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The effect of increasing pulse phase duration on neural responsiveness of the electrically-stimulated cochlear nerve

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Abstract

Objective: This study aimed to 1) investigate the effects of increasing the pulse phase duration (PPD) on the neural response of the electrically-stimulated cochlear nerve (CN) in children with cochlear nerve deficiency (CND), and 2) compare the results from the CND population to those measured in children with normal-sized CNs.

Design: Study participants included 30 children with CND and 30 children with normal-sized CNs. All participants used a Cochlear™ Nucleus® device in the test ear. For each subject, electrically-evoked compound action potential (eCAP) input/output (I/O) functions evoked by single biphasic pulses with different PPDs were recorded at three electrode locations across the electrode array. PPD durations tested in this study included 50, 62, 75 and 88 μ s/phase. For each electrode tested for each study participant, the amount of electrical charge corresponding to the maximum comfortable level measured for the 88 μ s PPD was used as the upper limit of stimulation. The eCAP amplitude measured at the highest electrical charge level, the eCAP threshold (i.e., the lowest level that evoked an eCAP) and the slope of the eCAP I/O function were measured. Generalized Linear Mixed effect Models (GLMMs) with study group, electrode location and PPD as fixed effects and subject as the random effect were used to compare these dependent variables measured at different electrode locations and PPDs between children with CND and children with normal-sized CNs.

Results: Children with CND had smaller eCAP amplitudes, higher eCAP thresholds and smaller slopes of the eCAP I/O function than children with normal-sized CNs. Children with CND who

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had fewer electrodes with a measurable eCAP showed smaller eCAP amplitudes and flatter eCAP I/O functions than children with CND who had more electrodes with eCAPs. Increasing the PPD did not show a statistically significant effect on any of these three eCAP parameters in the two subject groups tested in this study.

Conclusions: For the same amount of electrical charge, increasing the PPD from 50 to 88 μ s for a biphasic pulse with a 7 μ s interphase gap did not significantly affect CN responsiveness to electrical stimulation in human CI users. Further studies with different electrical pulse configurations are warranted to determine whether evaluating the eCAP sensitivity to changes in the PPD can be used as a testing paradigm to estimate neural survival of the CN for individual CI users.

Keywords

cochlear nerve; electrically evoked auditory compound action potentials; pulse phase duration; neural survival

INTRODUCTION

Cochlear nerve deficiency (CND) refers to a small (hypoplastic) or absent (aplastic) cochlear nerve (CN) as revealed by high-resolution magnetic resonance imaging (MRI). The proposed pathogenesis of CND is the arrested inner ear development during embryogenesis (Jackler et al., 1987), which results in a partially or completely undeveloped cochlear nerve (CN). The degree of damage in the CN depends on the time when the inner ear development stops, with earlier stops leading to greater damage.

Cochlear implantation has been used as a treatment option for children with CND for nearly two decades. Due to advances in imaging techniques and expansion in cochlear implant (CI) candidacy criteria, the number of children with CND who receive CIs at a young age has increased. This new clinical trend creates a tremendous challenge for clinicians who manage this unique patient population. Programming the speech processor of a CI for individual patients requires selecting appropriate stimulation parameters, including the number of active stimulating electrodes, the programming rate, the pulse phase duration (PPD), the stimulation level, etc., for individual electrodes. In adult CI users, these programming parameters can be selected based on behavioral responses and verbal descriptions. However, using the same process with young children can be challenging or even impossible due to a lack of reliable behavioral responses or sufficient language skills. Complicating programming efforts further is the fact that up to 60% of children with CND have concurrent neurological deficits (Birman et al., 2016; Huang et al., 2010), which limits their abilities to provide reliable behavioral responses regardless of age. Currently, the field lacks an effective evidence-based clinical practice for managing implanted children with CND.

In current practice, at least in an early post-implant stage, programming parameters used in children with CND are often similar to those used in typical pediatric CI users. Unfortunately, many children with CND show poor responsiveness to the electrical stimulation defined by these typical parameters due to a combined effect of the young age, the declined cochlear nerve (CN) health and the potentially impaired cognitive function. For

these children, it is very common for clinicians to increase the amount of electrical charge (PPD * current level per phase) delivered by individual electrodes with the attempt to improve the overall behavioral responsiveness. Due to the limit of electrode voltage compliance, increasing electrical charge often necessitates increasing the PPD. As a result, prolonged PPDs are often used in this unique patient population (Buchman et al., 2011; Teagle et al., 2010).

Results of previous studies have shown that the neural membrane of the CN functions as a leaky integrator (Abbas & Brown, 1991; Loeb et al., 1983; Miller et al., 1995; Parkins & Colombo, 1987; Shepherd & Javel, 1999; van den Honert & Stypulkowski, 1984). Specifically, with the same amount of electrical charge, longer pulses stimulate the CN less effectively than short pulses due to the electrical leakage occurring at the neural membrane. Therefore, using prolonged PPDs does not necessarily guarantee improved neural responsiveness to electrical stimulation. In other words, the reduced current-delivery-efficiency of prolonged pulses might counteract the boosting effect of high electrical charge on CN responsiveness. In addition, delivering excessive electrical charge using prolonged PPDs can lead to reduced CI battery life due to high power consumption. Therefore, it is clinically important to investigate whether pulses with prolonged PPDs can effectively stimulate the CN in implanted children with CND. In this study, the effective stimulation is defined/judged in a relative manner. It refers to the capability of a biphasic pulse with different PPDs to evoke a neural response generated by CN fibers. The stimulations are determined to be equally effective if neural responses evoked by pulses with different PPDs are comparable.

Neural responsiveness to electrical stimulation in the CN can be evaluated using electrophysiological measures of the electrically-evoked compound action potential (eCAP). The eCAP is a near-field recorded neural response generated by CN fibers. The eCAP recorded using an intra-cochlear electrode in human CI users consists of a negative peak (N1) within a time window of 0.2 – 0.4 ms after stimulus onset followed by a positive peak (P2) occurring around 0.6 – 0.8 ms (e.g., Brown & Abbas, 1990; Abbas et al., 1999). The presence of the eCAP depends on the existence of sufficient CN fibers responding synchronously to electrical stimulation. Therefore, it can be used to assess how well CN fibers near each CI electrode respond to electrical stimulation (i.e., CN responsiveness).

