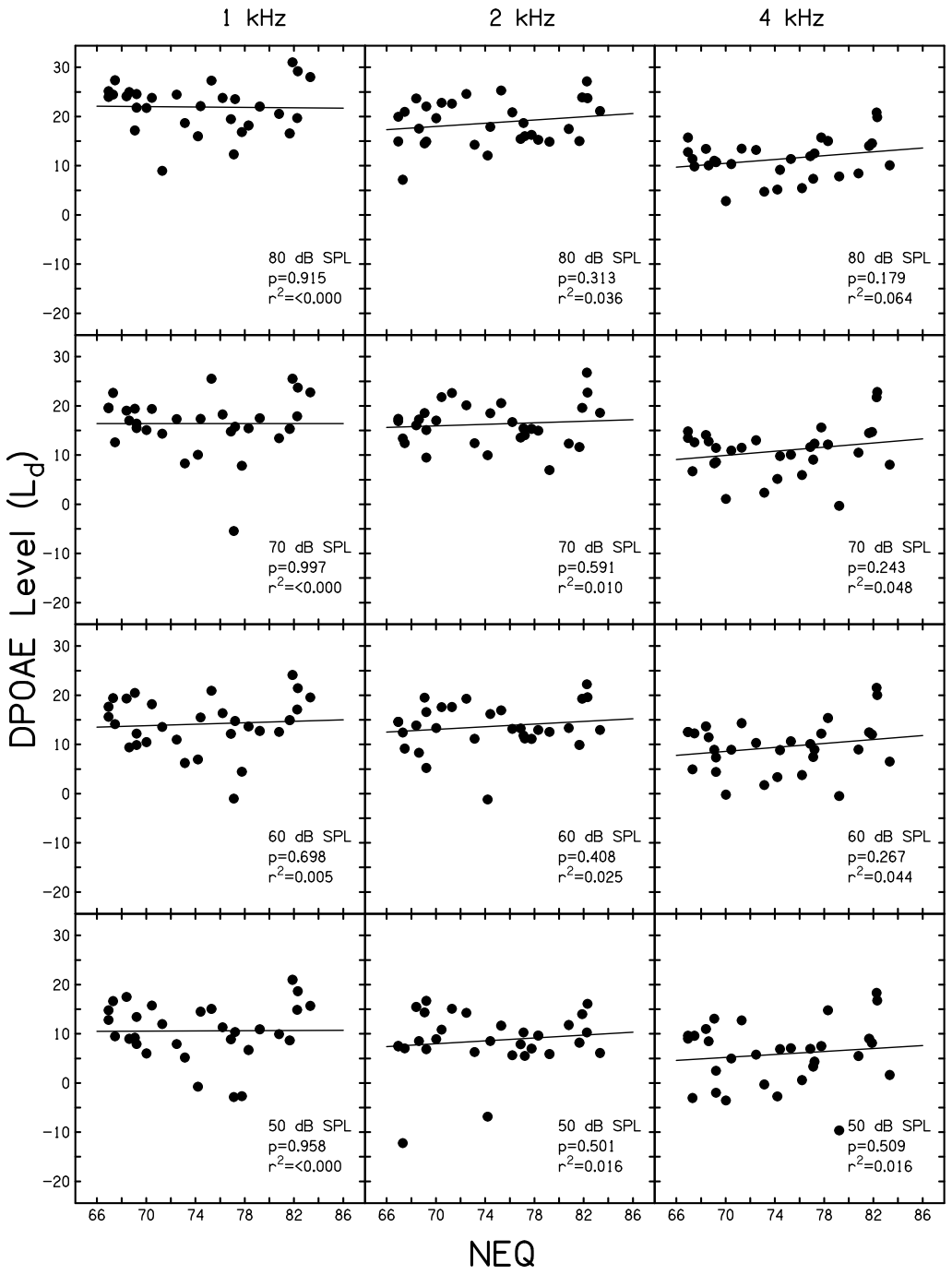

Figure 4: Supra-threshold DPOAE level as a function of NEQ. Results are shown for f_2's of 1 kHz (left column), 2 kHz (middle column) and 4 kHz (right column) when L_2 was 80 dB SPL (top row), 70 dB SPL (second row), 60 dB SPL (third row) and 50 dB SPL (bottom row). Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed in each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

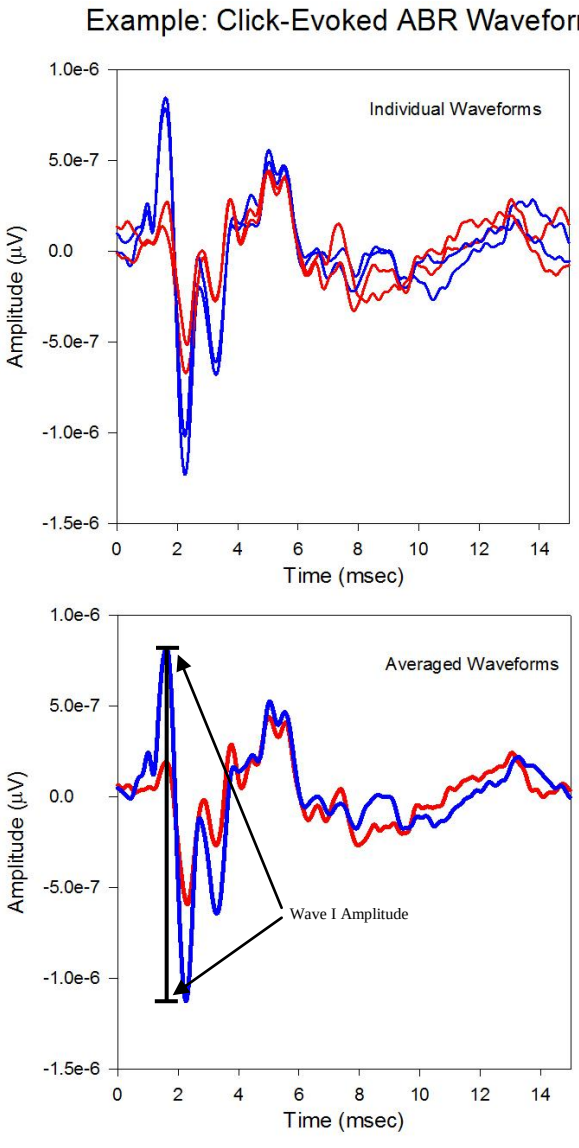

Figure 5: Example ABR waveforms in response to a click stimulus presented at 90 dB nHL from one subject. Individual waveforms are shown in the top panel and averaged waveforms are shown in the bottom panel. ABR tracings shown in blue represent recordings obtained with a tympanic membrane electrode and tracings shown in red represent recordings obtained with a mastoid electrode. The time scale is 15 msec.

