# Effects of Age and Noise Exposure History on Auditory Nerve Response Amplitudes: A Systematic Review, Study, and Meta-Analysis

James W. Dias
Carolyn M. McClaskey
April P. Alvey
Abigail Lawson
Lois J. Matthews
Judy R. Dubno
Kelly C. Harris

Medical University of South Carolina
Department of Otolaryngology – Head and Neck Surgery

**Corresponding Author:**
James W. Dias
Medical University of South Carolina
Department of Otolaryngology
135 Rutledge Avenue, MSC 550
Charleston, SC 29425-5500
Email: diasj@musc.edu

**Funding Sources**
This work was supported (in part) by grants from the National Institute on Deafness and Other Communication Disorders (NIDCD) (P50 DC000422, R01 DC017619, R01 DC021064, R21 DC020559, and T32 DC014435) and the Hearing Health Foundation. The project also received support from the South Carolina Clinical and Translational Research (SCTR) Institute with an academic home at the Medical University of South Carolina, National Institute of Health/National Center for Research Resources (NIH/NCRR) Grant number UL1 TR001450. This investigation was conducted in a facility constructed with support from Research Facilities Improvement Program Grant Number C06 RR14516 from the National Center for Research Resources, NIH.

The authors declare no competing financial interests.

Abstract

Auditory nerve (AN) function has been hypothesized to deteriorate with age and noise exposure. Here, we perform a systematic review of published studies and find that the evidence for age-related deficits in AN function is largely consistent across the literature, but there are inconsistent findings among studies of noise exposure history. Further, evidence from animal studies suggests that the greatest deficits in AN response amplitudes are found in noise-exposed aged mice, but a test of the interaction between effects of age and noise exposure on AN function has not been conducted in humans. We report a study of our own examining differences in the response amplitude of the compound action potential N1 (CAP N1) between younger and older adults with and without a self-reported history of noise exposure in a large sample of human participants (63 younger adults 18-30 years of age, 103 older adults 50-86 years of age). CAP N1 response amplitudes were smaller in older than younger adults. Noise exposure history did not appear to predict CAP N1 response amplitudes, nor did the effect of noise exposure history interact with age. We then incorporated our results into two meta-analyses of published studies of age and noise exposure history effects on AN response amplitudes in neurotypical human samples. The meta-analyses found that age effects across studies are robust (r=-0.407), but noise-exposure effects are weak (r=-0.138). We conclude that noise-exposure effects may be highly variable depending on sample characteristics, study design, and statistical approach, and researchers should be cautious when interpreting results. The underlying pathology of age-related and noise-induced changes in AN function are difficult to determine in living humans,

creating a need for longitudinal studies of changes in AN function across the lifespan and histological examination of the AN from temporal bones collected post-mortem.

Key Words: ABR; aging; auditory nerve; CAP; cochlear synaptopathy; hidden hearing loss; meta-analysis; noise exposure; systematic review

## Introduction

The auditory nerve (AN) is the only pathway connecting the inner ear to the central auditory system. It encodes acoustic information as differences in spike timing and transmission rates among neural fibers. Results of studies of AN pathology from animals and human temporal bones suggest that the AN is vulnerable to aging and noise exposure, more so than other cochlear structures (Fernandez et al., 2015; Kujawa & Liberman, 2015; Makary et al., 2011; Wu et al., 2019). The audiogram is the primary clinical tool for assessing hearing loss, but AN pathology can occur with or without measurable changes in pure-tone thresholds. For example, in chinchilla, only mild pure-tone threshold shifts were observed following carboplatin-induced 80% loss of inner hair cells and synaptic connections to AN fibers (Lobarinas et al., 2013). The resulting loss of AN fibers would result in an under-sampling of the auditory signal (Lopez-Poveda & Barrios, 2013). While this under-sampling may not affect the detection of pure tones, it may disrupt the encoding of complex information, like speech. This can be especially problematic in noisy listening environments, where higher resolution of neural encoding is needed to preserve salient information within the acoustic signal. As such, loss or dysfunction of AN fibers is hypothesized to result in functional deficits that negatively impact speech-in-noise perception (Hickox & Liberman, 2014; Plack et al., 2014; Schaette & McAlpine, 2011).

Because pure-tone thresholds may not be a sensitive indicator of AN fiber loss, there is a need for clinically appropriate and non-invasive measures that are reliable indicators of AN function. In this pursuit, several non-invasive physiologic measures have been developed with the goal of assessing AN function in humans (for a review,

see Harris & Bao, 2022). The sole non-invasive technique for directly assessing AN function in humans remains electroencephalography (EEG), specifically the measurement of Wave I of the auditory brainstem response (ABR WI) or the analogous N1 of the compound action potential (CAP N1). ABR WI and CAP N1 are potentials evoked by a brief auditory stimulus – measured from surface electrodes (ABR) or from the tympanic membrane (CAP) – and are thought to represent the action potentials at the distal AN (for a review, see Gibson, 2017). The capacity for these electrophysiologic measures to assess AN function is appealing because the methods for eliciting and measuring ABR WI and CAP N1 are already available in clinical settings. The accessibility of these techniques has contributed to a dramatic increase in the number of research studies employing EEG to assess AN function. This research has largely focused on two factors hypothesized to negatively impact AN function: 1) aging – age-related neurophysiologic changes in the AN, including synapse loss, AN fiber loss, and changes in AN myelin structure, can result in poorer AN function (e.g., Harris et al., 2021; Heeringa & Köppl, 2019; Kaewsiri et al., 2015; Konrad-Martin et al., 2012) – and 2) noise exposure – the noise-induced loss of cochlear synapses (cochlear synaptopathy) is thought to result in poor AN function in individuals with normal pure-tone thresholds, often referred to as ‘hidden hearing loss’ (e.g., Kim & Han, 2023; Plack et al., 2016).

AN function is largely comparable across mammalian species, with similar responses in rodents and humans (Burkard & Sims, 2001; Rumschlag et al., 2022). In rodent models, it is well-established that a loss of AN synapses and axons attributed to age or noise exposure can result in a significant decrease in ABR WI response

amplitude (Kujawa & Liberman, 2015). Attempts to translate these contributing factors to specific aspects of AN function in humans, however, has generated mixed results (for reviews, see Bramhall et al., 2019; Le Prell, 2019; Ripley et al., 2022). Effects of age on AN response amplitudes are fairly consistent, with older adults exhibiting decreased ABR WI and CAP N1 amplitudes relative to younger adults (Burkard & Sims, 2001; Harris et al., 2021; Johannesen et al., 2019; but see Prendergast et al., 2019). Consistent with these electrophysiologic results from older humans, there is strong histological evidence from human temporal bones showing that aging contributes to AN pathology, specifically structural deficits in the AN, including a loss of cochlear synapses and AN fibers, as well as defects in the myelin structure of the remaining AN fibers (Makary et al., 2011; Nayagam et al., 2011; Wu et al., 2019; Xing et al., 2012). In contrast, associations between AN response amplitudes and a history of noise exposure (typically derived from self-report assessments) are mixed, with several studies reporting reduced ABR WI and CAP N1 response amplitude in individuals with a history of noise exposure (e.g., Bramhall et al., 2018a; Bramhall et al., 2017; Grose et al., 2017; Ridley et al., 2018; Skoe & Tufts, 2018), and others reporting a lack of significant associations (Fulbright et al., 2017; Grinn et al., 2017; Guest et al., 2019; Prendergast et al., 2019; Spankovich et al., 2017). Several factors have been identified that may contribute to discrepancies across these studies of noise exposure history, including the age and sex of participants and the methods used to assess noise exposure history and AN function (Le Prell, 2019). This is important because both increased age and noise exposure history are hypothesized to contribute to changes in ABR WI and CAP N1 response amplitudes. Most studies of noise-induced AN dysfunction have included

participants in their 20s and 30s, few studies have included middle-aged and older adults, and among those, few test or control for age effects, and none test for interactions between the effects of age and noise exposure (Johannesen et al., 2019; Megha et al., 2021; Prendergast et al., 2019). A study of the effects of age and noise exposure history on AN response amplitudes within a single large sample can help disentangle how they each independently affect AN function and how they may interact to exacerbate AN dysfunction in older adults with a history of noise exposure.

**Current Investigation**

To clarify the independent effects of age and noise exposure on electrophysiological measures of AN function and determine how these two factors may interact, we tested the degree to which age and self-reported noise exposure history predict CAP N1 amplitudes in a large sample of younger (N=63) and older (N=103) adults. Results provide the first systematic examination of the interaction between age and noise exposure history on AN response amplitudes in human subjects. We then integrated the results of our study with those from prior studies in two meta-analyses to determine the average effects of age and noise exposure history on ABR WI and CAP N1 response amplitudes.

## Effects of Age and Noise Exposure History on CAP N1 response amplitudes

### Methods

**Participants.** CAPs were collected as part of several ongoing studies. Subsets of these data have been published elsewhere (Harris et al., 2021; McClaskey et al., 2018; Rumschlag et al., 2022), though associations of age and noise exposure history (described below) have not yet been reported in this larger sample of participants. CAPs

were recorded in the right ears of 63 younger (18 to 30 years of age, M=23.873, SE=0.403, 46 female) and 103 older (50 to 86 years of age, M=66.476, SE=0.709, 70 female) adults. Younger participants were graduate and undergraduate student volunteers from the Medical University of South Carolina and the College of Charleston in Charleston, SC. Older participants consisted of volunteers from the greater Charleston, SC area. Puretone audiometric thresholds for these participants are reported in **Figure 1**. The group of younger adults had audiometric thresholds ≤25 dB HL through 8 kHz. The group of older adults had audiometric thresholds that ranged from normal to mild-to-moderate sensorineural hearing loss, with more hearing loss in the higher test frequencies. Self-reported noise exposure history was recorded in 58 younger and 85 older adults (Dubno et al., 2013). This study was approved by the Institutional Review Board of the Medical University of South Carolina and all participants provided written informed consent prior to participation.

**Compound Action Potentials.** CAPs were elicited by 100 microsecond alternating polarity rectangular pulses (clicks), presented at a rate of 11.1/s through an ER3C Insert Earphone (Etymotic Technologies) placed in the right ear. Stimuli and stimulus triggers were generated and controlled by RPvdsEx software from Tucker Davis Technologies (TDT). Stimuli were presented at 110 dB pSPL. CAPs were recorded from a tympanic membrane electrode (Sanibel) placed in the right ear, an inverting electrode placed on the contralateral (left) mastoid, and a low forehead grounding electrode. Auditory brainstem responses (ABRs) were simultaneously recorded for reference in identifying WI/N1 using a high forehead active electrode, an inverting mastoid electrode (on the right mastoid), and a low forehead grounding

electrode (not shown). Responses were recorded in two blocks of 1100 trials (550 of each polarity) at a sampling rate of 20 kHz using a custom TDT headstage connected to the bipolar channels of a Neuroscan SynAmpsRT amplifier in AC mode with 2010x gain (Compumedics). Testing was done in an acoustically and electrically shielded booth. Participants reclined in a chair and were encouraged to rest quietly or sleep during recording.