Evaluating the eCAP sensitivity to changes in the PPD can have a targeted impact on implanted children with CND by establishing whether electrical pulses with prolonged PPDs serve as effective stimulations for these patients. In addition, this line of research potentially has a broader impact on the field of cochlear implantation by determining whether this testing paradigm can be used to assess neural survival of CN fibers in human CI users. In guinea pigs, it has been shown that the electrically-evoked auditory brainstem response (eABR) threshold (i.e., the lowest stimulation level that can elicit an eABR) and the current level required to evoke an eABR with equal amplitude decreases as the PPD increases (Miller et al., 1995; Prado-Guitierrez et al., 2006). The magnitude of this effect is reduced in animals with losses of spiral ganglion neurons, with a larger reduction associated with greater neural loss (Prado-Guitierrez et al., 2006). In human CI users, it has also been shown that behavioral detection thresholds decreased as the PPD increased (e.g., Moon et al., 1993;

McKay & McDermott, 1997; Zeng et al., 1998; Bonnet et al., 2012; Chatterjee & Kulkarni, 2014). It should be pointed out that the current level tested at different PPDs was held constant in these studies. As a result, the amount of electrical charge used to stimulate neural tissues increased as the PPD increased, which led to lower eABR and behavioral detection thresholds and smaller increases in the current level required to evoke eABRs with equal amplitudes at longer PPDs. When holding the amount of electrical charge constant, Ramekers et al. (2014) reported that the effect of changing the PPD on the eCAP was partially abolished in guinea pigs and the magnitude of this effect was not associated with histological measures of neural degeneration of spiral ganglion neurons.

The results of several recent studies suggest that findings in animal models may not be easily generalizable to human listeners due to differences in species, stimulation level used in anesthetized animals vs awake human CI users, duration of deafness in acute deafened animals vs human CI users with years of deafness, and electrode placement in the cochlea. For example, it has been shown that anodic-leading, biphasic pulses are more effective than cathodic-leading ones for stimulating the auditory system in human CI users (e.g., Macherey et al., 2008; Undurraga et al., 2010; Undurraga et al., 2012; Undurraga et al., 2013; Hughes et al., 2017; Spitzer & Hughes, 2017; Hughes et al., 2018; Luo et al., 2019), which is opposite to most results obtained in animal models (e.g., Miller et al., 1997, 1998, 2001; Klop et al., 2004). Therefore, the null finding reported in Ramekers et al. (2014) does not completely exclude the possibility of using this eCAP testing paradigm to assess neural survival of the CN in human listeners. To date, the effect of increasing the PPD on the eCAP has not been systematically investigated in human CI users. This study was designed to address this need.

To investigate the potential association between the eCAP sensitivity to changes in the PPD and neural survival of the CN, results needed to be compared between two patient populations that differ in neural survival patterns. By definition, children with CND can be considered as a human model for poor CN survival. Therefore, comparing their results with those recorded in typical CI users who have normal-sized CNs provides an extremely valuable opportunity for verifying the effect of the PPD on the eCAP observed in animal models in human CI users.

In summary, it is clinically important to evaluate whether prolonged pulses provide effective stimulation for implanted children with CND. It is also scientifically important to determine whether the eCAP sensitivity to changes in the PPD can be used to assess neural survival of the CN in human CI users. This study measured the eCAP evoked by biphasic pulses with different PPDs in children with CND, and compared their results with those measured in children with normal-sized CNs. We hypothesized that longer pulses would be less effective than shorter pulses for stimulating the CN when the amount of electrical charge was kept constant due to electrical leakage occurring at the neural membrane. We expected that eCAPs evoked by prolonged pulses would have smaller amplitudes, shallower I/O functions and higher thresholds than those evoked by short pulses. We further hypothesized that poor CN survival would lead to reduced eCAP sensitivity to changes in the PPD. Children with CND were expected to show reduced PPD effects on the eCAP than children with normal-sized CNs.

MATERIALS AND METHODS

Subjects

Study participants included 30 children with CND (CND1-CND30) in the CND group and 28 children with normal-sized CNs (S1-S28) in the control group. Both ears were tested for two children with normal-sized CNs (S1 and S26). Only one ear was tested for all other study participants. Consequently, results of this study included data collected from 30 ears for each study group. Age at implantation ranged between 0.96 and 6.57 yrs (mean: 2.56 yrs, SD: 1.58 yrs) and between 0.84 and 5.73 yrs (mean: 2.57 yrs, SD: 1.39 yrs) for children with CND and children with normal-sized CNs, respectively. Age at testing ranged between 2.14 and 8.95 yrs (mean: 4.65 yrs, SD: 2.14 yrs) and between 1.98 and 17.35 yrs (mean: 5.30 yrs, SD: 2.11 yrs) for children with CND and children with normal-sized CNs, respectively. Results of two-tailed independent sample *t*-tests revealed no statistically significant difference in age at implantation ($t=-0.36$, $p=.719$) or age at testing ($t=-1.89$, $p=.063$) between these two study groups.

All study participants had congenital deafness and were Cochlear™ Nucleus® device (Cochlear Ltd., Macquarie, NSW, Australia) users with a full electrode insertion. All participants except for S2, S27 and S28 used an internal electrode array of 24RE[CA] in the test ear. The internal electrode array in the test ear was CI512 for S2 and S28, and CI532 for S27. The anatomical statuses of the CN and the inner ear were determined based on results of high resolution MRI and Computed Tomography (CT) temporal bone scans following the same protocol and criteria as described in He et al. (2018, 2019a). It should be pointed out that none of the study participants tested in He et al. (2018) participated in this study. There were 19 children with CND and one child with a normal-sized CN who were tested in this study and He et al. (2019a).

Detailed demographic information of these participants is listed in Table 1. The anatomical statuses of the CN and the inner ear are listed for each child with CND. Imaging results of all children included in the control group suggested normal inner ear anatomy. Therefore, their imaging results were not listed. The study was approved by the local Biomedical Institutional Review Board. Written, informed consents were obtained from study participants and/or their legal guardians prior to participation.

Procedures

Testing Electrodes—For children with normal-sized CNs, three electrodes across the electrode array were tested. These electrodes were typically electrodes 3, 12 and 21. For these subjects, electrode 3 and 21 was considered as the basal and the apical electrode, respectively. Electrode 12 was considered as the middle electrode. For children with CND, the eCAP could not be recorded at all stimulating electrode locations in all subjects, and the likelihood of measuring the eCAP reduces as the stimulating electrode moves from the base to the apex of the cochlea (He et al., 2018; He et al., 2019b). The method for selecting testing electrode locations for children with CND has been reported in detail in He et al. (2019a). Briefly, three electrodes across all electrode locations where an eCAP could be recorded were tested for each child with CND. These electrodes had a relatively equal

separation between “adjacent” electrode locations. Based on their relative locations among the electrodes with measurable eCAPs, these electrodes were considered as the “basal”, the “middle,” and the “apical” electrode in a relative manner in this study.

