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Responsiveness of the Electrically Stimulated Cochlear Nerve in Children with Cochlear Nerve Deficiency

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Abstract

Objective—This study aimed to 1) investigate the responsiveness of the cochlear nerve (CN) to a single biphasic-electrical pulse in implanted children with cochlear nerve deficiency (CND); and 2) compare their results with those measured in implanted children with normal-size CNs.

Design—Participants included 23 children with CND (CND1 – CND23) and 18 children with normal-size CNs (S1 – S18). All subjects except for CND1 used Cochlear[®] Nucleus cochlear implants (CIs) with contour electrode arrays in their test ears. CND1 was implanted with a Cochlear[®] Nucleus Freedom CI with a straight electrode array in the test ear. For each subject, the CN input/output (I/O) function and the refractory recovery function were measured using electrophysiological measures of the electrically evoked compound action potential (eCAP) at multiple electrode sites across the electrode array. Dependent variables included eCAP threshold, the maximum eCAP amplitude, slope of the I/O function, and time constants of the refractory recovery function. Slopes of I/O functions were estimated using statistical modeling with a sigmoidal function. Recovery time constants, including measures of the absolute refractory period and the relative refractory period, were estimated using statistical modeling with an exponential decay function. Generalized Linear Mixed effect Models were used to evaluate the effects of electrode site on the dependent variables measured in children with CND, and to compare results of these dependent variables between subject groups.

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Results—The eCAP was recorded at all test electrodes in children with normal-size CNs. In contrast, the eCAP could not be recorded at any electrode site in four children with CN. For all other children with CN, the percentage of electrodes with measurable eCAPs decreased as the stimulating site moved in a basal-to-apical direction. For children with CN, the stimulating site had a significant effect on the slope of the I/O functions and the relative refractory period, but showed no significant effect on eCAP threshold and the maximum eCAP amplitude. Children with CN had significantly higher eCAP thresholds, smaller maximum eCAP amplitudes, flatter slopes of I/O functions, and longer absolute refractory periods than children with normal-size CNs. There was no significant difference in the relative refractory period measured in these two subject groups.

Conclusions—In children with CN, the functional status of the CN varied along the length of the cochlea. Compared to children with normal-size CNs, children with CN showed reduced CN responsiveness to electrical stimuli. The prolonged CN absolute refractory period in children with CN might account for, at least partially, the observed benefit of using relatively slow pulse rate in these patients.

Keywords

cochlear implant; cochlear nerve deficiency; cochlear nerve; electrically evoked auditory compound action potentials; neural refractoriness

INTRODUCTION

Cochlear nerve deficiency (CND) refers to a small (hypoplastic) or absent (aplastic) cochlear nerve as revealed by the results of high-resolution magnetic resonance imaging (MRI). CND can occur as an isolated condition (Adunka et al., 2006; Nelson et al., 2001) or in combination with an inner ear malformation (e.g. Adunka et al., 2006; Buchman et al., 2011; Sennaroglu, 2010; Song et al., 2011; Yamasaki et al., 2015). It is estimated to be present in 1 – 5.3% of children with newly identified hearing loss (Adunka et al., 2006; Buchman et al., 2006; Nakano et al., 2013; Wu et al., 2014), and can occur in up to 50% of children with unilateral severe to profound hearing loss (Clemmens, et al., 2013; Nakano et al., 2013; Roche et al., 2010; Wu et al., 2014). The etiology of CND remains unknown. To date, two pathogeneses of CND have been speculated. For patients with concurrent inner ear malformations, CND is likely caused by the arrested inner ear development during embryogenesis, which results in a partially or completely underdeveloped cochlear nerve (Jackler et al., 1987). For patients with normal internal auditory canals and labyrinthine structures, CND is possibly caused by the cochlear nerve degeneration after the completion of canalicular ossification (Adunka et al., 2007).