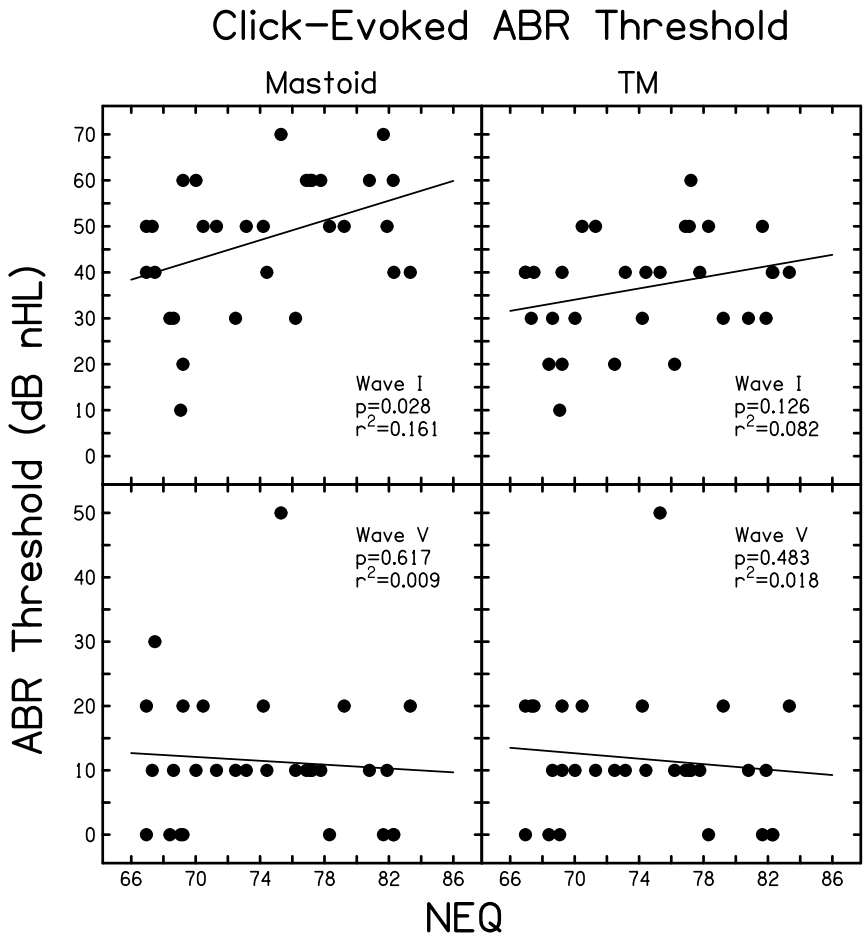

Figure 6: Click-evoked ABR threshold (dB nHL) as a function of NEQ value. Thresholds are shown for wave I (top row) and wave V (bottom row) for ABR recordings obtained using a mastoid (left column) and tympanic membrane (right column) recording electrode. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

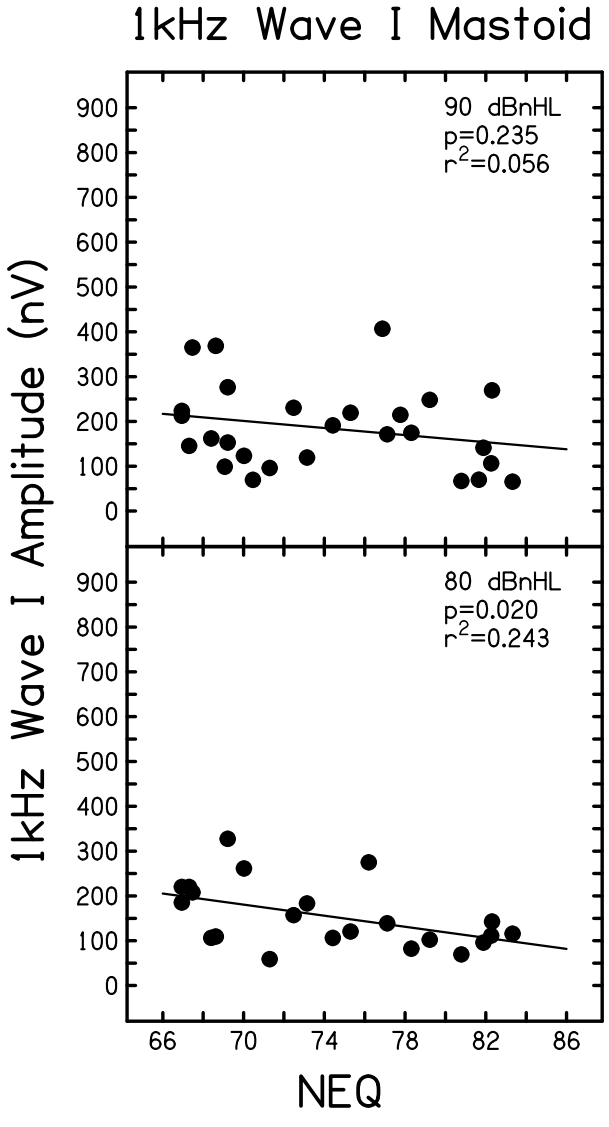

Figure 7: Supra-threshold ABR wave I amplitude recorded with a mastoid electrode in response to 1 kHz tone bursts presented at 90 (top panel; n=27) and 80 (bottom panel; n=22) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

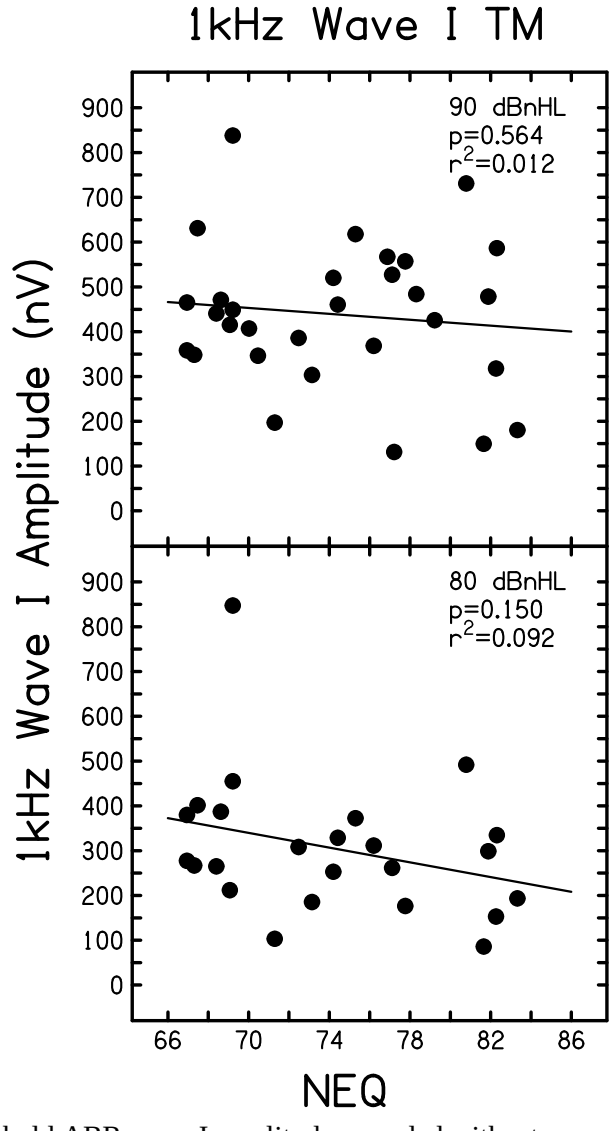

Figure 8: Supra-threshold ABR wave I amplitude recorded with a tympanic membrane electrode in response to 1 kHz tone bursts presented at 90 (top panel; n=30) and 80 (bottom panel; n=24) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