Stimulus—The stimulus was a biphasic, charge-balanced, cathodic-leading, electrical pulse. This is the standard stimulus used in clinical stimulation. Therefore, it was used in this study to ensure clinical relevance of the results. The stimulus was presented in a monopolar-coupled stimulation mode. The interphase gap was 7 μ s. PPDs tested in this study included 50, 62, 75 and 88 μ s/phase. The eCAP cannot be evoked using 25 or 37 μ s PPD in many children with CND (He et al., 2018; He et al., 2019b). Removing artifact contamination on the eCAP is challenging or even impossible for PPDs of 100 μ s or longer (He et al., 2019b). Therefore, these PPDs were not tested in this study.

eCAP Measures—The eCAP was recorded using the Advanced Neural Response Telemetry (NRT) (v. 4.3 and v. 5.1) function implemented in the Custom Sound EP commercial software (Cochlear Ltd, Macquarie, NSW, Australia). Responses were recorded using the two-pulse forward masking testing paradigm (Brown & Abbas, 1990). The stimulus was sent to individual CI electrodes via a N6 sound processor interfaced with a programming pod. Other parameters used for eCAP measures included a masker-probe-interval of 400 μ s, a 15 Hz probe rate, an effective sampling rate of 20 kHz, sampling delays ranged between 98 and 122 μ s, an amplifier gain of 40 dB, and 100 sweeps for the averaged eCAP response measured at all PPDs tested in this study.

For each electrode location tested for each study participant, the amount of current charge corresponding to the maximum comfortable level (i.e., the C level) measured for the 88 μ s PPD was used as the upper limit of stimulation level for all PPDs tested in this study. Shannon (1985) showed that pulses with shorter PPDs were perceived louder than those with longer PPDs by adult CI users when the amount of electrical current charge was held constant for PPDs of 100 – 500 μ s. As part of the pilot testing, the perceived loudness was compared for pulses with four different PPDs tested in this study when the amount of electrical charge was held constant in three children with CND and three children with normal-sized CNDs. These pilot data did not show a trend suggesting that pulses with shorter PPDs were perceived louder than pulses with longer PPDs. The discrepancy is probably due to differences in the step size of the PPD increment [13 μ s in this study vs 100 μ s in Shannon (1985)], the stimulus type [single pulse used in this study vs trains of biphasic pulses used in Shannon (1985)], the study participants [children tested in this study vs adults tested in Shannon (1985)] and the device type [24RE(CA) or newer CIs in this study vs the UCSF system in Shannon (1985)] tested in these two studies. For electrode 12 in the left ear of S26 (S26L), however, the electrical charge level needed to be decreased because the stimulation level in current level (CL) for shorter PPDs exceeded the upper limit of the stimulation level in CL for Cochlear™ Nucleus® devices. This study participant perceived the sound as “loud but comfortable” at all stimulation levels tested. No sign of discomfort was observed. In this case, we decided to use the electrical charge calculated for the 25 μ s PPD at 255 CLs as the upper limit of stimulation level. It should be pointed out that it was mathematically not feasible to use the same amount of electrical charge at different PPDs.

As a result, the highest electrical charge tested in this study slightly decreased (<0.48 nC) as the PPD decreased.

For each stimulating electrode tested in each study participant, the C level of the 88 μ s PPD was measured using the same procedure as that described in our previous studies (He et al., 2016, 2018, 2019a, 2019b; Luo et al., 2019). To record the eCAP I/O function, the first (masker) pulse was presented at the highest stimulation level in CL that was calculated based on the amount of electrical charge measured at the C level of the 88 μ s PPD. The second (probe) pulse was initially presented at 10 CLs below the masker level and then systematically decreased in steps of 3 CLs while the masker level was kept at 10 CLs higher than the probe level until no eCAP could be identified by the experimenter. A step size of 5 CL was occasionally used due to time constraints. Subsequently, the probe level was increased in steps of 1 CL until at least five eCAPs were recorded using this small step size. This procedure was repeated to obtain the eCAP I/O function for four PPDs. For each subject, it took up to six hours to complete all experiments.

Data Analysis

The presence/absence of the eCAP for each recorded trace was initially determined by the researcher who measured the eCAP and his/her decisions were subsequently confirmed by an experienced researcher (i.e., SH). Any disagreement between these two researchers were resolved through group discussions. Dependent variables (DVs) reflecting the neural responsiveness of the CN included the eCAP amplitude measured at the highest stimulation level, the eCAP threshold and the slope of the eCAP I/O function. The eCAP amplitude was measured as the difference in amplitude (in μ V) between the N1 and the P2 peak of the response. The eCAP threshold was defined as the lowest stimulation level (in nC) that could evoke an eCAP with an amplitude of 5 μ V or larger (Patrick et al., 2006). eCAP amplitudes were normalized to the eCAP amplitude recorded at the highest stimulation level measured for the 50 μ s PPD for each electrode tested in each study participant. These normalized amplitudes were plotted as a function of stimulation level in nC to obtain the eCAP I/O function. The slope of the eCAP I/O function was estimated using a sigmoidal regression function in the form of:

$$eCAP_N = d + \frac{a}{1 + e^{-b(L - L_0)}} \quad 1$$

where d represents the noise floor, a represents the upper bound of the normalized eCAP amplitude, L_0 represents the stimulation level (in nC) of the midpoint of the normalized eCAP amplitude, and b represents the estimated slope of the eCAP I/O function. The sigmoidal regression function was chosen for two reasons. First, it was used in Ramekers et al. (2014) to estimate the slope of the eCAP I/O functions when they investigated the eCAP sensitivity to changes in the PPD in guinea pigs. Second, the results of our previous studies (He et al., 2018; He et al., 2019a) showed that the sigmoidal regression function better characterized the eCAP I/O functions measured in children with CN than the linear regression function. For children with normal-sized CNs, these two regression functions could characterize the eCAP I/O function equally well. Statistical modeling was conducted using custom-designed MATLAB software (v.2019b, The Mathworks Inc., United States).

The parameters of the sigmoidal regression function were estimated using the trust-region-reflective algorithm with the default parameters implemented in MATLAB. This algorithm is a robust optimization technique for fitting nonlinear functions to experimental data (Branch et al., 1999). Outliers of the slope were determined based on goodness of fit (i.e., R^2) and the estimated values for each study group using the three scaled median absolute deviations criterion (Leys et al., 2013).

For 18 children with CND, the most apical electrode where an eCAP could be recorded was electrode 20, 21 or 22 (see Table 1). As a result, the electrodes tested in this subgroup of children with CND were similar to those tested in children with normal-sized CNs. These subjects were further classified as the CND group 2. In contrast, the remaining 12 children with CND only showed eCAPs at a small group of electrodes near basal regions of the cochlea. They were classified as the CND group 1.

All statistical analyses were conducted using SPSS Statistic 25 (IBM Corp.). Statistical significance was determined at the 95% confidence level (i.e. $p < .05$). Generalized Linear Mixed effect Models (GLMMs) allows response variables from different distributions and can robustly handle the missing data. Therefore, it was selected for analyzing the data of this study. The group difference in the eCAP between the CND group 1 and the CND group 2 was compared using GLMMs with study group as the fixed effect and subject as the random effect. If this initial data analysis revealed a non-significant difference between these two CND subgroups, their results were combined and compared with the data measured in children with normal-sized CNs. Otherwise, eCAP results were compared among three subject groups: the CND group 1, the CND group 2 and the control group (i.e., children with normal-sized CNs). GLMMs with study group, electrode location and PPD duration as the fixed effects and subject as the random effect were used to compare the effect of increasing the PPD on the eCAP at three electrode locations between children with CND and children with normal-sized CNs or among three subject groups. Including subject as a random factor would account for the potential non-independence of data points collected within the same subject.