Cochlear implantation has been used as a treatment option for children with CND for nearly two decades. Substantial variations in cochlear implant (CI) outcomes among these patients have been reported (e.g. Birman et al., 2016; Buchman et al., 2006, 2011; Kang et al., 2010; Teagle et al., 2010; Vincenti et al., 2014; Young et al., 2012). Whereas some patients showed no sound awareness with CIs (e.g. Birman et al., 2016; Buchman et al., 2011; Teagle et al., 2010), a few patients achieved open-set speech perception and spoken language skills (Kang et al., 2010; Vincenti et al., 2014; Young et al., 2012). For individual children with CND, CI

outcomes cannot be predicted based on results of pre-operative MRI or CT scan or the electrically evoked auditory brainstem response (Kutz et al., 2011; Song et al., 2011; Valero et al., 2012; Yamazaki et al., 2015). To date, neurophysiological mechanisms underlying inter-patient variations in speech and language outcomes in implanted children with CND are not well understood. As a result, there is still no clinical tool for predicting CI outcomes for individual patients. The wide range of CI outcomes and the lack of clinical tools for predicting CI benefit make it challenging to design an optimal management plan, and provide appropriate patient counseling for children with CND.

Electrical stimuli delivered by the CI are first encoded by the cochlear nerve (CN), and subsequently transmitted to, and processed by, higher level neural structures. The ability of the CN to faithfully encode and process electrical stimuli must therefore be important for CI outcomes. Results of recent studies suggest that the functional status of the CN (i.e. number and responsiveness of neurons) is an important factor for CI outcomes (e.g. Kirby & Middlebrooks, 2010, 2012; Kim et al., 2010; Garadat et al., 2013; Pfingst et al., 2014, 2015a, 2015b). Although anatomical characteristics of CND have been widely described in many studies based on MRI and CT results (e.g. Adunka et al., 2006, 2007; Buchman et al., 2006; Roche et al., 2010), the functional status of the CN in these patients remains unknown. Presumably, the hypoplastic CN has less and/or thinner neural fibers than the normal-size CN. However, it remains unknown whether all the CN fibers innervating the entire length of the cochlea are equally affected or the pathological insult mainly occurs in a subgroup of CN fibers. In addition, it is unknown how effectively the existing CN fibers respond to electrical stimuli delivered by the CI. Consequently, clinicians do not have an evidence-based guidance for selecting optimal programming parameters for these patients. A better understanding of the functional status of the CN is needed in order to develop an effective evidence-based clinical practice for managing children with CND.

Current CIs incorporate a “reverse” telemetry capability that allows near-field recordings of the electrically evoked compound action potential (eCAP) — a direct measurement of neural responses generated by the CN, which makes it feasible to exclusively evaluate the functional status of the CN. The eCAP represents synchronous responses generated by a group of electrically activated CN fibers. The amplitude of the eCAP is largely determined by the number of CN fibers activated by electrical stimuli and the discharge rate of each activated neuron (Miller et al., 2008). Results of animal studies show that the functional status of the CN influences basic response properties, including neural refractoriness and the response input/output (I/O) function (Miller et al., 2001; Pfingst et al., 2015a, 2015b). Therefore, as an initial step to characterize responsiveness of the CN to electrical stimuli in children with CND, this study focused on the I/O function and the refractory recovery function measured using the eCAP.

The primary variable of interest for the eCAP I/O function is the slope because it is positively associated with the density of the surviving neural population, with steeper slopes indicating greater density (e.g. Kim et al., 2010; Nehmé et al., 2014). In addition to the slope, two other parameters are commonly assessed: the lowest stimulation level that can evoke an eCAP (i.e. eCAP threshold) and the maximum eCAP amplitude. Both parameters

are believed to reflect, at least to some extent, the size of the electrically activated neural population (Miller et al., 1994; Ramekers et al., 2014).

The refractory recovery function can be measured using two biphasic, charge-balanced, electrical pulses. The eCAP to the second pulse (i.e. the probe) is measured as a function of the time interval between the first pulse (i.e. the masker) and the probe (i.e. the masker-probe-interval). The amplitude of the eCAP is affected by the refractoriness induced by the masker, with smaller eCAP amplitudes indicating greater refractoriness. Time constants, including t_0 and τ , derived from the refractory recovery function are important measures of the CN's refractory properties (e.g. Botros & Psarros, 2010; Morsnowski et al., 2006; Wiemes et al., 2016). Procedures used to derive these time constants are reported in the Data Analysis session. t_0 represents the minimum masker-probe-interval (MPI) that is needed to elicit the eCAP to the probe. It is aligned with the absolute refractory period. The prolonged absolute refractory period has been shown to be associated with reduced CN fiber density (Shepherd et al., 2004). τ is a measure of the speed of recovery from relative refractoriness. Conceptually, it reflects the relative refractory period. Slower relative refractory recovery (i.e. larger τ) has been suggested to be associated with better neural survival in CI patients (Botros & Psarros, 2010).