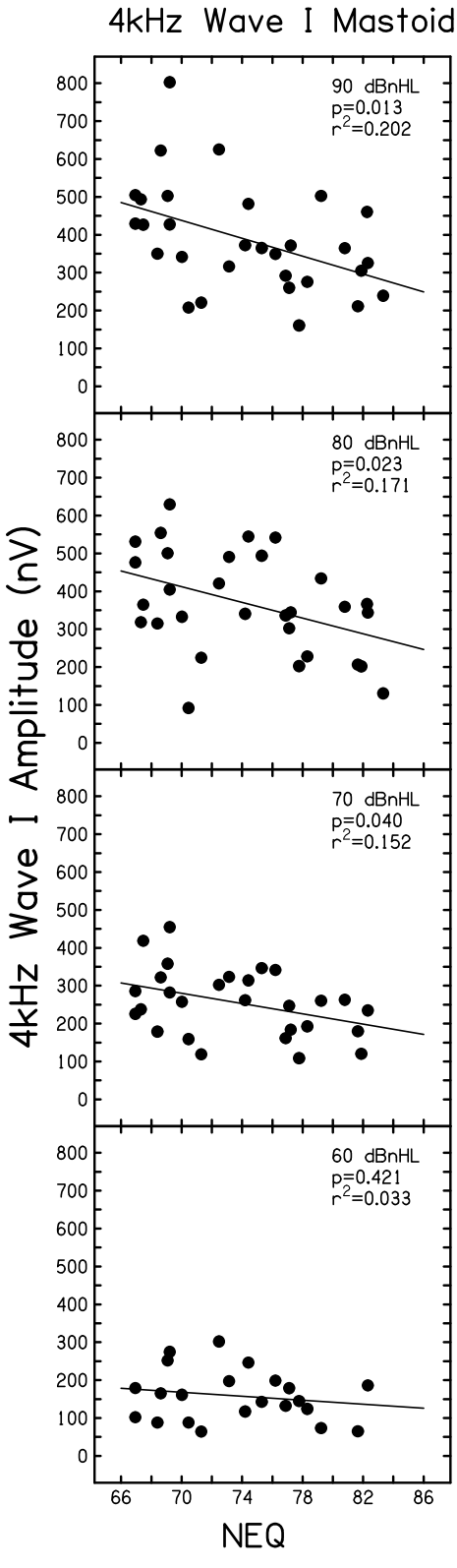

Figure 9: Supra-threshold ABR wave I amplitude recorded with a mastoid electrode in response to 4 kHz tone bursts presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=28) and 60 (bottom panel; n=22) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

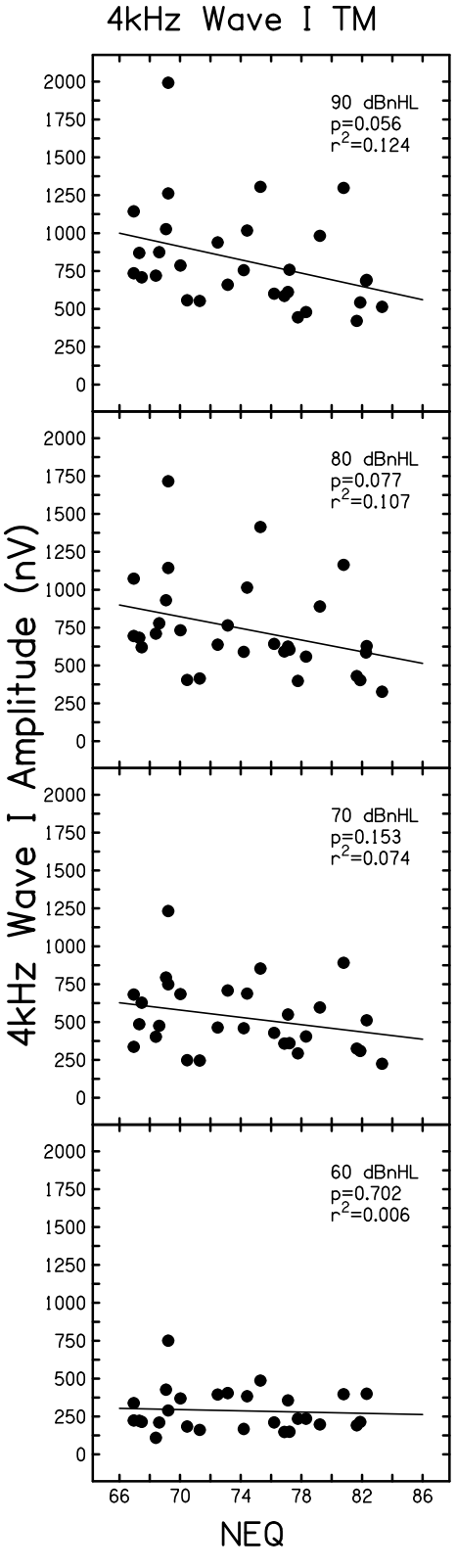

Figure 10: Supra-threshold ABR wave I amplitude recorded with a tympanic membrane electrode in response to 4 kHz tone bursts presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=29) and 60 (bottom panel; n=28) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