To rule out the possibility that the group difference in the eCAP was due to the difference in the stimulation levels, the same GLMMs were used to compare the highest stimulation level and the dynamic range among the CND group 1, the CND group 2 and the control group. The dynamic range was defined as the difference in stimulation level (in dB) between the eCAP threshold and the C level measured for the 88 μ s PPD.

RESULTS

Figure 1 shows eCAP waveforms and I/O functions measured at one apical electrode location in one child with CND (CND4) and one child with normal-sized CN (S1L). The upper and lower panels show the results measured in CND4 and S1L, respectively. eCAP waveforms measured at different PPDs are shown in panels listed in the first four columns, with each column showing results measured at one PPD. In each panel, the top and the bottom trace represent the eCAP recorded at the threshold and the highest stimulation level, respectively. In general, these eCAP responses consist of identifiable N1 and P2 peaks, and

are relatively free of electrical artifact contamination. Compared with responses recorded in CND4, the eCAPs measured in S1L had larger amplitudes and lower thresholds. Panels listed in the rightmost column show eCAP I/O functions measured at four PPDs in each study participant. For both study participants, there was substantial overlap in eCAP I/O functions measured at different PPDs.

eCAP Measures

Table 2 provides a summary of statistical findings in the eCAP. The details of the statistical findings for both between- and within-group comparisons are reported for each DV listed below.

The eCAP Amplitude—The results of GLMMs showed that there was no statistically significant difference in the eCAP amplitude between the CND group 1 and the CND group 2 ($F_{(1, 265.633)} = 0.060$, $p = .807$). Consequently, data measured in these two CND subgroups were combined and compared with those measured in children with normal-sized CNs.

Figure 2 shows the means and the standard deviations of eCAP amplitudes measured at the highest electrical charge level in children with CND (filled circles) and children with normal-sized CNs (open triangles). It is clear that children with CND had much smaller eCAP amplitudes than children with normal-sized CNs. Increasing the PPD did not strongly affect the eCAP amplitude at any electrode location in either subject group.

The results of GLMMs revealed statistically significant effects of study group ($F_{(1, 666.07)} = 156.146$, $p < .001$) and electrode location ($F_{(2, 494.13)} = 8.841$, $p < .001$). There was no statistically significant effect of PPD ($F_{(3, 320.87)} = 0.494$, $p = .687$). There was no statistically significant interaction among effects of study group, electrode location or PPD [group*electrode: $F_{(2, 494.13)} = 2.583$, $p = .077$; group*PPD: $F_{(3, 320.87)} = 0.545$, $p = .652$; electrode*PPD: $F_{(6, 240.61)} = 0.23$, $p = 1.00$; group*electrode*PPD: $F_{(6, 240.61)} = 0.018$, $p = 1.00$]. The results of pairwise comparisons with Bonferroni correction showed that eCAP amplitudes measured at the basal electrode were significantly larger than those measured at the middle ($p < .001$) and the apical ($p = .004$) electrode location. There was no statistically significant difference in the eCAP amplitude measured at the middle and the apical electrode location ($p = .785$).

An inspection of study results, along with the non-significant interaction between effects of study group and electrode location, suggests that children with CND had significantly smaller eCAP amplitudes than children with normal-sized CNs at all three electrode locations tested in this study. The non-significant PPD effect, along with the non-significant interaction between effects of study group and PPD, indicated that increasing the PPD did not significantly affect the eCAP amplitude in children with CND or children with normal-sized CNs.

In summary, children with CND had smaller eCAP amplitudes than children with normal-sized CNs at three electrode locations tested. Among the results recorded at three electrode locations, eCAPs recorded at the basal electrode location had the greatest eCAP amplitude.

When electrical charge was held constant, increasing the PPD did not significantly affect the eCAP amplitude in either study group.

The eCAP Threshold—The results of GLMMs showed a statistically significant difference in the eCAP threshold between the CND group 1 and the CND group 2 ($F_{(1, 333.52)} = 4.964, p=.027$). Therefore, results of these two CND subgroups were independently compared with data measured in children with normal-sized CNs.

Figure 3 depicts the means and the standard deviations of the eCAP threshold measured at different PPDs at three electrode locations in the CND group 1 (black circles), the CND group 2 (grey hexagons) and the control group (i.e., children with normal-sized CNs, black triangles). These data clearly show that both CND groups had much higher eCAP thresholds than the control group. The eCAP threshold measured in all study groups varied across electrode locations. These observations were confirmed by statistically significant effects of study group ($F_{(2, 675.09)} = 1252.650, p<.001$) and electrode location ($F_{(2, 459.26)} = 183.573, p<.001$), as revealed by the results of GLMMs. The results of pairwise comparisons with Bonferroni correction showed that the control group had significantly lower eCAP thresholds than the CND group 1 ($p<.001$) and the CND group 2 ($p<.001$). The eCAP thresholds measured in the CND group 2 were also significantly lower than those measured in the CND group 1 ($p=.013$). There was a significant difference in the eCAP threshold between any two electrode locations ($p<.001$ for all comparisons), with the apical electrode showing the highest eCAP threshold followed by the middle electrode. The basal electrode showed the lowest eCAP threshold.

It is apparent that the threshold variation pattern differed among groups. Consistent with this observation, the results of GLMMs showed a statistically significant interaction between effects of study group and electrode location ($F_{(4, 459.01)} = 54.777, p<.001$). The results of pairwise comparisons with Bonferroni correction showed that both CND groups had significantly higher eCAP thresholds than the control group at all three electrode locations ($p<.001$). The CND group 1 showed significantly higher eCAP thresholds than the CND group 2 only at the apical electrode location ($p<.001$). There was no significant difference in the eCAP threshold measured at the basal and the middle electrode location between these two CND groups ($p=1.000$). For both CND groups, the lowest eCAP threshold was recorded at the basal electrode location and the highest eCAP threshold was measured at the apical electrode location. The differences in the eCAP threshold measured between any two electrode locations were all statistically significant ($p<.001$). For children with normal-sized CNs, the eCAP threshold measured at the middle electrode location was significantly higher than those measured at the basal ($p<.001$) and the apical ($p<.001$) electrode location. There was no statistically significant difference in the eCAP threshold measured at the basal and the apical electrode location ($p=1.00$).

Inspection of Figure 3 also suggests that increasing the PPD did not have an apparent effect on the eCAP threshold at any electrode locations in any study groups. This observation was confirmed by the non-significant effect of PPD on the eCAP threshold ($F_{(3, 320.24)} = 0.093, p=.964$), the non-significant interaction between effects of PPD and electrode location ($F_{(6, 217.90)} = 0.075, p=.998$) and the non-significant interaction between effects of PPD and

study group ($F_{(6, 320.22)} = 0.218$, $p = .971$). There was no statistically significant interaction among effects of study group, electrode location and PPD ($F_{(12, 217.75)} = 0.116$, $p = 1.000$).

