The following sample size calculations were based on comparison of the mean difference between groups (or arms) on a continuously measured outcome (or continuous variable). The sample size was fixed and detectable EF (or Cohen's D) was calculated. The detectable point difference for a continuous outcome was then calculated by multiplying EF and SD for the outcome measure.

Specific Aim 1.1: to test the hypothesis that HIN performance correlates with CAP amplitudes in anesthetized humans with Normal OHC function.

n = 52 subjects

Statistical Methods: described in detail in the Data Analysis section of the Research Strategy.

1. ANOVA to determine whether anesthetized subjects exhibit less variability than non-anesthetized subjects
2. Univariate and multivariate models to determine the relationship between mean CAP amplitudes and the other independent variables listed in Table 3 in all subjects
3. ANCOVA or the regression model with indicator variable for Difficulty HIN vs. No Difficulty HIN groups will be utilized to compare statistically significant differences in anesthetized CAP amplitudes between the two groups
4. Cognitive and central auditory processing will be similarly analyzed to control for higher order effects on HIN
5. Multivariate regression models will be used to examine the interaction effect of two HIN groups with other independent variables (age and gender for example) on the dependent variable of mean CAP amplitudes

Power analysis: An ANCOVA model with 80% power on a continuously measured outcome assuming a significance level of 0.05 and a two group sample size of 52 (n=26 in each of the Difficulty HIN vs. No Difficulty HIN groups) will detect an effect size (EF) of 0.8 or above. We will able to detect a trued difference of 0.13 μV between two groups for the primary outcome of CAP amplitude assuming our current standard deviation of 0.166 for CAP amplitudes (triptodes) measured in the 57 subjects with PTA<12.5 dB HL in our existing database.

This effect size is less than desired for a large clinical trial. However, this size is appropriate given that the aim is to determine which method is the most effective in accurately measuring CAP in humans. Further, it is similar to the sample sizes of persons with $_{hf}$PTA < 12.5 dB HL in the database of our existing clinical trial using triptodes (n= 57) and TM wick electrodes (n= 59) in unanesthetized humans to which this comparison will be made. The ensuing experiments will increase the subject size and reduce the EF.

Specific Aim 1.2: to test the hypothesis that HIN performance is primarily governed by OHC, rather than AN function.

n = 600 subjects

Statistical Methods: described in detail in the Data Analysis section of the Research Strategy.

1. subjects will be rank ordered by $_{hf}$PTA, and either parametric or nonparametric coefficients of correlation will be run between subjective HIN difficulty, objective HIN assessments, OHC function, AN function, central auditory processing, and cognitive functions
2. a mixed effect model with variation between and within AN synaptopathy groups and OHC dysfunction groups (individual subjects will be considered as random) will be used to calculate:
    a. the percent of variance contribution to HIN function
    b. the variance component ratio of OHC dysfunction vs. AN dysfunction
3. univariate and multivariate models will be applied to the data as described in Specific Aim 1.1 to determine the relationship between mean HIN performance and the other independent

variables (Table 3) in all subjects in order to identify statistically significant factors that contribute to HIN performance

Power analysis: Using a mixed effect model with two OHC groups (Groups 2, 5; n=100 per group), two AN synaptopathy groups (Groups 1, 4; n=100 per group), and two mixed OHC and AH groups (Groups 3, 6; n=100 per group), we will be able to detect a minimum detectable variance component ratio of 0.45 on a continuously measured primary outcome with power of 80%.

Specific Aim 2: to determine whether specific strategies employed by HAs to optimize HIN performance effectively compensate for either OHC or AN dysfunction

n = 1,000 subjects

Statistical Methods: described in detail in the Data Analysis section of the Research Strategy.

1. subjects will be rank ordered by $_{hf}$PTA, and correlations will be calculated between $_{hf}$PTA and the remaining variables
2. subjects within each group will be categorized by $_{hf}$PTA as either Normal (0-12.5 dB HL), Minimal SNHL (12.6-25 dB HL), or Mild SNHL (< 26 dB HL)
    a. ANOVA will be used to determine statistically significant differences in objective HIN performance, OHC function, and AN function
3. ANCOVA will be run to compare these variables among HA feature or control groups

Power analysis: Again, using mean CAP amplitude as the primary outcome, two hundred (200) subjects per group with equal (100) number of subjects with or without difficulty HIN, we will be able to detect 0.28 EF difference among groups with 80% power and a significance of 0.05. This can be translated to a 0.046 SNR Loss difference on HIN performance (QuickSIN) measured by CAP amplitude (standard deviation= 0.166). For the experimental group and HIN difficulty interactions, we will be able to detect an EF of 0.325 which is equivalent to 0.054 μV on CAP amplitude.