Continuous AN activity was processed offline in MATLAB (MathWorks) using the EEGlab (Delorme & Makeig, 2004) and ERPLab (Lopez-Calderon & Luck, 2014) toolboxes. Continuous EEG signals were bandpass filtered between 0.150 and 3 kHz. The stimulus triggers sent by TDT RPvdsEx were shifted to account for the 1 ms delay introduced by the earphones and the 0.6 ms delay of the TDT digital-to-analog converter. The filtered data were epoched from -2 to 10 ms around stimulus onset and baseline corrected to a -2 ms to 0 ms prestimulus baseline (McClaskey et al., 2018). Individual trials were rejected if peak deflections exceeded 45 μV using an automatic artifact detection algorithm and visual inspection. Epoched responses for the remaining trials were averaged. N1 peak selection was performed by two independent and experienced reviewers and assessed for repeatability across the two runs. Although only the 110 dB pSPL condition is reported here, CAP responses were collected from 70 to 110 dB pSPL to aid peak detection (e.g., Harris et al., 2022). The N1 peak-to-baseline amplitude and peak latency were measured in ERPlab using custom MATLAB functions.

**Noise Exposure History Questionnaire.** Noise exposure history was assessed using a seven-item noise history questionnaire on occupational and non-occupational

noise exposure (**Supplementary Material**) (for details, see Dubno et al., 2013). Participants responded “yes” or “no” to whether they had been exposed to the following types of noise: occupational (including military), firearms, music, power tools, farm equipment, sudden loud noises, and other noises. Participants were identified as having a positive noise history if they reported exposure to at least one of the seven categories. Of the 58 younger and 85 older participants who completed the noise history questionnaire, 36 younger (25 female) and 51 older (26 female) reported a positive noise history. Evident from the distribution of responses were sex-related differences in noise exposure, especially for older participants. The proportion of older males who reported a positive noise exposure history (83%) was higher than the proportion of older females who reported a positive noise exposure history (47%).

**Analytical Approach.** We used linear regression models (LM) to test whether CAP N1 amplitudes were predicted by age group (younger or older) and noise exposure history (positive or negative). Participant sex was incorporated into our statistical analyses to evaluate whether sex-differences in AN response amplitudes and noise exposure history could account for variability in CAP N1 amplitudes explained by age and noise exposure history (Dewey et al., 2020; Fulbright et al., 2017; Grinn & Le Prell, 2022; e.g., Johannesen et al., 2019). Average pure-tone thresholds from 0.5 to 4 kHz were similarly incorporated into our statistical analyses to evaluate whether inter-subject variability in pure-tone thresholds across frequencies could account for variability in CAP N1 amplitudes explained by age and noise exposure history. Statistical analyses were performed in R (R Core Team, 2023).

## Results

Two LM models tested the degree to which CAP N1 response amplitudes are predicted by age and noise exposure history. Model 1 includes all participants and finds that CAP N1 response amplitudes are smaller (more positive) in older adults, compared to younger adults ($B=0.065$, $SE_B=0.030$, $\beta=0.339$, $SE_\beta=0.158$, $t(164)=2.140$, $p=0.034$). Adding participant sex and average audiometric threshold to Model 1 did not improve model fit, $\chi^2(2)=5.008$, $p=0.082$. Model 2 includes the subset of participants with noise history data and found that noise exposure was not a predictor of CAP N1 response amplitudes ($B=0.042$, $SE_B=0.030$, $\beta=0.116$, $SE_\beta=0.082$, $t(140)=1.402$, $p=0.163$), though age was still a significant predictor ($B=0.069$, $SE_B=0.030$, $\beta=0.392$, $SE_\beta=0.167$, $t(140)=2.341$, $p=0.021$) (**Figure 2**). Adding participant sex and average audiometric threshold to Model 2 did not improve model fit, $\chi^2(2)=3.921$, $p=0.141$. Noise exposure did not interact with age, nor did the inclusion of the interaction term in Model 2 improve model fit, $\chi^2(1)=0.110$, $p=0.740$.

**Summary**

The results suggest that CAP N1 response amplitudes were smaller in older than younger adults. In contrast, CAP N1 response amplitudes were not predicted by self-reported history of noise exposure after accounting for participant age. Importantly, the relationship between noise exposure history and CAP N1 response amplitudes did not differ between younger and older participants. There has been some evidence suggesting that not all types of noise exposure affect the AN equally. Impulse/impact noise, such as from firearms, has been found to be negatively associated with AN response amplitudes (e.g., Grinn & Le Prell, 2022; Pinsonnault-Skvarenina et al., 2022b). When our data were reanalyzed with noise exposure exclusively restricted to a

history of exposure to firearms, the pattern of relationships reported above did not change. We note, however, that our participants who reported a positive history of firearms exposure also largely reported using hearing protection.

Audibility is another factor to consider in studies of AN function. We controlled for effects of audiometric thresholds statistically by incorporating the average pure-tone threshold from 0.5 to 4 kHz as a covariate in our analyses. We found that pure-tone thresholds were not significant predictors of CAP N1 response amplitudes after accounting for age group. The pattern of results did not change when instead controlling for higher frequency thresholds (2 to 8 kHz), where more hearing loss was observed in our older participants. Alternatively, some studies control for audibility by restricting their sample to participants with normal hearing below 4 kHz, which may control for other pathologies that may affect AN function. Many studies that attribute differences in AN response amplitudes between noise-exposed and non-noise-exposed groups to noise-induced cochlear synaptopathy and “hidden hearing loss” have restricted their samples to those with normal hearing in this way (e.g., Bramhall et al., 2017; Prendergast et al., 2017a; Stamper & Johnson, 2015). To replicate these methods and more thoroughly control for cochlear pathologies that may underlie hearing loss and affect AN function, we reanalyzed our data in only those younger and older participants with pure-tone thresholds ≤25 dB HL at 0.5, 1, 2, 3, and 4 kHz. The pattern of relationships reported above did not change when our analyses included CAP N1 response amplitudes from only those participants, suggesting that statistical controls for audiometric thresholds were sufficient to account for the effects of audibility and that our results are not driven by additional pathologies that are comorbid with elevated audiometric thresholds.

Failing to find support for a hypothesized relationship between noise exposure history and AN function in our large cohort of participants is consistent with many past studies (Fulbright et al., 2017; Grinn et al., 2017; Guest et al., 2019; Prendergast et al., 2019; Spankovich et al., 2017). Our results suggest that studies finding positive noise history to negatively impact AN function in humans may be explained by uncontrolled factors, such as methodology and sample demographics, or they may capture a relationship that is small across the broader population.

## AN Function as Predicted by Age and Noise-Exposure History: Meta-Analyses

To further examine the relationship between AN function and age and between AN function and noise exposure, we performed two meta-analyses to measure these relationships across the broader literature.

### Methods

**Studies.** We first conducted a PubMed advanced search of key terms to find studies of ABR WI and CAP N1 in neurotypical adult human samples. For ABR studies, the advanced search included the terms “auditory brainstem responses” and “wave I”, excluded the terms “infants”, “children”, “schizophrenia”, “ADHD”, and “autism”, and were filtered to include only human studies. For CAP studies, the advanced search included the terms “compound action potential” and “auditory nerve”, excluded the term “eCAP”, and were filtered to include only human studies. The large number of studies returned by these search queries (1,278 ABR, 223 CAP) were checked by three experts (authors Dias, Harris, and McClaskey) to confirm they matched our search criteria and further filtered to include only those studies that measured ABR WI or CAP N1 amplitude and explicitly tested and reported the relationship between ABR WI or CAP

N1 amplitude and age or noise exposure. Of the studies that met these criteria, a citation search was performed in PubMed and Google Scholar for the most cited studies (e.g., Prendergast et al., 2017a; Stamper & Johnson, 2015) to find any other studies that may have met our inclusion criteria but were otherwise missed by the PubMed search. These procedures were completed on March 5, 2024, and resulted in 20 studies (14 different study sites) of age and ABR-WI/CAP-N1 amplitude and 29 studies (20 different study sites) of noise exposure and ABR-WI/CAP-N1 amplitude. We then incorporated our own CAP data reported in the previous section (listed as “Dias et al., 2024”) into this pool of studies for our meta-analyses. The final number of studies included in our meta-analysis of age and ABR-WI/CAP-N1 amplitude was 21 (14 different study sites) and the final number of studies included in our meta-analysis of noise exposure and ABR-WI/CAP-N1 amplitude was 30 (21 different study sites). When collecting studies for our systematic review and meta-analysis, we used conventional best practices as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Page et al., 2021a; Page et al., 2021b) and others (Cumming, 2012; Rosenthal, 1991).

**Analytical Approach.** Separate meta-analyses were performed to measure the average relationship between ABR-WI/CAP-N1 amplitude and age, and the relationship between ABR-WI/CAP-N1 amplitude and noise exposure history. For each study included in these meta-analyses, we computed the effect size ($r_{\text{Effect Size}}$) for each relationship between response amplitude and age or between response amplitude and noise exposure history from the descriptive and inferential statistics reported in each study. Studies often reported these relationships for multiple different conditions, which

can varying by participant characteristics (sex, age, and noise exposure), ear tested, electrode configuration (surface electrode configurations for ABRs and tympanic-membrane electrode configurations for CAPs), and stimulus characteristics (stimulus type, duration, intensity, and presentation rate). As such, we often extracted multiple values from within individual studies. All r-values were transformed into Z-scores using Fisher's transformation. For studies of ABR-WI/CAP-N1 response amplitude and age, if response amplitude decreased as age increased, then the Z-score was coded as negative and otherwise coded as positive. For studies of ABR-WI/CAP-N1 response amplitude and noise exposure history, if response amplitude decreased with more noise exposure history, then the Z-score of the relationships was coded as negative and otherwise coded as positive. These Z-scores were used as the outcome variables of our meta-analyses (e.g., Hansen et al., 2022; Rosenthal, 1991; Rosnow et al., 2000).

To account for the nestedness of the multiple relationships reported in many individual studies and to account for the nestedness of many studies that were conducted at the same institution (typically by the same research group), linear mixed effects regression (LMER) was used to conduct our meta-analyses. Accounting for the nestedness of studies within study sites is important because investigators often report results from overlapping samples to test different hypotheses in different studies. Different LMER models were used to perform separate meta-analyses for studies of ABR-WI/CAP-N1 response amplitude and age and for studies of ABR-WI/CAP-N1 response amplitude and noise exposure history. These LMER models included the Z transforms of relationship effect sizes as the outcome variable and study and study site as random factors (grouping variables). Each study was weighted by their reported

sample size. Weighting studies by sample size is important when calculating the average effect across a pool of studies (for a review, see Cumming, 2012), but we recognize that the sample sizes of our CAP study is disproportionate to most other studies in our meta-analyses. To ensure that the inclusion of our CAP study did not significantly bias the average effect calculated across studies, we performed a Z-test of the difference in effects between meta-analyses with our CAP study and without:

$$Z = \frac{B_1 - B_2}{\sqrt{{SE_{B_1}}^2 + {SE_{B_2}}^2}}$$

where $B_1$ is the coefficient (average Z-transformed effect across studies) for the meta-analysis with all studies and $B_2$ is the coefficient for the meta-analysis with all studies except our current CAP study. $SE_{B_1}$ and $SE_{B_2}$ are the standard errors for the respective coefficients (Clogg et al., 1995; Cohen et al., 2003; Dias et al., 2021; Dias et al., 2022; McClaskey et al., 2018; Paternoster et al., 1998).