In summary, children with CNDe had significantly higher eCAP thresholds than children with normal-sized CNs. The highest eCAP thresholds were measured at the apical electrode location in the group of children with CNDe who had fewer electrodes with measurable eCAPs. The eCAP threshold varied across electrode locations, with different variation patterns observed in different study groups. Increasing the PPD did not significantly affect the eCAP threshold when electrical charge was held constant.

The slope of eCAP I/O Function—The results of GLMMs revealed a statistically significant difference in slope of the eCAP I/O function between the CNDe group 1 and the CNDe group 2 ($F_{(1, 181.57)} = 6.494$, $p = .012$). Therefore, results of these two CNDe subgroups were not combined when compared with the data of the control group.

Figure 4 illustrates the means and the standard deviations of slopes of the eCAP I/O function estimated using sigmoidal regression at four PPDs for the CNDe group 1 (black circles), the CNDe group 2 (grey hexagons) and the control group (black triangles). Panels listed in each column show results obtained at one electrode location. An inspection of this figure suggests that subjects in both CNDe groups had smaller slopes than children with normal-sized CNs. This observation was confirmed by a significant effect of study group ($F_{(2, 432.79)} = 114.454$, $p < .001$), as shown in the results of GLMMs. The results of pairwise comparisons with Bonferroni correction showed that slopes measured in the control group were significantly greater than those measured in the CNDe group 1 ($p < .001$) and the CNDe group 2 ($p < .001$). Variations in slopes measured at different electrode locations seems to be negligible. Consistent with this observation, the results of GLMMs revealed a non-significant effect of electrode location ($F_{(2, 288.20)} = 0.543$, $p = .582$). The lack of significant interaction between effects of study group and electrode location ($F_{(4, 291.61)} = 0.939$, $p = .441$) suggested that the group difference in slope existed in results measured at all electrode locations.

Data shown in Figure 4 also suggest that increasing the PPD did not show a clear and consistent effect on the slope in any study group. This observation was confirmed by the lack of a statistically significant effect of PPD ($F_{(3, 209.99)} = 0.972$, $p = .407$), the non-significant interaction between effects of study group and PPD ($F_{(6, 211.86)} = 0.822$, $p = .554$), and the non-significant interaction between effects of electrode location and PPD ($F_{(6, 145.13)} = 0.614$, $p = .719$). The interaction among effects of study group, electrode location and PPD was also not statistically significant ($F_{(12, 152.66)} = 0.479$, $p = .925$).

In summary, children with CNDe had significantly smaller slopes of the eCAP I/O function than children with normal-sized CNs at all three electrode locations. The smallest slopes were recorded in children with CNDe who only had eCAPs at a subgroup of electrodes near the basal end of the cochlea. Increasing the PPD did not show a statistically significant effect on the slope of the eCAP I/O function in children with CNDe or children with normal-sized CNs.

The Highest Stimulation Level and the Dynamic Range

Table 3 provides a summary of statistical findings for the highest stimulation level and the dynamic range used in different subject groups. The details of the statistical findings for these two stimulating parameters are reported below.

Figure 5 shows the means and the standard deviations of the highest stimulation level (in nC) used to evoke the eCAP at four PPDs and three electrode locations in three subject groups. It is apparent that the highest stimulation level varied among subject groups and electrode locations. In addition, the group difference in the highest stimulation level appeared to be larger at the apical electrode location than the other two electrode locations. These observations were confirmed by significant effects of subject group ($F_{(2, 677.68)} = 1278.693, p < .001$) and electrode location ($F_{(2, 456.34)} = 94.654, p < .001$), as well as a significant interaction between these two fixed effects ($F_{(4, 456.08)} = 33.181, p < .001$). The results of pairwise comparisons with Bonferroni correction showed that levels used in the CND group 1 were significantly higher than those used in the CND group 2 ($p = .003$). Levels used in the control group were significantly lower than those used in both CND subgroups ($p < .001$). There was a significant difference in the level between any two electrode locations ($p < .001$). The highest and the lowest level were used at the apical and the basal electrode location, respectively. The CND group 1 showed a significantly higher stimulation level than the CND group 2 only at the apical electrode location ($p < .001$). Both groups had higher stimulation levels than the control group at all electrode locations ($p < .001$). An inspection of Figure 5 indicates that increasing the PPD did not show an apparent effect on the stimulation level in any subject group at any electrode location tested. This observation was confirmed by the non-significant effect of PPD ($F_{(3, 318.40)} = 0.482, p = .695$), the non-significant interaction between PPD and any other fixed effects [group*PPD: $F_{(6, 318.38)} = 0.5027, p = 1.000$; electrode*PPD: $F_{(6, 214.92)} = 0.2011, p = 1.000$; group*electrode*PPD: $F_{(12, 214.77)} = 0.018, p = 1.000$].

Figure 6 depicts the means and the standard deviations of the dynamic range (in dB) of three subject groups measured at four PPDs and three electrode locations. These data clearly showed a group difference in the dynamic range that appeared to vary at different electrode locations. The results of GLMMs revealed significant effects of subject group ($F_{(2, 643.01)} = 55.697, p < .001$), electrode location ($F_{(2, 424.43)} = 32.340, p < .001$) and a significant interaction between effects of subject group and electrode location ($F_{(4, 424.19)} = 6.955, p < .001$). The results of pairwise comparisons with Bonferroni correction showed that the control group had significantly larger dynamic ranges than both CND subgroups ($p < .001$). There was no significant difference in the dynamic range between the CND group 1 and the CND group 2 ($p = 1.000$). The dynamic range measured at the basal electrode location was larger than those measured at the middle ($p < .001$) and the apical electrode location ($p < .001$). There was no significant difference in the dynamic range measured between results at the middle and the apical electrode location ($p = .594$). The significant interaction between effects of subject group and electrode location was due to different patterns observed in children with CND and children with normal-sized CNs. Specifically, for children in both CND groups, the dynamic range measured at the basal electrode location was significantly larger than those measured at the middle and the apical electrode location ($p < .05$). There

was no significant difference in the dynamic range measured at the middle and the apical electrode location ($p > .05$). In contrast, children with normal-sized CNs showed significantly smaller dynamic ranges at the middle electrode location compared with those measured at the basal and the apical electrode location ($p < .05$). There was no significant difference in the dynamic range measured at the basal and the apical electrode location ($p > .05$) in children with normal-sized CNs. The results of GLMMs also showed a non-significant effect of PPD ($F_{(3, 306.55)} = 0.684$, $p = .536$). No other interaction among effects of study group, electrode location, or PPD was statistically significant [group*PPD: $F_{(6, 306.40)} = 0.763$, $p = .600$; electrode*PPD: $F_{(6, 208.28)} = 0.035$, $p = 1.000$; group*electrode*PPD: $F_{(12, 209.37)} = 0.082$, $p = 1.000$].