The association between CI outcomes and each of these eCAP measures has been evaluated in previous studies (e.g. Brown et al., 1990; Finley et al., 1997; Lee et al., 2012; Turner et al., 2002). Overall, these studies showed inconsistent results. For example, some studies reported better speech perception scores measured in CI users with steeper slopes (Brown et al., 1990; Kim et al., 2010) or faster recovery from refractoriness (Brown et al., 1990; Fulmer et al., 2011; Kiefer et al., 2001). These associations were not observed in other studies (e.g. Franck & Norton, 2001; Finley et al., 1997; Lee et al., 2012; Turner et al., 2002). It should be pointed out that this study focused on using these eCAP measures to assess the functional status of the CN in children with CND. The inconsistencies that exist between previous studies do not undermine the value of this study since CN responsiveness to electrical stimulus has not been previously investigated in this specific patient population.

In summary, it is clinically challenging to manage implanted children with CND due to the lack of knowledge regarding the neurophysiological mechanisms underlying generally poor and widely varied CI outcomes. Developing an effective, evidence-based clinical management plan for these patients requires a better understanding of the functional status of the CN. This study aimed to compare responsiveness of the CN to a single biphasic-electrical pulse, as reflected by results of eCAP I/O functions and refractory recovery time constants, between implanted children with CND and implanted children with normal-size CNs. We hypothesized that the functional status of the CN in children with CND would vary along the cochlea. CN fibers innervating more apical locations of the cochlea were expected to show poorer functional status. This hypothesis was formulated based on the fact that the basal turn of the cochlear duct develops first, followed by the middle and the apical turn, and that the development of the CN is dependent on the neurotrophic factors secreted by hair cells located in the cochlear duct (Rubel & Fritzsche, 2002). We also hypothesized that CNs in children with CND would have poorer responsiveness to electrical stimuli than those in children with normal-size CNs. This hypothesis was formulated based on the fact that

implanted children with CND often require higher electrical charge per unit phase to achieve auditory perception than children with normal-size CNs (e.g. Buchman et al., 2011; Teagle et al., 2010). It was expected that children with CND would show flatter I/O functions, higher eCAP thresholds, smaller maximum eCAP amplitudes, larger t_0 , and smaller τ than children with normal-size CNs.

MATERIALS AND METHODS

Subjects

This study included two subject groups: the experimental group and the control group. The experimental group consisted of 23 children with CND (CND1 – CND23) ranging in age between 2.79 and 14.30 yrs (mean: 6.58 yrs, SD: 2.90 yrs). The control group included 18 children with normal-size CNs (S1 – S18) ranging in age between 2.49 and 16.60 yrs (mean: 7.06 yrs, SD: 3.47 yrs). All subjects except for one (CND1) were implanted with a Cochlear® Nucleus device with a contour electrode array, either a Freedom (24RE[CA]) or a Nucleus 5 (N5) CI, in the test ear. CND1 was implanted with a Freedom device with a straight electrode array (24RE[ST]). The electrode array was partially inserted in CND1 and CND2 due to Incomplete Partition Type II (IP-II). All other subjects had a normal cochlea and a full electrode insertion. All subjects had at least six months of listening experience with their devices prior to testing.

The anatomical status of the CN was determined based on results of MRI scan following a similar protocol that has been previously described in detail (Adunka et al., 2006; Buchman et al., 2006; Roche et al., 2010). Briefly, the imaging protocol includes sagittal unenhanced T1-weighted images, the axial fluid attenuation inversion recovery, T2-weighted images through the brain, and the Continuous Interference in a Steady-State (CISS) sequence. For each subject, the CISS images were reconstructed in a coronal oblique plane traversing the internal auditory canal (IAC) in a perpendicular orientation, which resulted in images that visualized the four cranial nerve bundles (facial, cochlear, superior vestibular, and inferior vestibular nerves) traversing the IAC. The term CND refers to either a small or absent cochlear nerve as determined by the MRI scan. The cochlear nerve was considered to be absent if it could not be identified on axial, coronal, or reconstructed coronal oblique IAC images. It was considered to be small when the nerve was present, but smaller than the other nerves in the IAC or smaller than the cochlear nerve in the contralateral ear. The CN was considered to be normal in size in cases where MRI findings were negative.