We also considered whether electrode configuration (surface or TM) or stimulus characteristics (stimulus, stimulus duration, stimulus intensity, and presentation rate) modulated the relationships of interest in our meta-analyses, but none were found to be significant predictors ($p>0.4$) and their inclusion in the LMER models did not improve model fit ($p>0.2$).

Meta-analyses were performed using the *meta* (Balduzzi et al., 2019) and *metafor* (Viechtbauer & Cheung, 2010) packages for *R* (Harrer et al., 2021; R Core Team, 2023).

**Results**

The meta-analysis of the relationship between ABR-WI/CAP-N1 response amplitude and age found that the average effect across studies is significant (B=-0.432, SE=0.127, t=-3.393, p=0.002). The forest plot in **Figure 3** illustrates the Fisher Z-transforms of the relationships reported in each study and the average Z-transformed relationship between ABR-WI/CAP-N1 amplitude and age across studies, which when reverse transformed equates to an average effect of r=-0.407, 95% CI [-0.693, -0.171]. Response amplitudes of ABR WI and CAP N1 are smaller in older than in younger adults. The average effect did not significantly change when removing our current CAP study from the meta-analysis, Z=0.092, p=0.464.

The meta-analysis of the relationship between ABR-WI/CAP-N1 response amplitude and noise exposure history found that the average relationship across studies is significant (B=-0.139, SE=0.040, t=-3.496, p<0.001). The forest plot in **Figure 4** illustrates the Fisher Z-transforms of the relationships reported in each study and the average Z-transformed relationship between ABR-WI/CAP-N1 response amplitude and noise exposure history across studies, which when reverse transformed equates to an average effect of r=-0.138, 95% CI [-0.218, -0.061]. ABR WI and CAP N1 response amplitudes are smaller in individuals with a positive noise exposure history. The average effect did not change when removing our current CAP study from the meta-analysis, Z=0.017, p=0.493.

**Summary**

The meta-analyses found that both age and noise exposure history are predictors of AN response amplitudes across studies. ABR-WI/CAP-N1 response amplitudes decline with age and with noise exposure history. Importantly, the average

effects of age and noise exposure history calculated across studies were not biased by the inclusion of our larger CAP study. The small average effect size of the relationship between noise exposure history and AN response amplitude is not surprising, given the number of individual studies that failed to find support for a relationship between noise exposure history and AN response amplitudes, including our own. It should be considered that the meta-analyses included only published studies, subject to publication bias, and consideration should be given to “file-drawer” studies that never made it to publication (Rosenthal, 1979; Rosenthal, 1991).

## Discussion

The goal of the systematic review, study, and meta-analyses reported here was to determine the extent to which age and noise exposure history impacted AN function. We focused on the most often reported aspect of AN function: suprathreshold ABR WI and CAP N1 response amplitudes. We first examined the extent to which age and noise exposure history predict CAP N1 response amplitude in a large cohort of younger and older adults. Our results suggest that CAP N1 response amplitudes decline with age, but noise exposure history was unrelated. Although prior animal studies have suggested an interaction between noise exposure and age, with a greater decrease in AN function in aged animals with prior noise exposure than those without noise exposure (Fernandez et al., 2015), the interaction between age and noise exposure history was not a significant factor in our CAP study. The meta-analyses found that ABR WI/CAP N1 response amplitudes are smaller in older than younger adults and in adults with a positive rather than negative noise exposure history. While the relationship between age and AN function is fairly conclusive, with a robust effect across studies (r=-0.407, **Figure**

**3**), the association between noise exposure history and AN response amplitudes is weak (r=-0.138, **Figure 4**), requiring further discussion of how to interpret effects of noise exposure on AN function.

**Effects of Age on AN Response Amplitudes**

Significant effects of age on AN response amplitudes were observed in our CAP study and in our meta-analysis, adding to a growing literature suggesting that AN function declines with age. Findings from animal models suggest that aging accelerates AN damage associated with environmental exposures (Fernandez et al., 2015). Despite these findings in animals, few studies have tested both the effects of age and noise exposure on AN response amplitudes in humans (Johannesen et al., 2019; Megha et al., 2021; Prendergast et al., 2019). Unfortunately, these studies did not include participants over the ages of 60 (Prendergast et al., 2019), 65 (Megha et al., 2021), and 68 (Johannesen et al., 2019). The results are also conflicting between studies, with one study finding an effect of both age and noise exposure history (Megha et al., 2021), another finding no effect of either age or noise exposure (Prendergast et al., 2019), and the last study finding an effect of age, but not noise exposure (similar to our own CAP study) (Johannesen et al., 2019). Critically, none of these studies examined how an interaction between age and noise exposure history may affect AN response amplitudes. In our CAP study, we did not find a significant interaction between age and noise exposure history. Even though we found that CAP N1 response amplitudes were smaller in older than younger adults, a positive noise exposure history did not exacerbate age-related deficits in AN function.

**Effects of Noise Exposure History on AN Response Amplitudes**

One goal of the present study was to resolve the often-conflicting reports regarding the effects of noise exposure history on the AN (for reviews, see Bramhall et al., 2019; Le Prell, 2019; Ripley et al., 2022). Evident across the literature are many different methods for eliciting and recording responses from the AN (**Figure 4**), which can contribute to the variability in results seen among studies. Nevertheless, the meta-analysis did not find evidence suggesting that the relationship between noise exposure and AN response amplitudes reported across the literature varied by the methods used to elicit (stimulus, duration, intensity, and presentation rate) or record (surface electrodes for ABRs and TM electrodes for CAPs) AN responses.

It is important to consider not just the methods for eliciting and recording AN responses, but also to consider the composition of the study sample. Sex differences in self-reported noise exposure history and AN response amplitudes have been reported in other studies, with males more likely to report a positive noise exposure history and exhibit smaller AN response amplitudes than females (Dewey et al., 2020; Fulbright et al., 2017; Grinn & Le Prell, 2022; e.g., Johannesen et al., 2019). Previous studies of noise exposure history and AN function that have investigated and controlled for sex differences in the relationship between noise exposure and AN response amplitudes have failed to identify a significant relationship between noise exposure history and AN function in either males or females (Dewey et al., 2020; Fulbright et al., 2017; Grinn & Le Prell, 2022; Grinn et al., 2017; Washnik et al., 2023). It is possible that the negative relationship between noise exposure history and AN function reported in some studies that do not control for participant sex can be explained by a sample comprised of more males with higher rates of positive noise exposure histories and smaller ABR WI/CAP

N1 amplitudes than females. In other words, relationships between noise exposure history and AN function could potentially represent sex differences in both variables. In the future, researchers should control for sex differences in noise history exposure and AN function when studying the relationship between noise exposure history and AN function.

Methods for assessing noise exposure must also be considered. In animals, noise exposure can be controlled with a high degree of precision. In humans, however, researchers have largely used self-report measures of noise exposure history, relying on participants' recollection and subjective assessment of their own noise exposure. While some have employed more rigorous self-report methods, such as detailed structured interviews, to try to better capture the type and amount of noise participants are exposed to, there is little evidence to suggest that these more rigorous approaches result in measures of noise exposure that are more accurate or more sensitive to hearing outcomes or AN function (e.g., Couth et al., 2020; De Poortere et al., 2023; Dewey et al., 2020; Pinsonnault-Skvarenina et al., 2022b). Using more objective measures of prolonged noise exposure – evaluated using a combination of questionnaires and body-worn dosimeters to capture the noise levels and exposure times of participants working in factory jobs – has also failed to find a relationship between noise exposure and AN response amplitudes (Pinsonnault-Skvarenina et al., 2022a; Skoe & Tufts, 2018), though one study did find that noise exposure related to longer ABR WI latencies (Skoe & Tufts, 2018).

A final important factor contributing to the inconsistent relationship between noise exposure history and AN response amplitudes observed between studies is the small

effect size calculated across studies (**Figure 4**). Typically, small effect sizes of this kind suggest that larger samples are required to increase statistical power and overcome the probability of a type II error (false negative). We performed a simple a priori power analysis in G*Power to determine the sample size required for the average noise exposure effect size of r=-0.138 to reach 85% power for a two-tailed test at α=0.05 (Faul et al., 2009; Faul et al., 2007). The results of the power analysis suggested that a sample of 468 participants is needed to reliably capture the effect of noise exposure on AN function. (For comparison, a power analysis for the average age effect size of r=-0.407 determined that a sample of 51 participants is needed to reach 85% power for a two-tailed test at α=0.05.) Of the studies testing the relationship between noise exposure history and AN function, no single study has a large enough sample (enough statistical power) to confidently assess the relationship. In fact, the studies with the largest samples, including our current CAP study, do not find a relationship between noise exposure and AN function (Couth et al., 2020; Kamerer et al., 2019; Prendergast et al., 2017a; Smith et al., 2019).

Taken together, the evidence for noise-induced effects on AN function in humans is weak, subject to extraneous variables that covary with noise exposure history and AN function and the unknown reliability of self-report assessments of prior noise exposure. The average effect calculated across studies suggests that any effect of noise exposure history on AN response amplitudes is small, requiring large samples to confidently test and capture the relationship. We can conclude from the results of our own study and our meta-analysis that researchers investigating noise-induced AN damage in humans should be cautious when designing studies, analyzing data, and interpreting results.

**Characteristics of Age-Related and Noise-Induced Auditory Nerve Pathology**

The reduced amplitude of the ABR WI following noise exposure has been suggested as a proxy for cochlear synaptopathy based on experiments in noise-exposed animals. These animal studies involved carefully titrated noise and often included histologic confirmation of synapse loss. The presence of such synapse loss in humans cannot be confirmed *in vivo*, and so ABR WI/CAP N1 response amplitudes have been used by many researchers as a proxy for both age-related and noise-induced cochlear synaptopathy. Age-related and noise-induced changes in ABR WI/CAP N1 amplitudes may, however, reflect changes in multiple characteristics of the peripheral auditory system, including cochlear damage, synapse loss, axon degeneration, and even myelin degradation, which is consistent with evidence from human temporal bones from older donors (Makary et al., 2011; Viana et al., 2015; Xing et al., 2012). To date, the specific pathology underlying reduced AN response amplitudes can only be identified with post-mortem histological assessment. Longitudinal studies are warranted to assess changes in AN function across the lifespan and how such changes in AN function relate to AN structure evaluated post-mortem (for reviews and similar recommendations, see Bramhall et al., 2019; Le Prell, 2019; Shehabi et al., 2022).

**Alternative Methods**

The focus of the current systematic review, study, and meta-analysis was on AN suprathreshold response amplitudes. The use of the ABR WI/CAP N1 remains the only *in vivo* method for measuring AN function. While studies to-date have primarily used AN response amplitudes as the sole metric for AN function, other metrics derived from the

AN response should be considered for future studies (Harris et al., 2017). Alternative methods besides the AN response have been hypothesized to relate to AN dysfunction, most of which have focused on the loss of synapses. These techniques include behavioral assessments and middle ear reflex measures. The inclusion of these methods is beyond the scope of the current report, but the advantages and disadvantages of these techniques have been reviewed in several papers (Bharadwaj et al., 2019; Bramhall et al., 2019; Harris & Bao, 2022; Le Prell, 2019).