In summary, children with CN had significantly higher stimulation levels and smaller dynamic ranges than children with normal-sized CNs. The highest stimulation levels were used in children with CN who only had eCAPs at a subgroup of electrodes near the basal end of the cochlea. Increasing the PPD did not show a statistically significant effect on the highest stimulation level or the dynamic range in any subject groups.

DISCUSSIONS

This study aimed to 1) evaluate the effect of increasing the PPD on the eCAP in children with CN, and 2) compare their results with those measured in children with normal-sized CNs. The proposed working hypotheses were 1) longer pulses were less effective than shorter pulses for stimulating the CN when the amount of electrical charge was kept constant, and 2) poor CN survival led to reduced eCAP sensitivities to changes in the PPD.

eCAPs Measured in Children with CN and Children with Normal-Sized CNs

Results of this study showed that children with CN had smaller eCAP amplitudes, higher eCAP thresholds and smaller slopes of the eCAP I/O function than children with normal-sized CNs at all PPDs tested in this study. These results are consistent with those reported in our previous studies for these two subject groups (He et al., 2018; He et al., 2019a). It is well known that the eCAP amplitude increases with the stimulation level before saturation. When all other factors are held constant, higher maximum eCAP amplitudes also lead to greater slopes of the eCAP I/O function. To exclude the possibility that the group differences in the eCAP were due to the group difference in the upper stimulation level and/or the dynamic range used for eCAP recording, these two stimulating parameters were compared among three subject groups. Results showed higher upper stimulation levels and smaller dynamic ranges for both CN subgroups than the control group, which should result in higher eCAP amplitudes and greater slopes of the eCAP I/O function for children with CN if the CN responsiveness is comparable among subject groups. However, our results showed the exact opposite pattern. Therefore, the observed group difference in the eCAP reflects the difference in the CN health among subject groups instead of the difference in these two stimulation parameters. Overall, these results are consistent with the literature showing the association between poor cochlear nerve survival and these eCAP parameters in human listeners and animal models (e.g., Miller et al., 1994; Kim et al., 2010; Prado-Guitierrez et al., 2006; Ramekers et al., 2014, 2015; Pfingst et al., 2017; He et al., 2018; He et al., 2019a).

In this study, children with CND showed the largest eCAP amplitudes and the lowest eCAP thresholds at the basal electrode location than at the middle and the apical electrode location. More interestingly, CND subjects who had fewer electrodes with a measurable eCAP showed smaller eCAP amplitudes and flatter eCAP I/O functions than CND subjects who had more electrodes with eCAPs. The observed electrode effect on the eCAP in children with CND as well as the difference between these two CND subgroups are consistent with the expected neural surviving pattern that is predicated based on the pathogenesis of CND. Specifically, the development of cochlear nerve fibers is expected to follow the base-to-apex sequence due to two reasons. First, both cochlear duct development and cochlear hair cell maturation follow a base-to-apex sequence (Rubel, 1978; Lavigne-Rebillard & Pujol, 1988; Arnold & Lang, 2001; Jeffery & Spoor, 2004; Yasuda et al., 2007). Second, the development of the cochlear nerve is dependent on the neurotrophic factors secreted by hair cells located in the cochlear duct (Rubel & Fritzsch, 2002). As a result, cochlear nerve fibers located near basal regions develop earlier than those located near apical regions of the cochlea. In cases of CND, the earlier interruption of the inner ear development leads to the greater damage in CN fibers expanding toward more basal regions of the cochlea. As a result, children with CND are expected to have better neural survival at the base than the apex of the cochlea. In addition, children with more severe CND are expected to have less neural survival at more regions of the cochlea. Consistent with the first predicted result, it has been shown that the likelihood of measuring the eCAP reduced as the stimulating electrode moved from the base to the apex of the cochlea, with many apical stimulation sites showing no measurable neural responses (He et al., 2018). Consistent with the second predicted result, data of this study showed that children with CND who had eCAPs only at basal electrodes (i.e., less neural survival due to more severe CND) showed reduced neural responsiveness to electrical stimulation compared with those who had eCAPs at both the base and the apex of the cochlea. Consistent with these eCAP results, the electrical charge measured at the C level increased as the stimulation electrode moved toward more apical regions in children with CND (Figure 5). In addition, children in the CND group 1 required more electrical charges for reaching the C level at the apical electrode location than children in the CND group 2 (Figure 5). These perceptual results further support our interpretation. Overall, these results indicated that the number of electrodes with eCAPs may provide an indicator for CN survival (a.k.a severity of CND) in children with CND.

The PPD Effect on the eCAP

The results of this study did not demonstrate a significant PPD effect on the eCAP amplitude, the eCAP threshold or the slope of the eCAP I/O function in children with CND or children with normal-sized CNs when the amount of electrical charge was held constant. These results are consistent with the data measured for the biphasic pulse with a 30 μ s interphase gap (IPG) in guinea pigs reported in Ramekers et al. (2014). The null effect of the PPD observed in both study groups with different neural survival patterns is also consistent with the non-significant correlation between the PPD effect on the eCAP and results of histological measures of neural degeneration in guinea pigs (Ramekers et al., 2014). Overall, these results do not support our proposed working hypotheses.

Strength-Duration Functions

Most previously published studies focused on the PPD effect on physiological or behavioral detection threshold (i.e., strength-duration function). Therefore, results of the eCAP strength-duration function measured in this study were compared with those published in animal models as well as in human CI users.

Comparison with Results of Animal Studies—Results of single fiber studies showed that less electrical charge was needed for biphasic pulses with shorter PPDs than those with longer PPDs to evoke an action potential in CN fibers of squirrel monkeys (Parkins & Colombo, 1987) and cats (van den Honert & Stypulkowski, 1984; Shepherd & Javel, 1999). These results were also confirmed by psychophysical strength-duration functions measured in monkeys (Pfingst et al., 1991) and cats (Smith & Finley, 1997). However, Ramekers et al. (2014) reported lower eCAP thresholds measured at longer PPDs in guinea pigs. There was no significant effect of the PPD on the eCAP threshold in children with CN or children with normal-sized CNs tested in this study. Factors accounting for the discrepancy in results reported among these studies remain unclear. We can only speculate that differences in species, PPDs and devices tested in these studies might have played a role.

Comparison with Results of Psychophysical Studies in Human CI Users—

Several studies have assessed the strength-duration function for behavioral detection threshold in human CI users (e.g., Shannon, 1985; Moon et al., 1993; Bonnet et al., 2012; Chatterjee & Kulkarni, 2014). Despite differences in the PPD, the duration of pulse-train stimulation, the device, the stimulation mode and the study participants tested in these studies, results of these studies consistently showed that behavioral detection thresholds decreased as the PPD increased when the current level was held constant at different PPDs. Results of this study, however, showed a non-significant effect of the PPD on the eCAP when the amount of electrical charge was held constant.