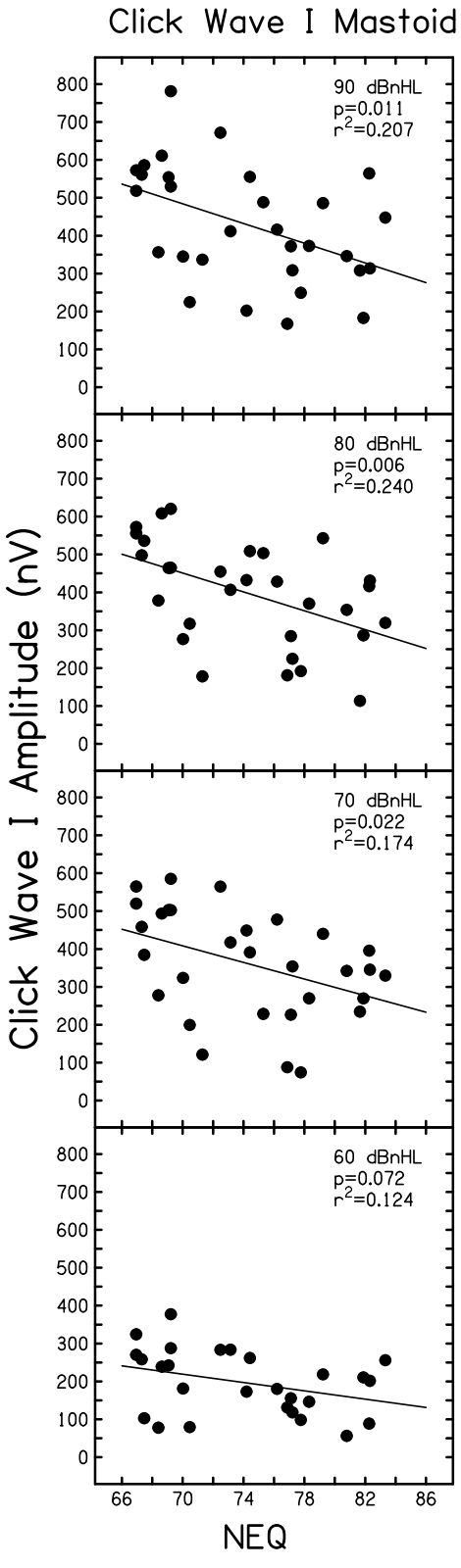

Figure 11: Supra-threshold ABR wave I amplitude recorded with a mastoid electrode in response to click stimuli presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=30) and 60 (bottom panel; n=27) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

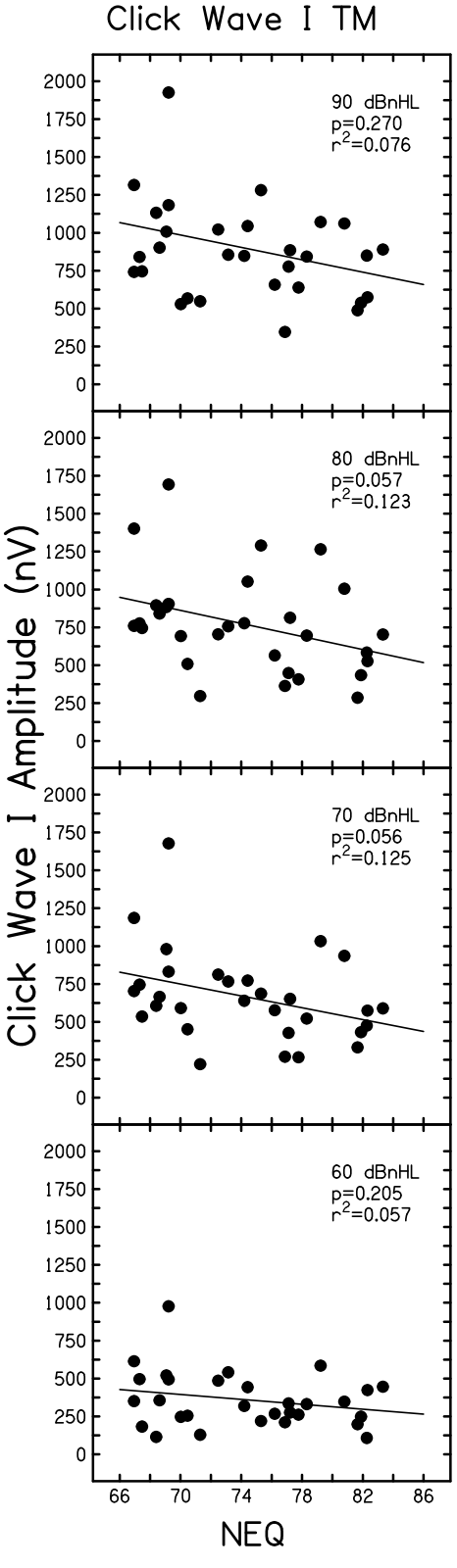

Figure 12: Supra-threshold ABR wave I amplitude recorded with a tympanic membrane electrode in response to click stimuli presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=30) and 60 (bottom panel; n=30) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

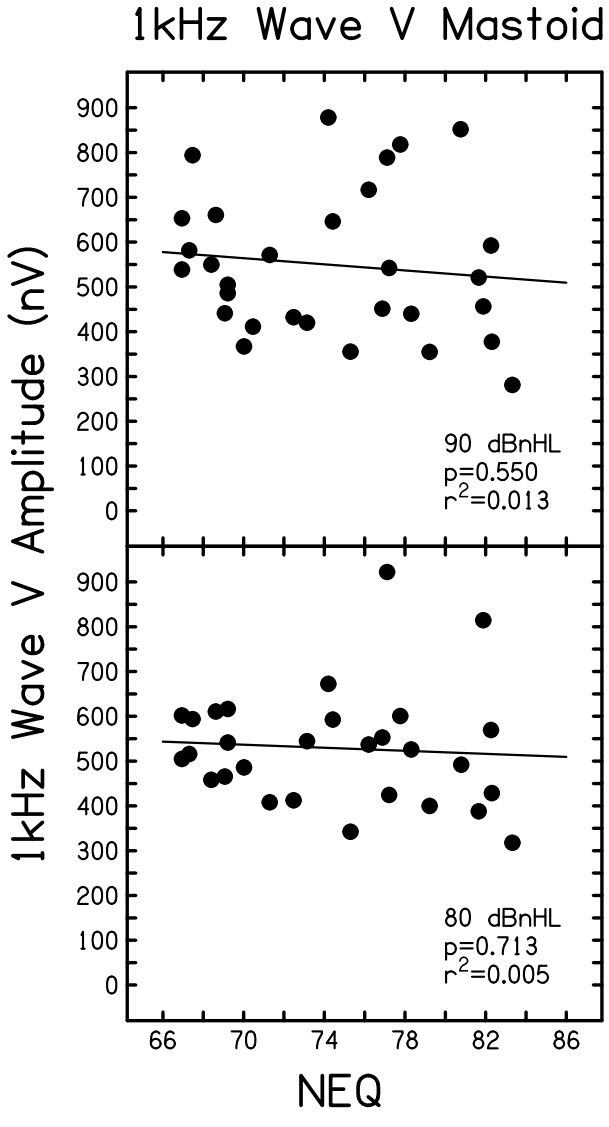

Figure 13: Supra-threshold ABR wave V amplitude recorded with a mastoid electrode in response to 1 kHz tone bursts presented at 90 (top panel; n=30) and 80 (bottom panel; n=29) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