**Conclusion**

The systematic review, study, and meta-analyses reported here suggest that age is a robust predictor of AN function, whereas noise exposure history is much less so. Our own study of how AN function relates to age and noise exposure history is consistent with our meta-analyses, finding that CAP N1 response amplitudes decline with age, but are unrelated to noise exposure history. Importantly, our CAP study allowed for the first time a test of how age may interact with noise exposure history to exacerbate age-related deficits in AN function, but we did not find a history of noise exposure to significantly contribute to the age-related deficits in AN function observed in older adults. The evidence from our CAP study and from our meta-analysis suggests that if noise exposure relates to human AN activity, the relationship is small and potentially subject to methodological choices and uncontrolled variables that may covary with AN function and noise-exposure history, including participant age and sex. These results are of clinical importance as AN deficits may contribute to speech recognition deficits, particularly in the presence of background noise (Bharadwaj et al.,

2019; Bramhall et al., 2019; Bramhall et al., 2015; Bramhall et al., 2018a; Grant et al., 2020; Harris et al., 2021).

References

Aedo-Sanchez, C., Oliveros, J., Aranguiz, C., Muñoz, C., Lazo-Maturana, C., & Aguilar-Vidal, E. (2023). Subclinical hearing loss associated with aging. *Journal of Otology*, *18*(3), 111-117. https://doi.org/10.1016/j.joto.2023.05.002

Anderson, S., Bieber, R., & Schloss, A. (2021). Peripheral deficits and phase-locking declines in aging adults. *Hearing Research*, *403*, 108188. https://doi.org/10.1016/j.heares.2021.108188

Balduzzi, S., Rücker, G., & Schwarzer, G. (2019). How to perform a meta-analysis with R: a practical tutorial. *Evidence Based Mental Health*, *22*(4), 153-160. https://doi.org/10.1136/ebmental-2019-300117

Bharadwaj, H. M., Mai, A. R., Simpson, J. M., Choi, I., Heinz, M. G., & Shinn-Cunningham, B. G. (2019). Non-Invasive Assays of Cochlear Synaptopathy - Candidates and Considerations. *Neuroscience*, *407*, 53-66. https://doi.org/10.1016/j.neuroscience.2019.02.031

Bhatt, I. S., & Wang, J. (2019). Evaluation of dichotic listening performance in normal-hearing, noise-exposed young females. *Hearing Research*, *380*, 10-21. https://doi.org/10.1016/j.heares.2019.05.008

Bramhall, N., Beach, E. F., Epp, B., Le Prell, C. G., Lopez-Poveda, E. A., Plack, C. J., Schaette, R., Verhulst, S., & Canlon, B. (2019). The search for noise-induced cochlear synaptopathy in humans: Mission impossible? *Hearing Research*, *377*, 88-103. https://doi.org/10.1016/j.heares.2019.02.016

Bramhall, N., Ong, B., Ko, J., & Parker, M. (2015). Speech perception ability in noise is correlated with auditory brainstem response wave I amplitude. *Journal of the*

*American Acadamy of Audiology*, *26*(05), 509-517. https://doi.org/10.3766/jaaa.14100

Bramhall, N. F., Konrad-Martin, D., & McMillan, G. P. (2018a). Tinnitus and auditory perception after a history of noise exposure: Relationship to auditory brainstem response measures. *Ear and Hearing*, *39*(5), 881-894. https://doi.org/10.1097/aud.0000000000000544

Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., & Griest, S. E. (2017). Auditory brainstem response altered in humans with noise exposure despite normal outer hair cell function. *Ear and Hearing*, *38*(1), e1-e12. https://doi.org/10.1097/aud.0000000000000370

Bramhall, N. F., McMillan, G. P., Kujawa, S. G., & Konrad-Martin, D. (2018b). Use of non-invasive measures to predict cochlear synapse counts. *Hearing Research*, *370*, 113-119. https://doi.org/10.1016/j.heares.2018.10.006

Bramhall, N. F., Niemczak, C. E., Kampel, S. D., Billings, C. J., & McMillan, G. P. (2020). Evoked potentials reveal noise exposure–related central auditory changes despite normal audiograms. *American Journal of Audiology*, *29*(2), 152-164. https://doi.org/10.1044/2019_AJA-19-00060

Burkard, R. F., & Sims, D. (2001). The human auditory brainstem response to high click rates: aging effects. *American Journal of Audiology*, *10*(2), 53-61. https://doi.org/10.1044/1059-0889(2001/008)

Burkard, R. F., & Sims, D. (2002). A comparison of the effects of broadband masking noise on the auditory brainstem response in young and older adults. *American Journal of Audiology*, *11*(1), 13-22. https://doi.org/10.1044/1059-0889(2002/004)

Chatrian, G. E., Wirch, A. L., Edwards, K. H., Turella, G. S., Kaufman, M. A., & Snyder, J. M. (1985). Cochlear summating potential to broadband clicks detected from the human external auditory meatus. A study of subjects with normal hearing for age. *Ear and Hearing*, *6*(3), 130-138. https://doi.org/10.1097/00003446-198505000-00002

Clogg, C. C., Petkova, E., & Haritou, A. (1995). Statistical methods for comparing regression coefficients between models. *American Journal of Sociology*, *100*(5), 1261-1293. https://doi.org/10.1086/230638

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2003). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. Lawrency Erlbaum Associates. https://doi.org/10.4324/9781410606266

Couth, S., Prendergast, G., Guest, H., Munro, K. J., Moore, D. R., Plack, C. J., Ginsborg, J., & Dawes, P. (2020). Investigating the effects of noise exposure on self-report, behavioral and electrophysiological indices of hearing damage in musicians with normal audiometric thresholds. *Hearing Research*, *395*, 108021. https://doi.org/10.1016/j.heares.2020.108021

Cumming, G. (2012). *Understanding The New Statistics: Effect Sizes, Confidence Intervals, and Meta-Analysis*. Taylor & Francis Group, LLC.

De Poortere, N., Verhulst, S., Degeest, S., Keshishzadeh, S., Dhooge, I., & Keppler, H. (2023). Evaluation of lifetime noise exposure history reporting. *Journal of Speech, Language, and Hearing Research*, *66*(12), 5129-5151. https://doi.org/10.1044/2023_JSLHR-23-00266

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9-21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dewey, R. S., Francis, S. T., Guest, H., Prendergast, G., Millman, R. E., Plack, C. J., & Hall, D. A. (2020). The association between subcortical and cortical fMRI and lifetime noise exposure in listeners with normal hearing thresholds. *NeuroImage*, *204*, 116239. https://doi.org/10.1016/j.neuroimage.2019.116239

Dias, J. W., McClaskey, C. M., & Harris, K. C. (2021). Early auditory cortical processing predicts auditory speech in noise identification and lipreading. *Neuropsychologia*, *161*, 108012. https://doi.org/10.1016/j.neuropsychologia.2021.108012

Dias, J. W., McClaskey, C. M., Rumschlag, J., & Harris, K. C. (2022). Sensory tetanization to induce LTP-like plasticity: A review and reassessment of the approach. *European Journal of Neuroscience*, *56*(12), 6115-6140. https://doi.org/10.1111/ejn.15847

Dubno, J. R., Eckert, M. A., Lee, F.-S., Matthews, L. J., & Schmiedt, R. A. (2013). Classifying human audiometric phenotypes of age-related hearing loss from animal models. *Journal of the Association for Research in Otolaryngology*, *14*(5), 687-701. https://doi.org/10.1007/s10162-013-0396-x

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175-191. https://doi.org/10.3758/BF03193146

Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C., & Kujawa, S. G. (2015). Aging after noise exposure: Acceleration of cochlear synaptopathy in "recovered" ears. *Journal of Neuroscience*, *35*(19), 7509-7520. https://doi.org/10.1523/jneurosci.5138-14.2015

Fulbright, A. N. C., Le Prell, C. G., Griffiths, S. K., & Lobarinas, E. (2017). Effects of recreational noise on threshold and suprathreshold measures of auditory function. *Seminars in Hearing*, *38*(04), 298-318. https://doi.org/10.1055/s-0037-1606325

Gibson, W. P. (2017). The clinical uses of electrocochleography. *Frontiers in Neuroscience*, *11*, 274. https://doi.org/10.3389/fnins.2017.00274

Grant, K. J., Mepani, A. M., Wu, P., Hancock, K. E., de Gruttola, V., Liberman, M. C., & Maison, S. F. (2020). Electrophysiological markers of cochlear function correlate with hearing-in-noise performance among audiometrically normal subjects. *Journal of Neurophysiology*, *124*(2), 418-431. https://doi.org/10.1152/jn.00016.2020

Grinn, S. K., & Le Prell, C. G. (2022). Evaluation of hidden hearing loss in normal-hearing firearm users. *Frontiers in Neuroscience*, *16*, 1005148. https://doi.org/10.3389/fnins.2022.1005148

Grinn, S. K., Wiseman, K. B., Baker, J. A., & Le Prell, C. G. (2017). Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve response amplitude in humans. *Frontiers in Neuroscience*, *11*, 465. https://doi.org/10.3389/fnins.2017.00465

Grose, J. H., Buss, E., & Elmore, H. (2019). Age-related changes in the auditory brainstem response and suprathreshold processing of temporal and spectral modulation. *Trends in Hearing*, *23*. https://doi.org/10.1177/2331216519839615

Grose, J. H., Buss, E., & Hall, J. W. (2017). Loud music exposure and cochlear synaptopathy in young adults: Isolated auditory brainstem response effects but no perceptual consequences. *Trends in Hearing*, *21*. https://doi.org/10.1177/2331216517737417

Guest, H., Munro, K. J., & Plack, C. J. (2019). Acoustic middle-ear-muscle-reflex thresholds in humans with normal audiograms: No relations to tinnitus, speech perception in noise, or noise exposure. *Neuroscience*, *407*, 75-82. https://doi.org/10.1016/j.neuroscience.2018.12.019

Guest, H., Munro, K. J., Prendergast, G., Howe, S., & Plack, C. J. (2017). Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy. *Hearing Research*, *344*, 265-274. https://doi.org/10.1016/j.heares.2016.12.002

Hansen, C., Steinmetz, H., & Block, J. (2022). How to conduct a meta-analysis in eight steps: A practical guide. *Management Review Quarterly*, *72*(1), 1-19. https://doi.org/10.1007/s11301-021-00247-4

Harrer, M., Cuijpers, P., Furukawa, T. A., & Ebert, D. D. (2021). *Doing Meta-Analysis with R: A Hands-On Guide*. Chapman and Hall/CRC. https://doi.org/10.1201/9781003107347

Harris, C. S., Vaden, K. I., McClaskey, C. M., Dias, J. W., & Dubno, J. R. (2017). Complementary metrics of human auditory nerve function derived from compound action potentials. *Journal of Neurophysiology*, *119*, 1019-1028. https://doi.org/10.1152/jn.00638.2017

Harris, K. C., Ahlstrom, J. B., Dias, J. W., Kerouac, L. B., McClaskey, C. M., Dubno, J. R., & Eckert, M. A. (2021). Neural presbyacusis in humans inferred from age-related differences in auditory nerve function and structure. *Journal of Neuroscience*, *41*(50), 10293-10304. https://doi.org/10.1523/jneurosci.1747-21.2021

Harris, K. C., & Bao, J. (2022). Optimizing non-invasive functional markers for cochlear deafferentation based on electrocochleography and auditory brainstem responses. *Journal of the Acoustical Society of America*, *151*(4), 2802-2808. https://doi.org/10.1121/10.0010317

Harris, K. C., Dias, J. W., McClaskey, C. M., Rumschlag, J., Prisciandaro, J., & Dubno, J. R. (2022). Afferent loss, GABA, and central gain in older adults: Associations with speech recognition in noise. *Journal of Neuroscience*, *42*(38), 7201-7212. https://doi.org/10.1523/jneurosci.0242-22.2022

Heeringa, A. N., & Köppl, C. (2019). The aging cochlea: Towards unraveling the functional contributions of strial dysfunction and synaptopathy. *Hearing Research*, *376*, 111-124. https://doi.org/10.1016/j.heares.2019.02.015

Hickox, A. E., & Liberman, M. C. (2014). Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus? *Journal of Neurophysiology*, *111*(3), 552-564. https://doi.org/10.1152/jn.00184.2013

Johannesen, P. T., Buzo, B. C., & Lopez-Poveda, E. A. (2019). Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits. *Hearing Research*, *374*, 35-48. https://doi.org/10.1016/j.heares.2019.01.017

Johannesen, P. T., & Lopez-Poveda, E. A. (2021). Age-related central gain compensation for reduced auditory nerve output for people with normal audiograms, with and without tinnitus. *Iscience*, *24*(6), 102658. https://doi.org/10.1016/j.isci.2021.102658

Kaewsiri, S. I., Waseenon, V., Navacharoen, N., Panyathong, R., & Phuackchantuck, R. (2015). Correlation between age and gender, and parameters of auditory brainstem evoked response. *Chiang Mai Medical Journal*, *54*(4), 163-169.