Direct comparison between results of this study and those reported in psychophysical studies is difficult due to two reasons. The first reason is the difference in the stimulus used. Single biphasic pulses were used to evoke the eCAP in this study. In comparison, trains of biphasic pulses were used to measure behavioral detection thresholds in these psychophysical studies. It is well known that the eCAP threshold is not a strong predictor for the behavioral detection threshold for individual CI users (e.g., Abbas et al., 1999; Gordon et al., 2002, 2004; Thai-Van et al., 2004; McKay et al., 2005; Holdstad et al., 2009), presumably due to auditory temporal integration [see Gerken et al. (1990), for review]. The second reason is the difference in the stimulating parameter that was held constant in these studies. Whereas the electrical charge was kept constant in this study, the current level in μA was kept constant in these psychophysical studies. This critical difference makes comparing results across studies difficult.

Consideration for Clinical Applications

Results of this study have three potential clinical applications. First, as mentioned previously, data from this study indicate that the number of electrodes with measureable eCAPs appears to provide an indicator for the degree of CN damage in children with CN.

It has been shown that the mere presence of the eCAP predicts speech perception performance in children with CN (Teagle et al., 2010; Buchman et al., 2011). Prior to this study, the neurophysiological mechanisms underlying this predictive relationship were unknown. Results of this study suggest that the degree of CN damage, as reflected by the presence/absence of the eCAP, accounts for, at least partially, the predictive relationship between the eCAP and the development of speech and language skills in children with CN. Taken together, these results suggest that the eCAP can potentially be used as a clinical tool for predicting CI outcomes for individual patients with CN at an early implant stage. This potential clinical application is important because a timely transition to other intervention strategies (e.g., the auditory brainstem implant) is crucial for the achievement of maximum potential of speech and language development for children with CN.

Second, results from this study confirm our previous finding showing greater CN damage near more apical regions of the cochlea in children with CN. These results suggest the importance of assessing how many CI electrodes can serve as functional channels (i.e., CI electrodes that can deliver sufficient information for auditory detection and discrimination) for individual children with CN. Currently, we are combining the eCAP and the electrically evoked auditory event-related potentials to investigate this issue.

Finally, the results of this study demonstrate that increasing the PPD while keeping the electrical charge level constant does not significantly reduce the neural responsiveness of the electrically-stimulated CN to biphasic pulses with an interphase gap of 7 μ s in human CI users. Clinically, these results support the practice of providing more electrical charge by increasing the PPD for children with CN. However, these results cannot be interpreted as suggesting that biphasic pulses with different PPDs work equally well for CI users because longer pulses produce less spatially selective stimulation (Grill & Mortimer, 1996; McKay & McDermott, 1997) and reduce the effective pulse rate compared with shorter pulses, which could potentially result in worse speech perception performance (e.g., Loizou et al., 2000; Frijns et al., 2003; Runge et al., 2018). In other words, the benefit of improved audibility due to high electrical charge may be diminished by the disadvantages of fewer discrete functional channels and reduced temporal information delivered by the need to use slower pulse rates because of the prolonged PPDs.

Consideration for Scientific Application

Results of this study revealed that there was no difference in the size of the PPD effect on the eCAP between children with CN and children with normal-sized CNs. In general, this result does not prove the idea that eCAP sensitivity to the PPD effect can provide an indicator for CN survival in human CI users, at least for the configuration of biphasic pulse and PPDs tested in this study.

Study Limitations

One study limitation was that only four PPDs were tested in this study, primarily due to the poor responsiveness of the CN to electrical stimulation in children with CN and the challenge of removing electrical artifact contamination on the eCAP at prolonged PPDs. As a result, it remains unknown whether stronger PPD effects on the eCAP could be observed at

other PPDs. The other study limitation was the slightly reduced electrical charge level used at shorter PPDs. However, this difference is less than 0.48 nC in all study participants. Therefore, we do not believe that this trivial difference in electrical charge level across PPDs could account for the null findings of this study. Finally, a more robust PPD effect was reported for biphasic pulses with a 2.1 μ s IPG in Ramekers et al. (2014). In addition, it has been shown that the PPD effect is not consistent among CI users with different devices. Specifically, all study participants with Cochlear™ Nucleus® device tested in Chatterjee & Kulkarni (2014) showed decreased detection thresholds with increased PPDs. This effect was not consistently observed in study participants with Advanced Bionics™ devices. One noticeable difference between these two devices is the duration of the IPG implemented in the biphasic pulses. Whereas an IPG of 7 μ s was used as one of the default stimulating parameters in Cochlear™ Nucleus® devices, the biphasic pulse used in Advanced Bionics™ device does not include an IPG. These data suggest that the configuration of the biphasic pulse used for stimulation is an important factor for evaluating the PPD effect in human CI users. Unfortunately, we did not evaluate the PPD effect using pulses with different configurations in this study due to time constraints. As a result, it remains unknown whether significant PPD effects could have been observed if biphasic pulses with shorter or no IPG tested.

CONCLUSIONS

For a given amount of electrical charge, increasing the PPD from 50 to 88 μ s/phase for a biphasic pulse with an IPG of 7 μ s does not significantly affect how well CN fibers near each CI electrode respond to electrical stimulation in children with CND and in children with normal-sized CNs. Evaluating the eCAP sensitivity to changes in the PPD with different pulse configurations is warranted in order to determine whether this testing paradigm is clinically useful for assessing neural survival of the CN for individual CI users.

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Figure 1. eCAP responses and eCAP I/O functions measured at electrode 1 in CND4 (upper panels) and electrode 3 in S1L (lower panels). Subject and electrode numbers are indicated in each panel. Normalized eCAP amplitudes measured at different PPDs are indicated using different symbols with different colors.

Figure 2.

The means and the standard deviations of the eCAP amplitude measured at the highest stimulation for different PPDs and three electrode locations in two study groups. Results measured in children with CND and children with normal-sized CNs (i.e., control) are indicated using filled circles and open triangles, respectively. Each column shows results recorded at one electrode location (i.e., basal, middle or apical electrode).

Figure 3.

The means and the standard deviations of the eCAP threshold measured at different PPDs and electrode locations in the CND group 1 (black circles), the CND group 2 (grey hexagons) and the control group (black triangles). Each column shows results recorded at one electrode location (i.e., basal, middle or apical electrode).

Figure 4.

The means and the standard deviations of the slope of the eCAP I/O function estimated using the sigmoidal regression function for results measured at different PPDs and three electrode locations in the CND group 1 (black circles), the CND group 2 (grey hexagons) and the control group (black triangles). Each column shows results recorded at one electrode location (i.e., basal, middle or apical electrode).

Figure 5.

The means and the standard deviations of the highest stimulation level used in the CND group 1 (black circles), the CND group 2 (grey hexagons) and the control group (black triangles). Each column shows results recorded at one electrode location (i.e., basal, middle or apical electrode).

Figure 6.