Detailed demographic information of these subjects is listed in Table 1. The anatomical status of the CN and the cochlea is listed for each child with CND. It should be pointed out that the concurrent malformation in the vestibular system and/or internal auditory canal stenosis was not listed for these subjects. All subjects included in the control group had no sign of anatomy malformation in the inner ear or the CN. Their imaging results were not listed in Table 1. The study was approved by the local Biomedical Institutional Review Board. All subjects received payment for their participation, and written, informed consents were obtained from legal guardians prior to participation.

Procedures

For Cochlear Nucleus devices, electrodes 1 and 22 are typically placed near the base and the apex of the cochlea, respectively. eCAPs were measured using the Advanced Neural Response Telemetry (NRT) function that is implemented in the Custom Sound EP (v. 4.3) commercial software (Cochlear Ltd, Macquarie, NSW, Australia) via a Freedom or N5 sound processor interfaced with a programming pod. The effective sampling rate used for eCAP measures was 20 kHz. The stimulus was a biphasic, cathodic-leading, charge-balanced pulse presented in a monopolar-coupled mode. The MPI used to measure the eCAP I/O function was 400 μ s. The maximum comfortable level (C level) of the stimulus was measured for each stimulating electrode in each subject using the same procedure as that described in He et al. (2016).

For subjects with normal-size CNs, the pulse duration and the inter-phase-gap used in this study was 25 μ s/phase and 8 μ s, respectively. The probe rate was 15 Hz. The recording electrode was located two electrodes away apically from the stimulating electrode. The sampling delay was between 98 and 122 μ s, and the amplifier gain was 50 dB. The number of sweeps for the averaged eCAP response was 50. eCAP measures were conducted for seven stimulating electrodes (electrodes 3, 6, 9, 12, 15, 18, and 21) in all subjects except for S8, S10, S12 and S16. For these four subjects, one of the selected electrodes was disabled due to either open- or short-circuits. Therefore, only six electrodes were tested. Electrodes tested in individual patients are listed in Table 1. For each control subject, it took about two to three hours to complete all experiments.

For subjects with CND, all stimulating and recording parameters were adjusted for individual patients in order to obtain eCAPs with optimized morphologies. The pulse duration ranged from 37 to 88 μ s/phase. The inter-phase-gap was 8 μ s. The probe rate ranged from 5 to 15 Hz. The recording electrode was typically located two electrodes away in the basal direction from the stimulating electrode. The sampling delay was typically between 98 and 142 μ s, and the amplifier gain was 40 dB to avoid saturating the recording amplifier due to high electrical charge used in these subjects. The number of sweeps for the averaged eCAP response was 100. Test electrodes varied among these patients due to time constraints, variations in the length of electrode insertion, and differences in the number of electrodes with artifact-free eCAPs. Electrodes tested for individual patients are listed in Table 1. Due to the extensive amount of time required for optimizing stimulating and recording parameters for eCAP measures, the test session lasted around five to eight hours for each subject with CND.

eCAP I/O function—The eCAP I/O function was measured using a 2-pulse forward-masking-paradigm (Brown et al., 1990). The masker pulse was presented at the C level. The probe pulse was initially presented at the C level, decreased in steps of 5 clinical units (CUs) until no response could be visually identified, and subsequently increased in steps of 1 CU until at least five eCAPs were measured using this small step size.

eCAP refractory recovery function—Figure 1 shows a schematic illustration of the masked-response-extraction-paradigm (Miller et al., 2000) that was used to measure the

eCAP refractory recovery function. Traces evoked by two masker-probe pairs were measured in this paradigm. The MPI of the first masker-probe pair systematically varied from 100 to 10,000 μ s. As the MPI increased, the CN gradually recovered from the refractoriness induced by the masker, which resulted in larger eCAPs at longer MPIs. Subtracting trace “B” from trace “A” (i.e. A–B) yielded the artifact and the eCAP evoked by the probe. The MPI of the second masker-probe pair was 300 μ s, which minimized the neural response evoked by the probe pulse (Morsnowski et al., 2006). Subtracting trace “D” from trace “C” (i.e. C–D) resulted in the artifact evoked by the probe. The difference between these two derived traces (i.e. A–B–[C–D]) was the eCAP evoked by the first probe. For each subject, the refractory recovery function was measured at the C level for all test electrodes with measurable eCAPs.