Kamerer, A. M., Harris, S. E., Kopun, J. G., Neely, S. T., & Rasetshwane, D. M. (2022). Understanding self-reported hearing disability in adults with normal hearing. *Ear and Hearing*, *43*(3), 773-784. https://doi.org/10.1097/aud.0000000000001161

Kamerer, A. M., Kopun, J. G., Fultz, S. E., Allen, C., Neely, S. T., & Rasetshwane, D. M. (2019). Examining physiological and perceptual consequences of noise exposure. *Journal of the Acoustical Society of America*, *146*(5), 3947-3959. https://doi.org/10.1121/1.5132291

Kim, Y., & Han, W. (2023). Recommended auditory brainstem responses to stimulation and recording parameters for hidden hearing loss: A systematic review and meta-

analysis. *Audiology and Speech Research*, *19*(2), 77-90. https://doi.org/10.21848/asr.220086

Konrad-Martin, D., Dille, M. F., McMillan, G., Griest, S., McDermott, D., Fausti, S. A., & Austin, D. F. (2012). Age-related changes in the auditory brainstem response. *Journal of the American Acadamy of Audiology*, *23*(01), 18-35. https://doi.org/10.3766/jaaa.23.1.3

Kujawa, S. G., & Liberman, M. C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. *Hearing Research*, *330*(Pt B), 191-199. https://doi.org/10.1016/j.heares.2015.02.009

Lavoie, B. A., Hine, J. E., & Thornton, R. D. (2008). The choice of distracting task can affect the quality of auditory evoked potentials recorded for clinical assessment. *International Journal of Audiology*, *47*(7), 439-444. https://doi.org/10.1080/14992020802033109

Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32. https://doi.org/10.1080/14992027.2018.1534010

Liberman, M. C., Epstein, M. J., Cleveland, S. S., Wang, H., & Maison, S. F. (2016). Toward a differential diagnosis of hidden hearing loss in humans. *PLoS ONE*, *11*(9), e0162726. https://doi.org/10.1371/journal.pone.0162726

Lobarinas, E., Salvi, R., & Ding, D. (2013). Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. *Hearing Research*, *302*, 113-120. https://doi.org/10.1016/j.heares.2013.03.012

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: An open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*(213). https://doi.org/10.3389/fnhum.2014.00213

Lopez-Poveda, E. A., & Barrios, P. (2013). Perception of stochastically undersampled sound waveforms: A model of auditory deafferentation. *Frontiers in Neuroscience*, *7*, 124. https://doi.org/10.3389/fnins.2013.00124

Maele, T. V., Keshishzadeh, S., Poortere, N. D., Dhooge, I., Keppler, H., & Verhulst, S. (2021). The variability in potential biomarkers for cochlear synaptopathy after recreational noise exposure. *Journal of Speech, Language, and Hearing Research*, *64*(12), 4964-4981. https://doi.org/10.1044/2021_JSLHR-21-00064

Makary, C. A., Shin, J., Kujawa, S. G., Liberman, M. C., & Merchant, S. N. (2011). Age-related primary cochlear neuronal degeneration in human temporal bones. *Journal of the Association for Research in Otolaryngology*, *12*(6), 711-717. https://doi.org/10.1007/s10162-011-0283-2

McClaskey, C. M., Dias, J. W., Dubno, J. R., & Harris, K. C. (2018). Reliability of measures of N1 peak amplitude of the compound action potential in younger and older adults. *Journal of Speech, Language, and Hearing Research*, *61*(9), 2422-2430. https://doi.org/10.1044/2018_JSLHR-H-18-0097

Megha, K. N., Kappadi, S., Kaverappa, G. M., & Konadath, S. (2021). Effects of aging versus noise exposure on auditory system in individuals with normal audiometric thresholds. *Journal of International Advanced Otology*, *17*(4), 335-342. https://doi.org/10.5152/iao.2021.8789

Mitchell, C., Phillips, D. S., & Trune, D. R. (1989). Variables affecting the auditory brainstem response: Audiogram, age, gender and head size. *Hearing Research*, *40*(1), 75-85. https://doi.org/10.1016/0378-5955(89)90101-9

Nam, G. S., Kim, J. Y., Hong, S. A., Kim, S. G., & Son, E. J. (2021). Limitation of conventional audiometry in identifying hidden hearing loss in acute noise exposure. *Yonsei Medical Journal*, *62*(7), 615-621. https://doi.org/10.3349/ymj.2021.62.7.615

Nayagam, B. A., Muniak, M. A., & Ryugo, D. K. (2011). The spiral ganglion: Connecting the peripheral and central auditory systems. *Hearing Research*, *278*(1-2), 2-20. https://doi.org/10.1016/j.heares.2011.04.003

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021a). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . McKenzie, J. E. (2021b). PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ*, *372*, n160. https://doi.org/10.1136/bmj.n160

Parker, M. A. (2020). Identifying three otopathologies in humans. *Hearing Research*, *398*, 108079. https://doi.org/10.1016/j.heares.2020.108079

Paternoster, R., Brame, R., Mazerolle, P., & Piquero, A. (1998). Using the correct statistical test for the equality of regression coefficients. *Criminology*, *36*(4), 859-866. https://doi.org/10.1111/j.1745-9125.1998.tb01268.x

Pinsonnault-Skvarenina, A., Moïn-Darbari, K., Zhao, W., Zhang, M., Qiu, W., & Fuente, A. (2022a). No effect of occupational noise exposure on auditory brainstem response and speech perception in noise. *Frontiers in Neuroscience*, *16*. https://doi.org/10.3389/fnins.2022.915211

Pinsonnault-Skvarenina, A., Soucy, W., Noël, J., Doucet, F., Lévesque, É., Fuente, A., & Leroux, T. (2022b). Supra-threshold deficits in normal hearing military recruits exposed to impulse noise. *Journal of the Acoustical Society of America*, *152*(4), 2419-2433. https://doi.org/10.1121/10.0014829

Plack, C. J., Barker, D., & Prendergast, G. (2014). Perceptual consequences of "hidden" hearing loss. *Trends in Hearing*, *18*. https://doi.org/10.1177/2331216514550621

Plack, C. J., Léger, A., Prendergast, G., Kluk, K., Guest, H., & Munro, K. J. (2016). Toward a diagnostic test for hidden hearing loss. *Trends in Hearing*, *20*. https://doi.org/10.1177/2331216516657466

Prendergast, G., Couth, S., Millman, R. E., Guest, H., Kluk, K., Munro, K. J., & Plack, C. J. (2019). Effects of age and noise exposure on proxy measures of cochlear synaptopathy. *Trends in Hearing*, *23*. https://doi.org/10.1177/2331216519877301

Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A., Heinz, M. G., & Plack, C. J. (2017a). Effects of noise exposure on young adults with normal

audiograms I: Electrophysiology. *Hearing Research*, *344*, 68-81. https://doi.org/10.1016/j.heares.2016.10.028

Prendergast, G., Millman, R. E., Guest, H., Munro, K. J., Kluk, K., Dewey, R. S., Hall, D. A., Heinz, M. G., & Plack, C. J. (2017b). Effects of noise exposure on young adults with normal audiograms II: Behavioral measures. *Hearing Research*, *356*, 74-86. https://doi.org/10.1016/j.heares.2017.10.007

Prendergast, G., Tu, W., Guest, H., Millman, R. E., Kluk, K., Couth, S., Munro, K. J., & Plack, C. J. (2018). Supra-threshold auditory brainstem response amplitudes in humans: Test-retest reliability, electrode montage and noise exposure. *Hearing Research*, *364*, 38-47. https://doi.org/10.1016/j.heares.2018.04.002

Pürner, D., Schirkonyer, V., & Janssen, T. (2022). Changes in the peripheral and central auditory performance in the elderly—A cross-sectional study. *Journal of Neuroscience Research*, *100*(9), 1791-1811. https://doi.org/10.1002/jnr.25068

R Core Team. (2023). *R: A language and environment for statistical computing*. In R Foundation for Statistical Computing. https://www.R-project.org/

Ridley, C. L., Kopun, J. G., Neely, S. T., Gorga, M. P., & Rasetshwane, D. M. (2018). Using thresholds in noise to identify hidden hearing loss in humans. *Ear and Hearing*, *39*(5), 829-844. https://doi.org/10.1097/aud.0000000000000543

Ripley, S., Xia, L., Zhang, Z., Aiken, S. J., & Wang, J. (2022). Animal-to-human translation difficulties and problems with proposed coding-in-noise deficits in noise-induced synaptopathy and hidden hearing loss. *Frontiers in Neuroscience*, *16*. https://doi.org/10.3389/fnins.2022.893542

Roque, L., Karawani, H., Gordon-Salant, S., & Anderson, S. (2019). Effects of age, cognition, and neural encoding on the perception of temporal speech cues. *Frontiers in Neuroscience*, *13*. https://doi.org/10.3389/fnins.2019.00749

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin*, *86*(3), 638. https://doi.org/10.1037/0033-2909.86.3.638

Rosenthal, R. (1991). *Meta-Analytic Procedures for Social Research*. Sage Publications. https://doi.org/10.3102/0013189X015008018

Rosnow, R. L., Rosenthal, R., & Rubin, D. B. (2000). Contrasts and correlations in effect-size estimation. *Psychological Science*, *11*(6), 446-453. https://doi.org/10.1111/1467-9280.00287

Rumschlag, J. A., McClaskey, C. M., Dias, J. W., Kerouac, L. B., Noble, K. V., Panganiban, C., Lang, H., & Harris, K. C. (2022). Age-related central gain with degraded neural synchrony in the auditory brainstem of mice and humans. *Neurobiology of Aging*, *115*, 50-59. https://doi.org/10.1016/j.neurobiolaging.2022.03.014