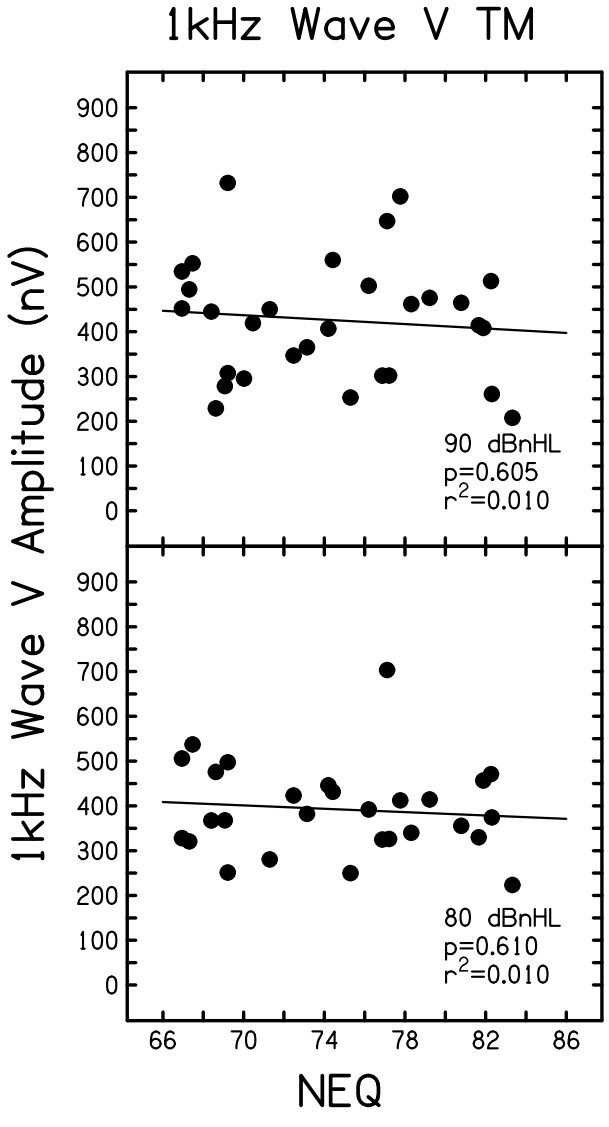

Figure 14: Supra-threshold ABR wave V amplitude recorded with a tympanic membrane electrode in response to 1 kHz tone bursts presented at 90 (top panel; n=30) and 80 (bottom panel; n=28) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

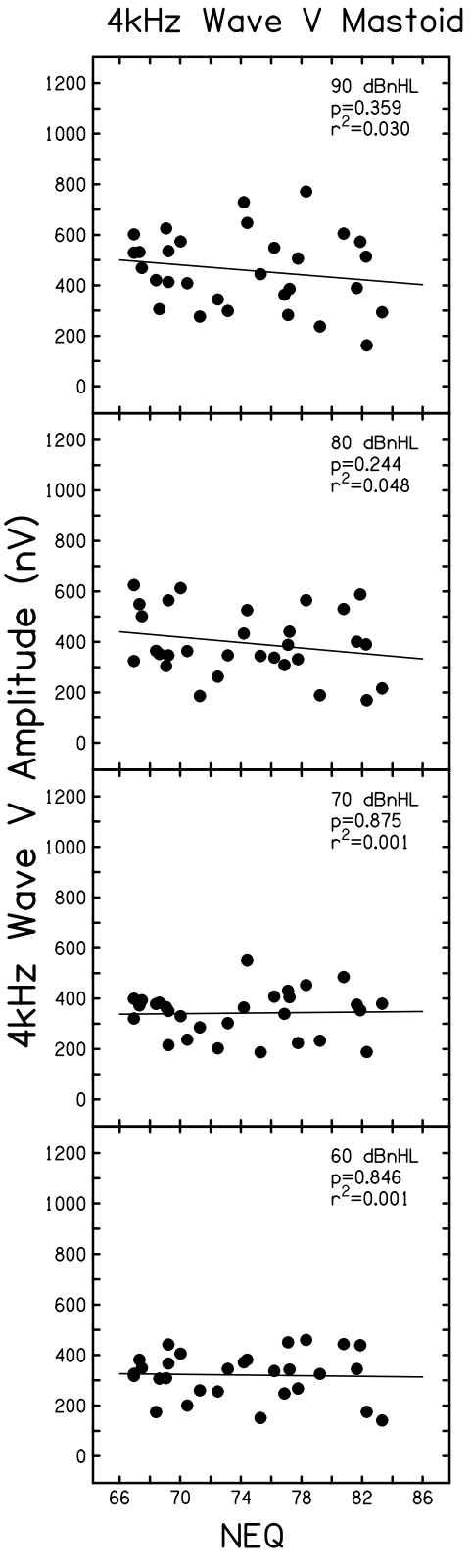

Figure 15: Supra-threshold ABR wave V amplitude recorded with a mastoid electrode in response to 4 kHz tone bursts presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=29) and 60 (bottom panel; n=29) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

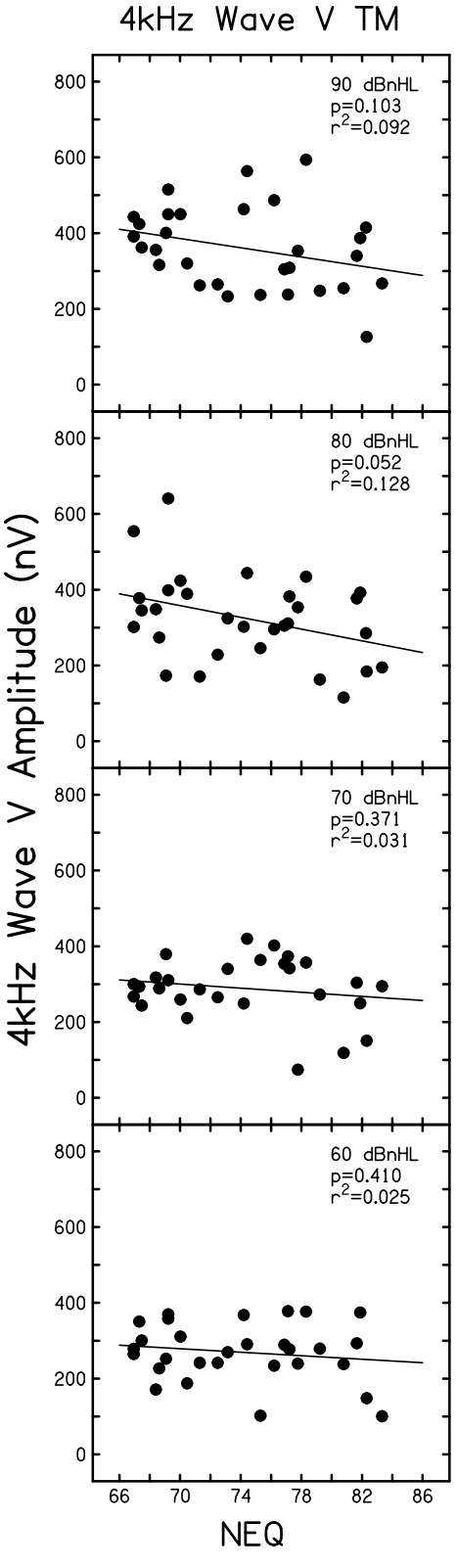

Figure 16: Supra-threshold ABR wave V amplitude recorded with a tympanic membrane electrode in response to 4 kHz tone bursts presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=28) and 60 (bottom panel; n=29) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