Data Analysis

Custom-designed MATLAB (Mathworks) software was used to conduct statistical modeling of this study. Parameters of the mathematical functions used in statistical modeling were estimated using the trust-region-reflective algorithm. All other statistical analyses were conducted using SPSS Statistic 22 (IBM Corp.).

eCAP I/O function—Due to variations in pulse phase duration among subjects, stimulation levels were converted to units of electrical charge per phase (nC). The lowest stimulation level that could evoke an eCAP response was defined as the eCAP threshold. eCAP amplitude was measured as the amplitude difference between the negative (N1) and positive (P1) peaks of the response (Lai & Dillier, 2000).

For each subject and each stimulating electrode, response amplitudes were normalized to the largest eCAP amplitude. The eCAP I/O function was obtained by plotting the normalized eCAP amplitude as a function of stimulation level. Figure 2 shows eCAP waveforms (upper panels) and I/O functions (lower panels) recorded in two subjects with normal-size CNs (S13 and S15) and two subjects with CND (CND9 and CND4). Stimulation levels used to evoke these eCAP responses are labelled for these traces in upper panels. The pulse phase duration used in S13 and S15 was 25 μ s. Pulse phase durations used at electrode 3 in CND3 and CND4 were 88 μ s and 75 μ s, respectively. Despite variations in response amplitude and threshold, eCAPs were recorded in all four subjects. More importantly, inter-subject variations in overall shape of the I/O function are apparent. While the function measured at electrode 18 in S15 is relatively linear, functions measured in other subjects are nonlinear in nature.

Linear regression is the most commonly used method for characterizing the eCAP I/O function (e.g. Brown et al., 1990; Schwartz-Leyzak & Pflugst, 2016). However, eCAP I/O functions reported in many studies are not linear (e.g. Abbas & Brown, 2015; Cohen et al., 2009; Lai & Dillier, 2007). Two nonlinear functions could potentially be used to characterize the eCAP I/O function: an exponential function and a sigmoidal function. Lai and Dillier (2007) suggested that eCAP I/O functions measured in CI users were exponential in nature. Results of simulation and animal studies showed that the discharge rate vs. stimulation level function of CN fibers could be characterized by sigmoidal functions (e.g. Galambos &

Davis, 1943; Heil et al., 2011; Sachs & Abbas, 1974; Wen et al., 2009). The eCAP I/O function measured in implanted cats using monopolar stimulation also follows a sigmoidal function (Abbas et al., 2003). To date, no study has directly compared which of these three functions can best characterize the eCAP I/O function measured in CI users. Therefore, I/O functions measured in this study were initially fitted using all three functions. For each subject group, the goodness of fit (i.e. R^2) of all three functions was compared using one-way repeated measures analysis of variance (ANOVA) with repeated contrasts. These results revealed a significant difference in the goodness of fit calculated for the three functions for both subject groups (children with CND: $F_{(1.65, 160.18)} = 12.72$, $p < 0.05$; children with normal-size CNs: $F_{(1.45, 176.67)} = 163.53$, $p < 0.05$), and the sigmoidal regression yielded the best fit for both subject groups. Therefore, the sigmoidal function was selected to characterize eCAP I/O functions measured in this study. Equations used for these regression functions and results of R^2 calculated for each fitting function are listed in Table A1 – A2 in the Appendix.