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: Physiological evidence for hidden hearing loss and computational model. *Journal of Neuroscience*, *31*(38), 13452-13457. https://doi.org/10.1523/jneurosci.2156-11.2011

Shehabi, A. M., Prendergast, G., & Plack, C. J. (2022). The relative and combined effects of noise exposure and aging on auditory peripheral neural deafferentation: A narrative review. *Frontiers in Aging Neuroscience*, *14*. https://doi.org/10.3389/fnagi.2022.877588

Skoe, E., & Tufts, J. (2018). Evidence of noise-induced subclinical hearing loss using auditory brainstem responses and objective measures of noise exposure in humans. *Hearing Research*, *361*, 80-91. https://doi.org/10.1016/j.heares.2018.01.005

Smith, S. B., Krizman, J., Liu, C., White-Schwoch, T., Nicol, T., & Kraus, N. (2019). Investigating peripheral sources of speech-in-noise variability in listeners with normal audiograms. *Hearing Research*, *371*, 66-74. https://doi.org/10.1016/j.heares.2018.11.008

Spankovich, C., Le Prell, C. G., Lobarinas, E., & Hood, L. J. (2017). Noise history and auditory function in young adults with and without type 1 diabetes mellitus. *Ear and Hearing*, *38*(6), 724-735. https://doi.org/10.1097/AUD.0000000000000457

Stamper, G. C., & Johnson, T. A. (2015). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172-184. https://doi.org/10.1097/aud.0000000000000107

Suresh, C. H., & Krishnan, A. (2021). Search for electrophysiological indices of hidden hearing loss in humans: Click auditory brainstem response across sound levels and in background noise. *Ear and Hearing*, *42*(1), 53-67. https://doi.org/10.1097/aud.0000000000000905

Valderrama, J. T., Beach, E. F., Yeend, I., Sharma, M., Van Dun, B., & Dillon, H. (2018). Effects of lifetime noise exposure on the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility. *Hearing Research*, *365*, 36-48. https://doi.org/10.1016/j.heares.2018.06.003

Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., Merchant, S. N., Liberman, L. D., & Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hearing Research*, *327*, 78-88. https://doi.org/10.1016/j.heares.2015.04.014

Viechtbauer, W., & Cheung, M. W.-L. (2010). Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods*, *1*(2), 112-125. https://doi.org/10.1002/jrsm.11

Washnik, N. J., Bhatt, I. S., Phillips, S. L., Tucker, D., & Richter, S. (2020). Evaluation of cochlear activity in normal-hearing musicians. *Hearing Research*, *395*, 108027. https://doi.org/10.1016/j.heares.2020.108027

Washnik, N. J., Bhatt, I. S., Sergeev, A. V., Prabhu, P., & Suresh, C. (2023). Auditory electrophysiological and perceptual measures in student musicians with high sound exposure. *Diagnostics*, *13*(5), 934. https://doi.org/10.3390/diagnostics13050934

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary neural degeneration in the human cochlea: Evidence for hidden hearing loss in the aging ear. *Neuroscience*, *407*, 8-20. https://doi.org/10.1016/j.neuroscience.2018.07.053

Xing, Y., Samuvel, D. J., Stevens, S. M., Dubno, J. R., Schulte, B. A., & Lang, H. (2012). Age-related changes of myelin basic protein in mouse and human auditory nerve. *PLoS ONE*, *7*(4), e34500. https://doi.org/10.1371/journal.pone.0034500

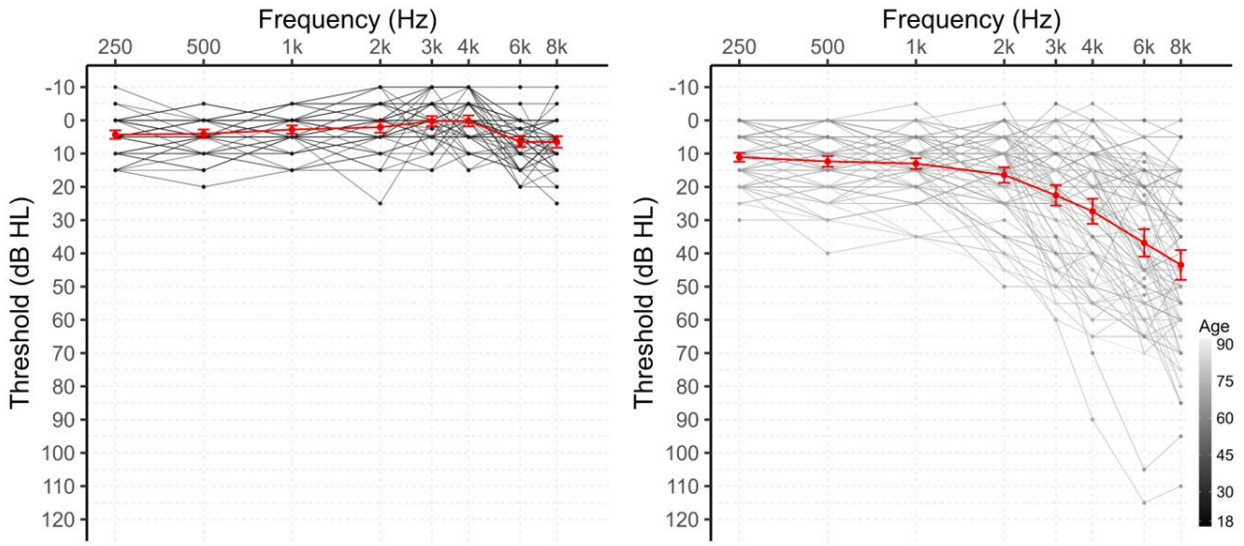



**Figure 1.** Audiometric thresholds for the right (test) ear of the younger (left) and older (right) participants in our CAP cohort. Colored lines represent the average audiogram across participants. Error bars represent 95% confidence intervals. Grey lines plot the audiograms of individual participants. Darker lines are younger participants.

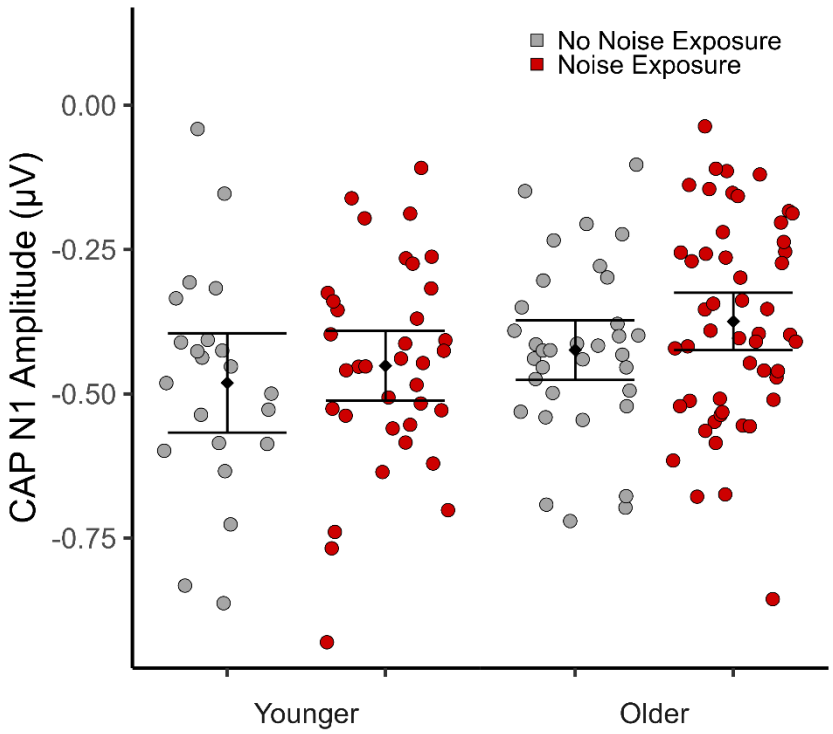



**Figure 2.** Dot plots of the CAP N1 amplitudes of the younger (left) and older (right) participants in our CAP cohort. Black diamonds mark the group average. Error bars identify the 95% confidence intervals for each group.

| Study | N | Sex | Ear(s) | Electrode | Stimulus | Duration | Intensity (dB pSPL) | Rate (Hz) | Effect (Z) [95% CI] |
|---|---|---|---|---|---|---|---|---|---|
| Aedo-Sanchez et al., 2023 | 45 | MF | R | Surface | Click | 100 µs | 110.0 | 21.1 | 0.00 [-0.30, 0.30] |
| Anderson et al., 2021 | 53 | MF | LR | Surface | Click | 100 µs | 80.0 | 21.1 | -0.38 [-0.65, -0.10] |
| Bramhall et al., 2015 | 57 | MF | LR | Surface | Tone 4 kHz | 1 ms | 110.0 | 13.3 | -0.35 [-0.62, -0.09] |
| Burkard & Sims, 2002 | 22 | MF | LR | TM | Click | 100 µs | 115.0 | 25.0 | -0.53 [-0.98, -0.08] |
| Chatrian et al., 1985 | 60 | MF | L | Surface | Click | 100 µs | 110.0 | 8.3 | -0.45 [-0.71, -0.19] |
| Chatrian et al., 1985 | 60 | MF | R | Surface | Click | 100 µs | 110.0 | 8.3 | -0.59 [-0.85, -0.33] |
| Dias et al., 2024 | 143 | MF | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.19 [-0.36, -0.03] |
| Grose et al., 2019 | 20 | MF | LR | Surface | Click | 100 µs | 95.0 | 7.7 | -1.48 [-1.96, -1.00] |
| Grose et al., 2019 | 20 | MF | LR | Surface | Click | 100 µs | 105.0 | 7.7 | -1.52 [-2.00, -1.05] |
| Harris et al., 2021 | 95 | MF | R | TM | Click | 100 µs | 80.0 | 11.1 | -0.11 [-0.32, 0.09] |
| Harris et al., 2021 | 95 | MF | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.41 [-0.61, -0.21] |
| Harris et al., 2022 | 77 | MF | R | TM | Click | 100 µs | 100.0 | 11.1 | -0.28 [-0.51, -0.05] |
| Johannesen et al., 2021 | 63 | F | LR | Surface | Click | 100 µs | 105.0 | 11.0 | -0.62 [-0.87, -0.36] |
| Johannesen et al., 2021 | 30 | M | LR | Surface | Click | 100 µs | 105.0 | 11.0 | -0.64 [-1.02, -0.26] |
| Kamerer et al., 2019 | 97 | MF | LR | Surface | Tone 1.5 kHz | 1 ms | 110.0 | 11.0 | -0.39 [-0.60, -0.19] |
| Kamerer et al., 2019 | 97 | MF | LR | Surface | Tone 4 kHz | 1 ms | 110.0 | 11.0 | -0.48 [-0.68, -0.28] |
| Kamerer et al., 2021 | 111 | MF | LR | Surface | Tone 1.5 kHz | 1 ms | 110.0 | 11.0 | -0.45 [-0.64, -0.26] |
| Kamerer et al., 2021 | 111 | MF | LR | Surface | Tone 4 kHz | 1 ms | 110.0 | 11.0 | -0.45 [-0.64, -0.26] |
| Konrad-Martin et al., 2012 | 131 | MF | LR | Surface | Click | 100 µs | 110.0 | 11.0 | -0.23 [-0.40, -0.06] |
| Lavoie et al., 2008 | 30 | F | LR | Surface | Click | 100 µs | 81.0 | 20.0 | -0.37 [-0.74, 0.01] |
| McClaskey et al., 2018 | 44 | MF | R | TM | Click | 100 µs | 80.0 | 11.1 | -0.31 [-0.62, -0.00] |
| McClaskey et al., 2018 | 44 | MF | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.31 [-0.62, -0.00] |
| Mitchell et al., 1989 | 177 | MF | LR | Surface | Click | 100 µs | 110.0 | 10.0 | -0.31 [-0.46, -0.16] |
| Parker, 2020 | 218 | MF | LR | Surface | Tone 4 kHz | 1 ms | 80.0 | 13.3 | -0.76 [-0.90, -0.63] |
| Prendergast et al., 2019 | 156 | MF | LR | Surface | Click | 100 µs | 100.0 | 11.0 | -0.08 [-0.24, 0.08] |
| Purner et al., 2022 | 59 | MF | LR | Surface | Click | 100 µs | 80.0 | 20.0 | -0.98 [-1.25, -0.72] |
| Purner et al., 2022 | 58 | MF | LR | Surface | Click | 100 µs | 80.0 | 20.0 | -1.03 [-1.30, -0.77] |
| Roque et al., 2019 | 60 | MF | LR | Surface | Click | 100 µs | 80.0 | 21.1 | -0.69 [-0.95, -0.43] |
| Rumschlag et al., 2022 | 96 | MF | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.32 [-0.52, -0.11] |
| Averge Effect Across Studies | | | | | | | | | -0.43 [-0.69, -0.17] |