The means and the standard deviations of the dynamic range of the CND group 1 (black circles), the CND group 2 (grey hexagons) and the control group (black triangles). Each column shows results recorded at one electrode location (i.e., basal, middle or apical electrode).

Table 1.

Demographic information of study participants who participated in this study. M = male, F = female, L = left, R = right, AAI: age at implantation, AAT: age at testing, CN: cochlear nerve, IP-II: incomplete partition type II, IAC: internal auditory canal, BCNC: bony cochlear nerve canal.

Subject number	Gender	Ear tested	AAI (yrs)	AAT (yrs)	Imaging results			Electrode tested	
					CN in the IAC	IAC	BCNC	Cochlea	
CND1	F	L	3.36	5.90	Two small nerves	Narrow	Normal	Normal	3,10,16
CND2	F	R	2.81	5.39	Single nerve	Normal	Stenosis	Normal	1,4,7
CND3	F	R	1.55	4.05	Two small nerves	Normal	Stenosis	Normal	3,12,22
CND4	M	R	2.23	2.79	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND5	M	L	6.03	8.31	Two small nerves	Narrow	Stenosis	Normal	1,3,7
CND6	M	L	1.86	2.58	Two small nerves	Normal	Stenosis	Normal	1,8,16
CND7	M	R	2.10	4.45	Two small nerves	Narrow	Stenosis	Normal	1,5,8
CND8	M	L	2.15	4.67	Two small nerves	Normal	Stenosis	Normal	3,12,21
CND9	M	L	1.24	2.31	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND10	F	L	0.96	3.69	Two small nerves	Normal	Stenosis	Normal	2,9,17
CND11	F	L	5.95	8.49	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND12	F	R	2.36	7.21	Single nerve	Normal	Normal	IP-2	3,12,21
CND13	M	R	6.57	8.95	Single nerve	Normal	stenosis	Normal	1,6,10
CND14	F	R	4.01	7.33	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND15	M	R	1.34	2.20	Two small nerves	Normal	Stenosis	Normal	3,12,21
CND16	F	L	4.65	6.93	Two small nerves	Narrow	Stenosis	Normal	1,12,21
CND17	F	R	1.40	4.06	Two small nerves	Normal	Stenosis	Normal	1,5,9
CND18	F	L	1.28	3.02	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND19	F	L	1.94	2.54	Single nerve	Narrow	Stenosis	Normal	3,12,21
CND20	F	L	1.17	2.85	Two small nerves	Narrow	Stenosis	IP-2	1,5,10
CND21	M	L	1.86	4.32	Two small nerves	Narrow	Stenosis	IP-2	1,3,6
CND22	M	R	2.55	4.42	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND23	M	R	1.01	2.33	Two small nerves	Narrow	Stenosis	Normal	3,12,21
CND24	F	R	1.20	2.17	Single nerve	Normal	Stenosis	Normal	1,4,8
CND25	F	L	2.57	4.69	Two small nerves	Narrow	Stenosis	Normal	1,5,11
CND26	F	R	2.98	5.82	Two small nerves	Normal	Stenosis	Normal	3,12,21

Subject number	Gender	Ear tested	AAI (yrs)	AAT (yrs)	Imaging results			Electrode tested
					CN in the IAC	IAC	BCNC	Cochlea
CND27	M	L	1.14	2.80	Two small nerves	Narrow	Stenosis	Normal
CND28	M	L	1.94	2.91	Two small nerves	Normal	Stenosis	Normal
CND29	F	R	4.64	8.34	Single nerve	Narrow	Stenosis	Normal
CND30	F	R	1.91	3.81	Two small nerves	Normal	Stenosis	IP-2
S1L	M	L	2.08	4.10				3,12,21
S1R	M	R	2.08	4.09				3,12,21
S2	F	R	2.84	4.82				3,12,21
S3	F	R	2.81	4.72				3,12,21
S4	F	R	1.71	2.61				3,12,21
S5	F	L	1.98	5.89				3,12,21
S6	F	R	1.83	4.06				3,12,21
S7	M	R	3.28	6.27				3,12,21
S8	F	L	1.33	3.97				3,12,21
S9	F	L	5.17	8.54				3,12,21
S10	F	R	1.98	6.49				5,12,21
S11	F	R	5.51	10.38				3,12,20
S12	M	R	4.31	6.82				3,12,21
S13	M	R	4.29	7.88				3,12,21
S14	F	L	1.21	1.98				3,12,21
S15	M	L	2.57	5.42				3,12,21
S16	M	L	0.92	2.55				4,12,21
S17	F	R	1.98	5.43				3,12,21
S18	M	R	5.73	9.34				3,12,21
S19	F	L	1.97	5.80				3,12,20
S20	M	R	1.62	5.30				3,12,21
S21	M	R	1.69	5.45				3,12,21
S22	M	R	0.84	2.64				3,12,21
S23	F	R	1.31	2.97				3,12,21
S24	F	R	3.45	6.07				3,12,21
S25	M	R	2.26	4.12				3,12,21

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Subject number	Gender	Ear tested	AAI (yrs)	AAT (yrs)	CN in the IAC			Imaging results		Electrode tested
					IAC	BCNC	Cochlea			
S26L	M	L	0.96	12.94						3,12,21
S26R	M	R	0.96	12.94						3,12,21
S27	F	L	3.45	4.93						3,12,21
S28	M	L	5.10	6.58						3,12,21

Table 2.

A summary of statistical findings in the eCAP. PPD: Pulse Phase Duration, CND: Cochlear Nerve Deficiency, CND1: the CND group1; CND2: the CND group 2, B: Basal, M: Middle, A: Apical, N.S.: Non-Significant

Effect	Amplitude	Threshold	Slope
Group	CND<Control	CND1>CND2 >Control	CND1<CND2<Control
Electrode	A and M < B	A>M>B	N.S.
PPD	N.S.	N.S.	N.S.
Group*Electrode	N.S.	CND1 and CND2: A>M>B; Control: B and A< M; CND1>CND2 @A;	N.S.
Group*PPD	N.S.	N.S.	N.S.
Electrode*PPD	N.S.	N.S.	N.S.
Group*Electrode*PPD	N.S.	N.S.	N.S.

Table 3.

A summary of statistical findings in the highest stimulation level and the dynamic range. PPD: Pulse Phase Duration, CND: Cochlear Nerve Deficiency, CND1:CND group1; CND2: CND group 2, B: Basal, M: Middle, A: Apical, N.S.: Non-Significant

Effect	Stimulation Level	Dynamic Range
Group	CND1>CND2>Control	Control >CND1 and CND2
Electrode	A > M > B	B > A and M
PPD	N.S.	N.S.
Group*Electrode	CND1 and CND2: A>M>B; Control: B and A< M; CND1>CND2 @A;	CND1 and CND2: B>M and B; Control: B and A> M;
Group*PPD	N.S.	N.S.
Electrode*PPD	N.S.	N.S.
Group*Electrode*PPD	N.S.	N.S.