Slopes of I/O functions were estimated based on results of statistical modeling with a sigmoidal function of the form:

$$eCAP_N = \frac{a}{1 + e^{-b(t-t_0)}} \quad (1)$$

where $eCAP_N$ represents the normalized eCAP amplitude, a is the upper limit of the performance, t_0 is the midpoint of the function, and b is the slope, with larger values representing steeper functions. Unfortunately, the asymptotic maximum eCAP amplitude could not be recorded in most CI patients due to subject discomfort, limitation of CI output level, and increased likelihood of stimulus artifact contamination at high stimulation levels. As a result, the true upper limit of the eCAP amplitude in human listeners remains unknown. In this study, we first fitted a total of 122 I/O functions measured in children with normal-size CNs using this sigmoidal function without any constraint of the upper limit. After excluding extreme outliers using the 3* inter-quartile-range (IQR) criterion, the maximum value of 2.23 was chosen and used as the constraint for the parameter a in the sigmoidal regression. The eCAP I/O function measured in each subject for each stimulating electrode was modeled using the sigmoidal function with this newly defined upper limit constraint.

eCAP refractory recovery function—For each subject and each stimulating electrode, eCAP amplitudes were normalized to the amplitude of the eCAP measured at the longest MPI (i.e. 10 ms). The refractory recovery function was obtained by plotting the normalized eCAP amplitude as a function of MPIs. Upper panels of Figure 3 show eCAPs recorded at different MPIs for electrode 18 in S15 and electrode 15 in CND9. These data show that the eCAP response becomes larger as the MPI increases for both subjects. Lower panels show refractory recovery functions obtained for these results. A commonly used exponential decay function (e.g. Botros & Psarros, 2010; Fulmer et al., 2011; Morsnowski et al., 2006), given in equation (2), was used to characterize the refractory recovery function.

$$eCAP_N = A \left[1 - e^{\frac{-(MPI - t_0)}{\tau}} \right], \quad (2)$$

where $eCAP_N$ represents the normalized eCAP amplitude, t_0 is aligned with the absolute refractory period, τ is a measure of the speed of recovery from relative refractoriness, and A represents the maximum eCAP amplitude evoked by the probe after a sufficiently long MPI. The solid line in Figure 3 shows results of data fitting using this exponential decay function.

Statistical Comparison—Dependent variables evaluated in this study include eCAP threshold, the maximum eCAP amplitude, slope of the I/O function, t_0 , and τ . Outliers determined based on the 1.5* IQR criterion were excluded from statistical analysis. Generalized Linear Mixed effect Models (GLMMs) with subject group and electrode location as the fixed effects were used to compare dependent variables measured between groups. The GLMM can robustly handle missing data, does not depend on the assumption that the missing data are completely random, and allows comparisons between datasets with different distributions (McCulloch & Neuhaus, 2005). Therefore, it is the most appropriate statistical analysis test for this study. eCAPs were not recorded in four subjects (CND19-CND22). Results recorded in CND12 were outliers based on the 1.5* IQR criterion. Therefore, group comparisons were conducted based on results recorded in 18 children with CND and 18 children with normal-size CNs.

Relationships among three dependent variables that are the primary interests of this study (i.e. slope of the I/O function, t_0 , and τ) measured at the seven most commonly tested electrode sites in both groups (i.e. electrodes 3, 6, 9, 12, 15, 18, and 21) were evaluated using one-tailed Spearman's rank-order correlation tests. This evaluation was conducted separately for each electrode site within each subject group.

RESULTS

eCAPs were recorded at C levels for all test electrodes in all subjects with normal-size CNs. In contrast, results recorded in subjects with CND varied among patients. There were seven subjects with CND who had eCAPs at all test electrodes. Responses were not recorded at any test electrode in four subjects with CND (CND19-CND22). For all other subjects with CND, eCAPs were recorded at some but not all test electrodes. Overall, the percentage of test electrodes with measurable eCAPs decreased from 79% to 20% as the stimulating electrode moved in a basal-to-apical direction in children with CND. Electrodes with measurable eCAPs tested in individual subjects are listed in Table 1. Figure 4 shows percentages of test electrodes with measurable eCAPs for both study groups. Results are only shown for the seven most commonly tested electrodes in both groups (i.e. electrodes 3, 6, 9, 12, 15, 18, and 21). Results of independent samples Mann-Whitney U test showed that children with CND had a lower percentage of test electrodes with measurable eCAPs than children with normal-size CNs ($p < 0.05$). For children with CND, results of Spearman's rank order correlation test showed a significant negative correlation between the percentage of test electrodes with measurable eCAPs and the electrode number ($\rho = -0.85$, $p < 0.05$). These

results suggested that the likelihood of measuring the eCAP reduces as the stimulating electrode moved toward the apical sites in subjects with CND.