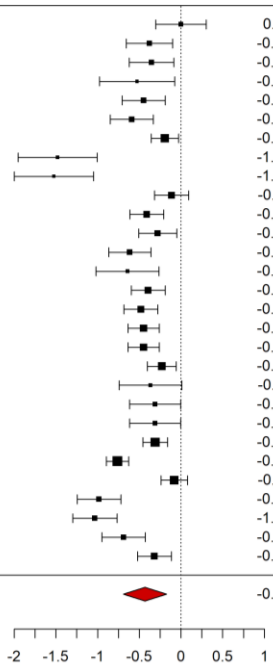
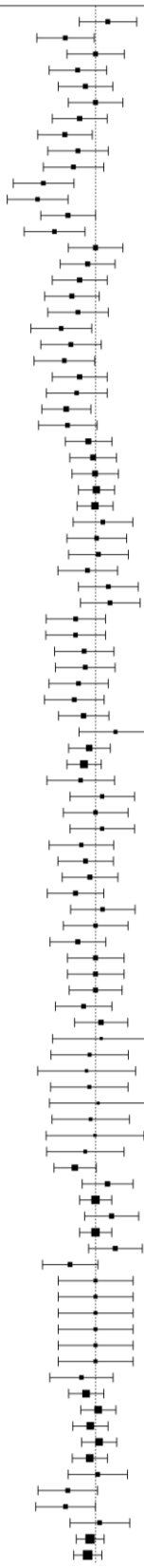



**Figure 3.** Forest plot of the studies included in our meta-analysis of age effects on AN response amplitudes. The right columns illustrate the magnitude and 95% confidence interval of the Z-transformed effect size for each study. The size of the box for the effect of each study represents the study sample size. The average effect across studies is represented by the red diamond.

| Study | N | Sex | Mean Age | Ear(s) | Electrode | Stimulus | Duration | Intensity (dB pSPL) | Rate (Hz) | Effect (Z) [95% CI] |
|---|---|---|---|---|---|---|---|---|---|---|
| Bhatt et al., 2019 | 32 | F | 26.5 | R | Surface | Click | 100 µs | 85.7 | 11.1 | 0.16 [-0.21, 0.52] |
| Bhatt et al., 2019 | 32 | F | 26.5 | R | Surface | Click | 100 µs | 85.7 | 71.1 | -0.38 [-0.75, -0.02] |
| Bhatt et al., 2019 | 32 | F | 26.5 | L | Surface | Click | 100 µs | 85.7 | 11.1 | 0.00 [-0.36, 0.36] |
| Bhatt et al., 2019 | 32 | F | 26.5 | L | Surface | Click | 100 µs | 85.7 | 71.1 | -0.23 [-0.59, 0.14] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 1 kHz | 4 ms | 80.0 | 11.1 | -0.13 [-0.47, 0.22] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 1 kHz | 4 ms | 90.0 | 11.1 | 0.00 [-0.35, 0.35] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 1 kHz | 4 ms | 100.0 | 11.1 | -0.20 [-0.55, 0.14] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 1 kHz | 4 ms | 110.0 | 11.1 | -0.39 [-0.73, -0.04] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 1 kHz | 4 ms | 80.0 | 11.1 | -0.22 [-0.61, 0.16] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 1 kHz | 4 ms | 90.0 | 11.1 | -0.28 [-0.66, 0.10] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 1 kHz | 4 ms | 100.0 | 11.1 | -0.66 [-1.05, -0.28] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 1 kHz | 4 ms | 110.0 | 11.1 | -0.74 [-1.12, -0.35] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 3 kHz | 2.5 ms | 110.0 | 11.1 | -0.35 [-0.69, -0.00] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 3 kHz | 2.5 ms | 110.0 | 11.1 | -0.52 [-0.91, -0.14] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 4 kHz | 2 ms | 80.0 | 11.1 | 0.00 [-0.35, 0.35] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 4 kHz | 2 ms | 90.0 | 11.1 | -0.10 [-0.45, 0.25] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 4 kHz | 2 ms | 100.0 | 11.1 | -0.20 [-0.55, 0.14] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 4 kHz | 2 ms | 110.0 | 11.1 | -0.30 [-0.65, 0.05] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 4 kHz | 2 ms | 80.0 | 11.1 | -0.22 [-0.61, 0.16] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 4 kHz | 2 ms | 90.0 | 11.1 | -0.44 [-0.82, -0.05] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 4 kHz | 2 ms | 100.0 | 11.1 | -0.31 [-0.70, 0.07] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 4 kHz | 2 ms | 110.0 | 11.1 | -0.40 [-0.78, -0.01] |
| Bramhall et al., 2017 | 35 | MF | 25.8 | LR | Surface | Tone 6 kHz | 1.5 ms | 110.0 | 11.1 | -0.20 [-0.55, 0.14] |
| Bramhall et al., 2017 | 29 | MF | 28.2 | LR | Surface | Tone 6 kHz | 1.5 ms | 110.0 | 11.1 | -0.24 [-0.62, 0.15] |
| Bramhall et al., 2018 | 43 | MF | 25.5 | LR | Surface | Tone 4 kHz | 2 ms | 110.0 | 11.1 | -0.37 [-0.68, -0.06] |
| Bramhall et al., 2018 | 31 | MF | 28.1 | LR | Surface | Tone 4 kHz | 2 ms | 110.0 | 11.1 | -0.35 [-0.72, 0.02] |
| Bramhall et al., 2020 | 47 | MF | 28.7 | LR | Surface | Tone 4 kHz | 2 ms | 100.0 | 11.1 | -0.09 [-0.39, 0.21] |
| Couth et al., 2020 | 47 | MF | 22.5 | LR | Surface | Click | 100 µs | 90.0 | 11.1 | -0.03 [-0.33, 0.26] |
| Couth et al., 2020 | 47 | MF | 22.5 | LR | Surface | Click | 100 µs | 110.0 | 11.1 | -0.01 [-0.30, 0.29] |
| Couth et al., 2020 | 76 | MF | 22.0 | LR | Surface | Click | 100 µs | 90.0 | 11.1 | 0.01 [-0.22, 0.24] |
| Couth et al., 2020 | 76 | MF | 22.0 | LR | Surface | Click | 100 µs | 110.0 | 11.1 | -0.01 [-0.24, 0.22] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 70.0 | 11.0 | 0.09 [-0.28, 0.47] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 70.0 | 11.0 | 0.01 [-0.36, 0.39] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 80.0 | 11.0 | 0.04 [-0.34, 0.41] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 80.0 | 11.0 | -0.10 [-0.48, 0.28] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 90.0 | 11.0 | 0.16 [-0.22, 0.54] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Click | 80 µs | 90.0 | 11.0 | 0.18 [-0.19, 0.56] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 0.5 kHz | 5 ms | 70.0 | 20.0 | -0.25 [-0.63, 0.12] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 0.5 kHz | 5 ms | 70.0 | 20.0 | -0.25 [-0.63, 0.12] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 1 kHz | 4 ms | 70.0 | 20.0 | -0.15 [-0.52, 0.23] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 1 kHz | 4 ms | 70.0 | 20.0 | -0.13 [-0.51, 0.25] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 4 kHz | 2 ms | 70.0 | 20.0 | -0.22 [-0.59, 0.16] |
| De Poortere et al., 2023 | 30 | MF | 20.0 | LR | Surface | Tone 4 kHz | 2 ms | 70.0 | 20.0 | -0.27 [-0.65, 0.11] |
| Dewey et al., 2020 | 41 | M | 32.5 | LR | Surface | Click | 100 µs | 102.0 | 11.1 | -0.15 [-0.47, 0.17] |
| Dewey et al., 2020 | 21 | F | 32.5 | LR | Surface | Click | 100 µs | 102.0 | 11.1 | 0.25 [-0.21, 0.71] |
| Dias et al., 2024 | 58 | MF | 23.8 | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.08 [-0.34, 0.19] |
| Dias et al., 2024 | 85 | MF | 66.9 | R | TM | Click | 100 µs | 110.0 | 11.1 | -0.15 [-0.36, 0.07] |
| Fullbright et al., 2017 | 24 | M | 21.1 | LR | Surface | Click | 100 µs | 106.4 | 21.1 | -0.19 [-0.62, 0.24] |
| Fullbright et al., 2017 | 26 | M | 21.1 | LR | Surface | Click | 100 µs | 116.4 | 21.1 | 0.08 [-0.32, 0.49] |
| Fullbright et al., 2017 | 26 | M | 21.1 | LR | Surface | Click | 100 µs | 126.4 | 21.1 | 0.00 [-0.41, 0.41] |
| Fullbright et al., 2017 | 26 | M | 21.1 | LR | Surface | Click | 100 µs | 135.4 | 21.1 | 0.08 [-0.32, 0.49] |
| Fullbright et al., 2017 | 26 | F | 20.4 | LR | Surface | Click | 100 µs | 106.4 | 21.1 | -0.18 [-0.59, 0.23] |
| Fullbright et al., 2017 | 34 | F | 20.4 | LR | Surface | Click | 100 µs | 116.4 | 21.1 | -0.13 [-0.48, 0.22] |
| Fullbright et al., 2017 | 34 | F | 20.4 | LR | Surface | Click | 100 µs | 126.4 | 21.1 | -0.07 [-0.42, 0.28] |
| Fullbright et al., 2017 | 33 | F | 20.4 | LR | Surface | Click | 100 µs | 135.4 | 21.1 | -0.25 [-0.61, 0.10] |
| Fullbright et al., 2017 | 26 | M | 21.1 | LR | Surface | Tone 4 kHz | 1.25 ms | 99.0 | 27.1 | 0.09 [-0.32, 0.50] |
| Fullbright et al., 2017 | 26 | M | 21.1 | LR | Surface | Tone 4 kHz | 1.25 ms | 99.0 | 27.1 | 0.00 [-0.41, 0.41] |
| Fullbright et al., 2017 | 34 | F | 20.4 | LR | Surface | Tone 4 kHz | 1.25 ms | 99.0 | 27.1 | -0.23 [-0.58, 0.13] |
| Fullbright et al., 2017 | 33 | F | 20.4 | LR | Surface | Tone 4 kHz | 1.25 ms | 99.0 | 27.1 | 0.00 [-0.36, 0.36] |
| Grinn & Le Prell, 2022 | 33 | M | 21.5 | LR | Surface | Click | 100 µs | 120.0 | 11.7 | 0.00 [-0.36, 0.36] |
| Grinn & Le Prell, 2022 | 37 | F | 21.5 | LR | Surface | Click | 100 µs | 120.0 | 11.7 | 0.00 [-0.34, 0.34] |
| Grinn & Le Prell, 2022 | 33 | M | 21.5 | LR | Surface | Tone 4 kHz | 1.25 ms | 120.0 | 11.7 | -0.15 [-0.51, 0.21] |
| Grinn & Le Prell, 2022 | 37 | F | 21.5 | LR | Surface | Tone 4 kHz | 1.25 ms | 120.0 | 11.7 | 0.07 [-0.27, 0.41] |
| Grinn et al., 2017 | 13 | M | 23.5 | LR | Surface | Click | 100 µs | 116.4 | 11.7 | 0.07 [-0.55, 0.69] |
| Grinn et al., 2017 | 19 | F | 23.5 | LR | Surface | Click | 100 µs | 116.4 | 11.7 | -0.08 [-0.57, 0.41] |
| Grinn et al., 2017 | 13 | M | 23.5 | LR | Surface | Tone 2 kHz | 2.5 ms | 116.4 | 11.7 | -0.11 [-0.73, 0.51] |
| Grinn et al., 2017 | 19 | F | 23.5 | LR | Surface | Tone 2 kHz | 2.5 ms | 116.4 | 11.7 | -0.08 [-0.57, 0.41] |
| Grinn et al., 2017 | 13 | M | 23.5 | LR | Surface | Tone 3 kHz | 1.67 ms | 116.4 | 11.7 | 0.03 [-0.59, 0.65] |
| Grinn et al., 2017 | 19 | F | 23.5 | LR | Surface | Tone 3 kHz | 1.67 ms | 116.4 | 11.7 | -0.06 [-0.55, 0.43] |
| Grinn et al., 2017 | 13 | M | 23.5 | LR | Surface | Tone 4 kHz | 1.25 ms | 116.4 | 11.7 | -0.01 [-0.63, 0.61] |
| Grinn et al., 2017 | 19 | F | 23.5 | LR | Surface | Tone 4 kHz | 1.25 ms | 116.4 | 11.7 | -0.13 [-0.62, 0.36] |
| Grose et al., 2017 | 57 | MF | 24.0 | L | Surface | Click | 100 µs | 95.0 | 7.7 | -0.26 [-0.53, 0.01] |
| Guest et al., 2017 | 40 | MF | 25.6 | LR | Surface | Click | 100 µs | 102.0 | 14.1 | 0.15 [-0.17, 0.47] |
| Kamerer et al., 2019 | 97 | MF | 53.0 | LR | Surface | Tone 1.5 kHz | 1 ms | 110.0 | 11.0 | 0.00 [-0.20, 0.20] |
| Kamerer et al., 2019 | 36 | MF | 29.4 | LR | Surface | Tone 1.5 kHz | 1 ms | 110.0 | 11.0 | 0.20 [-0.14, 0.54] |
| Kamerer et al., 2019 | 97 | MF | 53.0 | LR | Surface | Tone 4 kHz | 1 ms | 110.0 | 11.0 | 0.00 [-0.20, 0.20] |
| Kamerer et al., 2019 | 36 | MF | 29.4 | LR | Surface | Tone 4 kHz | 1 ms | 110.0 | 11.0 | 0.25 [-0.09, 0.59] |
| Liberman et al., 2016 | 34 | MF | 24.6 | ? | Surface | Click | 100 µs | 130.9 | 9.1 | -0.32 [-0.68, 0.03] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Click | 100 µs | 80.0 | 11.0 | 0.00 [-0.48, 0.48] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Click | 100 µs | 100.0 | 11.0 | 0.00 [-0.48, 0.48] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Click | 100 µs | 80.0 | 120.0 | 0.00 [-0.48, 0.48] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Click | 100 µs | 100.0 | 120.0 | 0.00 [-0.48, 0.48] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Tone 1 kHz | ? | 70.0 | 20.0 | 0.00 [-0.48, 0.48] |
| Maele et al., 2021 | 20 | MF | 21.5 | LR | Surface | Tone 4 kHz | ? | 70.0 | 20.0 | 0.00 [-0.48, 0.48] |
| Nam et al., 2021 | 27 | MF | 31.9 | LR | Surface | Click | 100 µs | 90.0 | 11.0 | -0.18 [-0.58, 0.22] |
| Pinsonnault-Skvarenina et al., 2022 | 80 | M | 24.8 | LR | TM | Click | 100 µs | 86.4 | 11.1 | -0.12 [-0.34, 0.10] |
| Pinsonnault-Skvarenina et al., 2022 | 80 | M | 24.8 | LR | TM | Click | 100 µs | 96.4 | 11.1 | 0.03 [-0.19, 0.26] |
| Pinsonnault-Skvarenina et al., 2022 | 80 | M | 24.8 | LR | TM | Click | 100 µs | 106.4 | 11.1 | -0.07 [-0.29, 0.16] |
| Pinsonnault-Skvarenina et al., 2022 | 80 | M | 24.8 | LR | TM | Click | 100 µs | 116.4 | 11.1 | 0.05 [-0.18, 0.27] |
| Pinsonnault-Skvarenina et al., 2022 | 80 | M | 24.8 | LR | TM | Click | 100 µs | 126.4 | 11.1 | -0.07 [-0.30, 0.15] |
| Pinsonnault-Skvarenina et al., 2022b | 30 | M | 21.5 | LR | Surface | Click | 100 µs | 91.4 | 11.1 | 0.03 [-0.35, 0.40] |
| Pinsonnault-Skvarenina et al., 2022b | 30 | M | 21.5 | LR | Surface | Click | 100 µs | 101.4 | 11.1 | -0.35 [-0.73, 0.02] |
| Pinsonnault-Skvarenina et al., 2022b | 30 | M | 21.5 | LR | Surface | Click | 100 µs | 111.4 | 11.1 | -0.38 [-0.76, -0.00] |
| Pinsonnault-Skvarenina et al., 2022b | 30 | M | 21.5 | LR | TM | Click | 100 µs | 111.4 | 11.1 | 0.05 [-0.32, 0.43] |
| Prendergast et al., 2017 | 125 | MF | 27.0 | LR | Surface | Click | 100 µs | 80.0 | 11.0 | -0.07 [-0.25, 0.11] |
| Prendergast et al., 2017 | 124 | MF | 27.0 | LR | Surface | Click | 100 µs | 100.0 | 11.0 | -0.10 [-0.28, 0.08] |