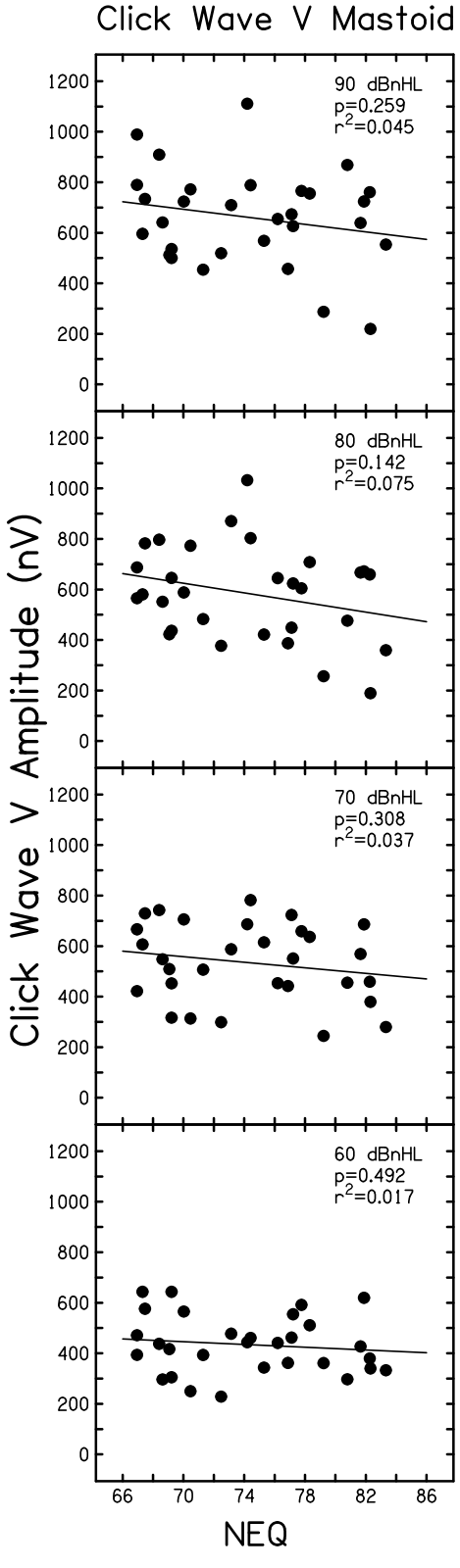

Figure 17: Supra-threshold ABR wave V amplitude recorded with a mastoid electrode in response to click stimuli presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=30) and 60 (bottom panel; n=30) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

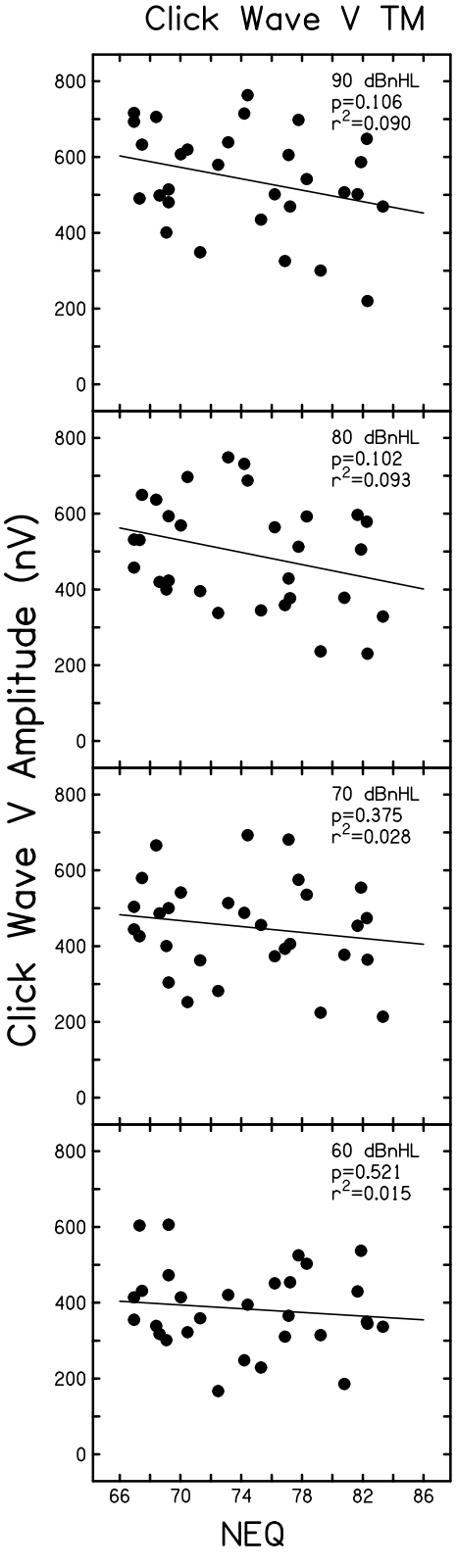

Figure 18: Supra-threshold ABR wave V amplitude recorded with a tympanic membrane electrode in response to click stimuli presented at 90 (top panel; n=30), 80 (second panel; n=30), 70 (third panel; n=30) and 60 (bottom panel; n=30) dB nHL plotted as a function of NEQ. Within each panel, symbols (filled circles) represent individual data. Linear regression analysis was completed for each panel and the resulting regression line, p-value and r^2 (coefficient of determination) are shown.