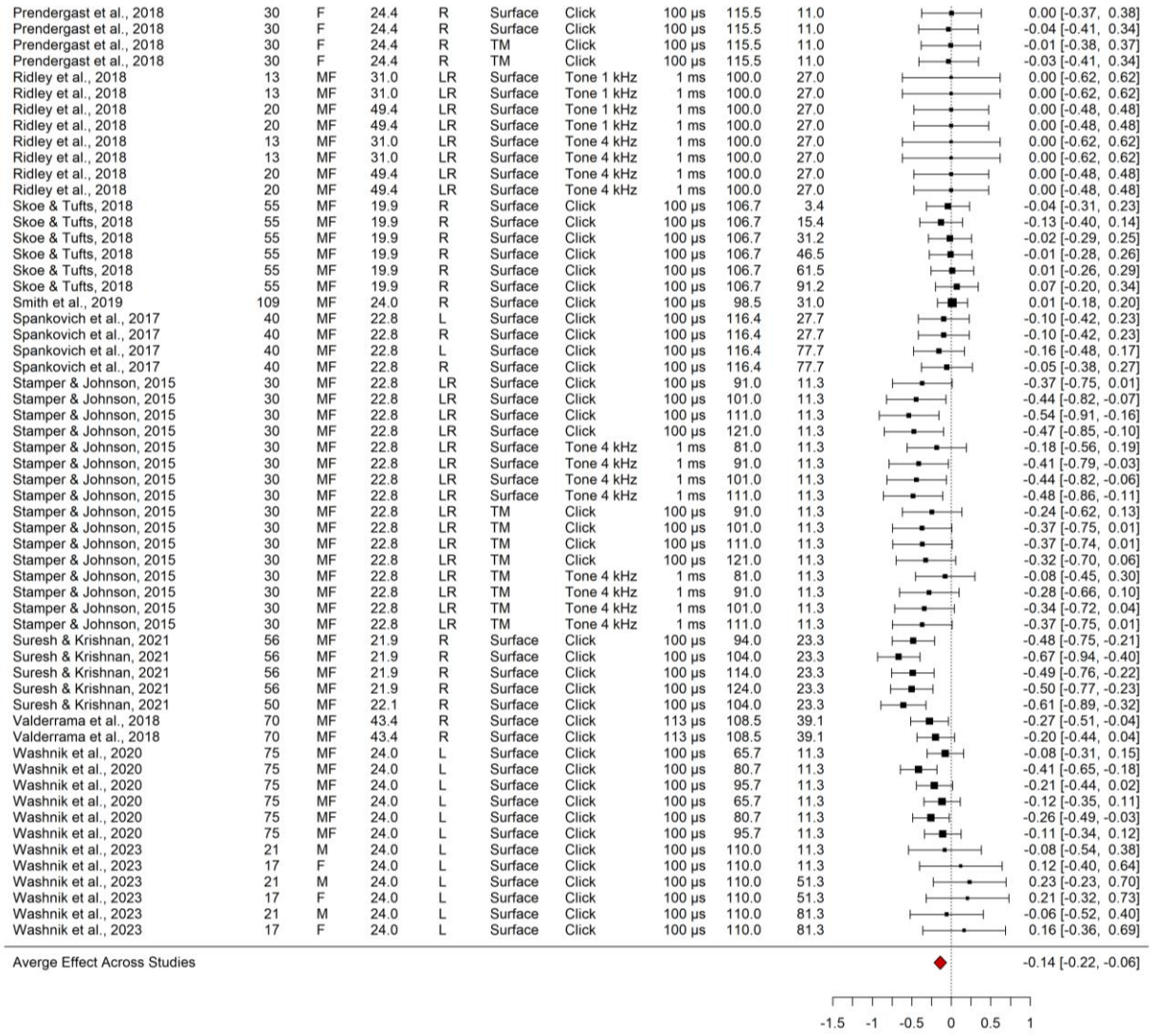



**Figure 4.** Forest plot of the studies included in our meta-analysis of noise-exposure effects on AN response amplitudes. The right columns illustrate the magnitude and 95% confidence interval of the Z-transformed effect size for each study. The size of the box for the effect of each study represents the study sample size. The average effect across studies is represented by the red diamond.