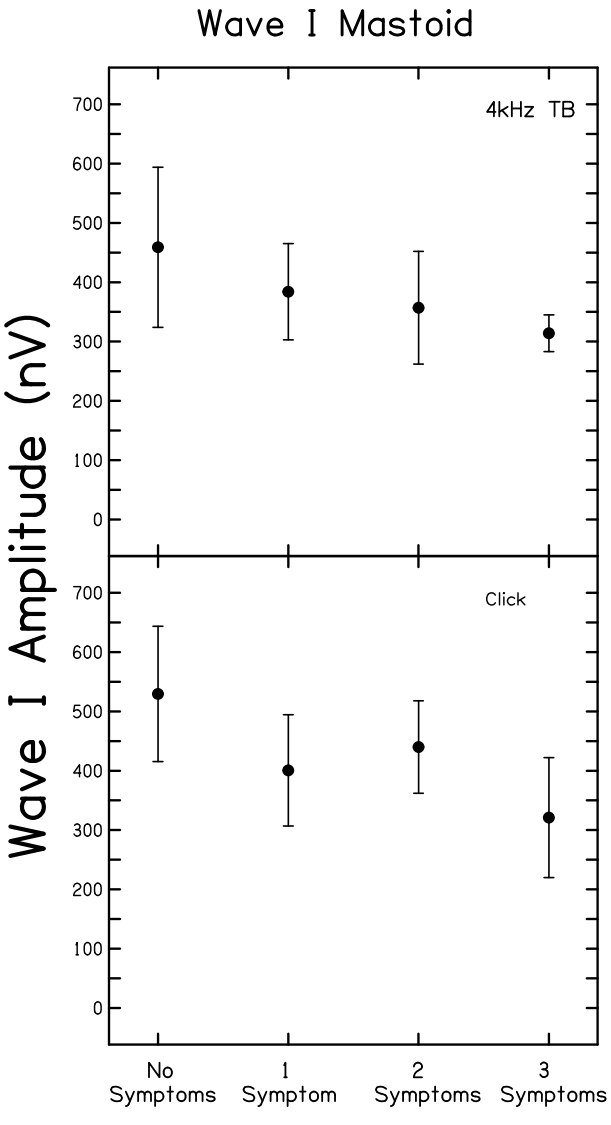

Figure 19: ABR wave I amplitude recorded with a mastoid electrode in response to 4 kHz tone bursts (top panel; n=30) and click stimuli (bottom panel; n=30) at 90 dB nHL plotted as a function of the number of accompanying auditory symptoms. Within each panel, symbols (filled circles) represent the mean amplitude and error bars represent ± 2 standard error of the mean (SEM).

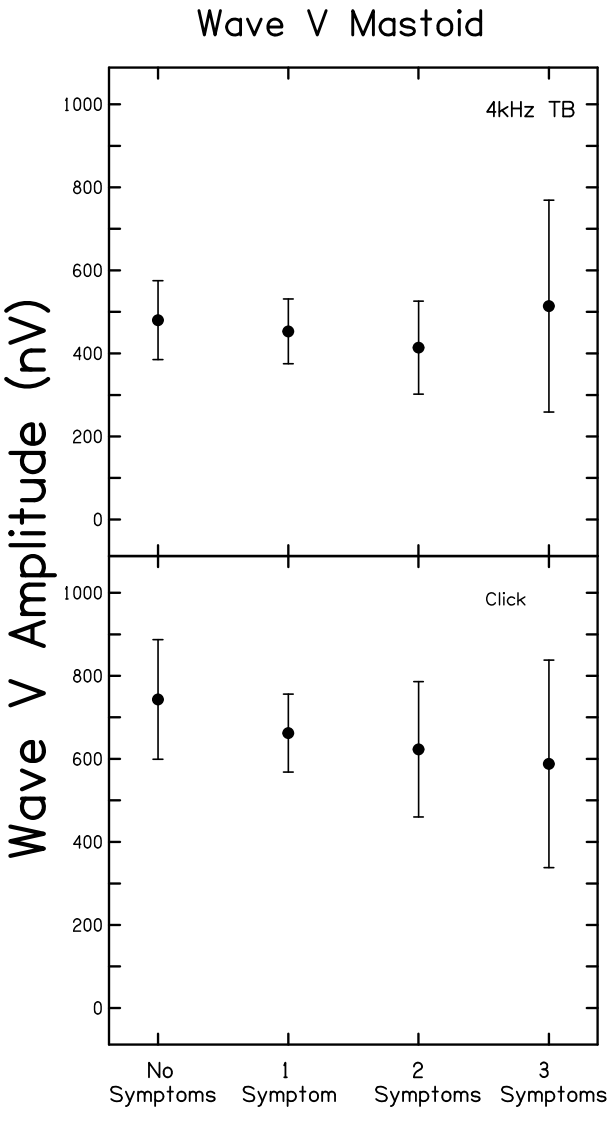

Figure 20: ABR wave V amplitude recorded with a mastoid electrode in response to 4 kHz tone bursts (top panel; n=30) and click stimuli (bottom panel; n=30) at 90 dB nHL plotted as a function of the number of accompanying auditory symptoms. Within each panel, symbols (filled circles) represent the mean amplitude and error bars represent ± 2 standard error of the mean (SEM).

Table 1: Supra-threshold DPOAE data. Results of a linear regression analysis (p-value and r^2) of DPOAE level as a function of NEQ are shown for each f_2 and L_2 recording combination.

L_2 Level (dB SPL)		f_2		
		1 kHz	2 kHz	4 kHz
80	*p-value*	0.915	0.313	0.179
	r^2	<0.000	0.036	0.064
75	*p-value*	0.701	0.804	0.227
	r^2	0.005	0.002	0.052
70	*p-value*	0.997	0.591	0.243
	r^2	<0.000	0.010	0.048
65	*p-value*	0.679	0.293	0.310
	r^2	0.006	0.039	0.037
60	*p-value*	0.698	0.408	0.267
	r^2	0.005	0.025	0.044
55	*p-value*	0.669	0.531	0.338
	r^2	0.006	0.014	0.033
50	*p-value*	0.958	0.501	0.509
	r^2	<0.000	0.016	0.016
45	*p-value*	0.997	0.835	0.596
	r^2	<0.000	0.002	0.010
40	*p-value*	0.746	0.585	0.854
	r^2	0.004	0.011	0.001
35	*p-value*	0.555	0.614	0.938
	r^2	0.013	0.009	<0.000
30	*p-value*	0.592	0.545	0.948
	r^2	0.010	0.013	<0.000
25	*p-value*	0.753	0.462	0.862
	r^2	0.004	0.019	0.001
20	*p-value*	0.691	0.152	0.532
	r^2	0.006	0.072	0.014
15	*p-value*	0.709	0.185	0.759
	r^2	0.005	0.062	0.003
10	*p-value*	0.358	0.244	0.454
	r^2	0.030	0.048	0.020
5	*p-value*	0.677	0.608	0.650
	r^2	0.006	0.010	0.007
0	*p-value*	0.850	0.995	0.984
	r^2	0.001	<0.000	<0.000

Table 2: Descriptive statistics of ABR recordings in response to 1 kHz and 4 kHz tone bursts and to click stimuli presented at 90 and 80 dB nHL. Mean values, standard deviations and sample sizes are shown for latencies (in milliseconds) and amplitudes (in nanovolts) of wave I and wave V collected with a mastoid and tympanic membrane electrode.

		ABR Recording Condition								
		1 kHz tone burst			4 kHz tone burst			Click		
Latency		Mean	SD	n	Mean	SD	n	Mean	SD	n
Wave I 90 dB nHL	TM	2.86	0.25	30	1.99	0.08	30	1.58	0.07	30
	Mastoid	2.90	0.27	27	2.00	0.09	30	1.60	0.10	30
Wave I 80 dB nHL	TM	3.15	0.26	24	2.16	0.09	30	1.64	0.08	30
	Mastoid	3.16	0.27	22	2.16	0.10	30	1.65	0.09	30
Wave V 90 dB nHL	TM	6.58	0.22	30	5.95	0.22	30	5.49	0.17	30
	Mastoid	6.54	0.25	30	5.96	0.17	30	5.52	0.18	30
Wave V 80 dB nHL	TM	6.77	0.25	28	6.03	0.20	30	5.57	0.17	30
	Mastoid	6.74	0.23	29	6.04	0.18	30	5.59	0.17	30
		1 kHz tone burst			4 kHz tone burst			Click		
Amplitude		Mean	SD	n	Mean	SD	n	Mean	SD	n
Wave I 90 dB nHL	TM	438.72	161.40	30	816.97	334.26	30	870.29	314.56	30
	Mastoid	184.82	94.22	27	386.88	141.30	30	428.01	153.73	30
Wave I 80 dB nHL	TM	306.27	154.86	24	738.76	316.14	30	769.13	329.61	30
	Mastoid	154.42	71.82	22	367.66	134.84	30	397.29	136.77	30
Wave V 90 dB nHL	TM	426.13	134.91	30	359.07	108.59	30	540.49	135.38	30
	Mastoid	549.50	162.06	30	459.43	149.53	30	661.25	188.89	30
Wave V 80 dB nHL	TM	392.43	100.80	28	324.48	115.82	30	494.75	142.04	30
	Mastoid	528.98	129.65	29	395.39	130.58	30	583.78	187.37	30

Table 3: Supra-threshold ABR wave I amplitude. Results of a linear regression analysis (p-value and r^2) of wave I amplitude as a function of NEQ are shown for each ABR recording condition. An asterisk (*) indicates the presence of a statistically significant relationship at the α=0.05 level.

		ABR Recording Condition					
		1 kHz		4 kHz		Click	
Stimulus Level		TM	Mastoid	TM	Mastoid	TM	Mastoid
90 dB nHL	*p-value*	0.564	0.235	0.056	0.013*	0.270	0.011*
	r^2	0.012	0.056	0.124	0.202	0.076	0.207
	n	30	27	30	30	30	30
80 dB nHL	*p-value*	0.150	0.020*	0.077	0.023*	0.057	0.006*
	r^2	0.092	0.243	0.107	0.171	0.123	0.240
	n	24	22	30	30	30	30
70 dB nHL	*p-value*			0.153	0.040*	0.056	0.022*
	r^2	DNT	DNT	0.074	0.152	0.125	0.174
	n			29	28	30	30
60 dB nHL	*p-value*			0.702	0.421	0.205	0.072
	r^2	DNT	DNT	0.006	0.033	0.057	0.124
	n			28	22	30	27
50 dB nHL	*p-value*			0.195		0.113	0.925
	r^2	DNT	DNT	0.083		0.094	0.001
	n			22	14	28	18
40 dB nHL	*p-value*					0.931	
	r^2	DNT	DNT			<0.000	
	n			11	5	22	12
30 dB nHL	*p-value*						
	r^2	DNT	DNT				
	n			2	3	12	6
20 dB nHL	*p-value*						
	r^2	DNT	DNT				
	n			2	1	5	2
10 dB nHL	*p-value*						
	r^2	DNT	DNT				
	n			1	0	1	1
0 dB nHL	*p-value*						
	r^2	DNT	DNT				
	n			0	0	0	0

Table 4: Supra-threshold ABR wave V amplitude. Results of a linear regression analysis (p-value and r^2) of wave V amplitude as a function of NEQ are shown for each ABR recording condition. An asterisk (*) indicates the presence of a statistically significant relationship at the α=0.05 level.

		ABR Recording Condition					
		1 kHz		4 kHz		Click	
Stimulus Level		TM	Mastoid	TM	Mastoid	TM	Mastoid
90 dB nHL	*p-value*	0.605	0.550	0.103	0.359	0.106	0.259
	r^2	0.010	0.013	0.092	0.030	0.090	0.045
	n	30	30	30	30	30	30
80 dB nHL	*p-value*	0.610	0.713	0.052	0.244	0.102	0.142
	r^2	0.010	0.005	0.128	0.048	0.093	0.075
	n	28	29	30	30	30	30
70 dB nHL	*p-value*			0.371	0.875	0.375	0.308
	r^2	DNT	DNT	0.031	0.001	0.028	0.037
	n			28	29	30	30
60 dB nHL	*p-value*			0.410	0.846	0.521	0.492
	r^2	DNT	DNT	0.025	0.001	0.015	0.017
	n			29	29	30	30
50 dB nHL	*p-value*			0.046*	0.476	0.738	0.958
	r^2	DNT	DNT	0.156	0.020	0.004	<0.000
	n			26	27	30	30
40 dB nHL	*p-value*			0.701	0.912	0.517	0.873
	r^2	DNT	DNT	0.008	0.001	0.016	0.001
	n			22	22	29	29
30 dB nHL	*p-value*			0.897	0.250	0.518	0.659
	r^2	DNT	DNT	0.001	0.082	0.016	0.007
	n			16	18	29	29
20 dB nHL	*p-value*					0.311	0.348
	r^2	DNT	DNT			0.038	0.034
	n			11	12	29	28
10 dB nHL	*p-value*					0.048*	0.048*
	r^2	DNT	DNT			0.191	0.181
	n			7	10	21	22
0 dB nHL	*p-value*						
	r^2	DNT	DNT				
	n			0	1	7	8

Table 5: Influence of behavioral threshold on supra-threshold ABR amplitude. Results of stepwise multiple linear regression analyses for the ten recording conditions where a statistically significant relationship existed between ABR supra-threshold amplitude and noise exposure background. At each recording condition, a p-value is reported for the NEQ and the behavioral threshold (BT). An asterisk (*) indicates the presence of a statistically significant relationship at the α=0.05 level. BT for click stimuli was defined as the BT average from 2 to 4 kHz.

				ABR Recording Condition		
	Stimulus Level	Electrode	Variable	1 kHz TB	4 kHz TB	Click
Wave I	90 dB nHL	Mastoid	NEQ	DNT	0.013*	0.011*
			BT		0.810	0.900
	80 dB nHL	Mastoid	NEQ	0.017*	0.023*	0.006*
			BT	0.146	0.630	0.662
	70 dB nHL	Mastoid	NEQ	DNT	0.040*	0.022*
			BT		0.784	0.764
Wave V	50 dB nHL	TM	NEQ	DNT	0.155	DNT
			BT		0.029*	
	10 dB nHL	TM	NEQ	DNT	DNT	0.048*
			BT			0.958
	10 dB nHL	Mastoid	NEQ	DNT	DNT	0.048*
			BT			0.864

Table 6: Coefficient of variation (CV) for ABR amplitude. CV is defined as 100 x [Standard Deviation/Mean].

			Coefficient of Variation (%)		
	Stimulus Level	Electrode	1 kHz TB	4 kHz TB	Click
Wave I	90 dB nHL	TM	36.79	40.91	36.14
		Mastoid	50.98	36.52	35.92
	80 dB nHL	TM	50.56	42.79	42.85
		Mastoid	46.51	36.68	34.43
Wave V	90 dB nHL	TM	31.66	36.68	25.05
		Mastoid	29.49	30.24	28.57
	80 dB nHL	TM	25.69	35.69	28.71
		Mastoid	24.51	33.03	32.10