eCAP I/O Function

Slope—For children with CND, the goodness of fit (i.e. R^2) of the statistical model with the sigmodal function ranged from 0.66 to 0.99 (mean = 0.88, SD = 0.09). For children with normal-size CNs, the R^2 ranged from 0.79 to 1.00 (mean = 0.97, SD = 0.04). Results of Levene's test revealed unequal variance in the R^2 measured in these two subject groups ($F = 12.89$, $p < 0.01$). Therefore, the independent samples Mann-Whitney U test was used to compare the R^2 between subject groups. Results showed that the sigmoidal function better characterized I/O functions measured in children with normal-size CNs than those measured in children with CND ($p < 0.01$). Slopes estimated in children with CND ranged from 0.15 to 1.67/nC (mean = 0.72/nC, SD = 0.38/nC). For children with normal-size CNs, slopes ranged from 0.29 to 1.78/nC (mean = 0.88/nC, SD = 0.31/nC).

Open bars in Figure 5 represent the slopes of eCAP I/O functions measured in children with CND. Results measured for a total of 15 test electrodes are shown in this figure for these subjects. For electrodes 8, 10, 11, 13, 14, 19 and 22, data were only available in one subject after excluding outliers. Therefore, no data is shown for these electrodes. These data indicate that children with CND generally had steeper slopes as electrode sites move apically across the electrode array. This observation was confirmed by a significant overall effect of the electrode site on the slope of the I/O function in children with CND ($F_{(14, 8.04)} = 13.45$, $p < 0.01$). However, pairwise comparisons with Bonferroni correction failed to show any significant difference in the slope between any two electrode sites.

Filled bars in Figure 5 represent slopes of eCAP I/O functions measured in children with normal-size CNs. For these subjects, slopes estimated at electrodes 3, 6, 9, 12, 15, 18 and 21 are shown in this figure. Results of GLMMs showed that children with CND had significantly smaller slopes than children with normal-size CNs ($F_{(1, 115.48)} = 4.99$; $p < 0.05$), which was likely accounted for by the smaller slopes estimated in children with CND for electrodes 3, 6, 9, 12 and 15 than those estimated in children with normal-size CNs. The effect of the stimulating electrode site was not statistically significant for slopes estimated for these seven electrodes ($F_{(6, 35.75)} = 1.66$, $p = 0.16$). Even though results estimated for electrodes 18 and 21 in these two groups showed different patterns, the interaction between group and electrode site was not statistically significant ($F_{(6, 36.28)} = 0.99$; $p = 0.44$).

eCAP threshold and maximum amplitude—For children with CND, eCAP threshold ranged from 6.22 to 51.32 nC (mean = 24.61 nC, SD = 9.96 nC), and maximum eCAP amplitude ranged from 18.44 to 644.46 μ V (mean = 109.51 μ V, SD = 143.03 μ V). Results of GLMMs showed no significant effect of the electrode site on eCAP threshold ($F_{(17, 8.17)} = 10.29$, $p = 0.98$) or maximum eCAP amplitude ($F_{(14, 12.13)} = 0.99$, $p = 0.51$) measured in these subjects.

For children with normal-size CNs, eCAP threshold ranged from 0.64 to 19.41 nC (mean = 8.40 nC, SD = 2.71 nC), and maximum eCAP amplitude ranged from 21.17 to 900.61 μ V (mean = 241.70 μ V, SD = 165.29 μ V).

For group comparison, results of GLMMs showed that children with CNL had significantly higher eCAP thresholds ($F_{(1, 185)}=274.04$, $p<0.05$) and significantly smaller maximum eCAP amplitudes ($F_{(1, 186)}=31.42$, $p<0.05$) than children with normal-size CNs. These group difference were not significantly affected by the electrode site as evidenced by nonsignificant interactions between study group and electrode site (eCAP threshold: $F_{(6, 185)}=0.56$, $p=0.76$; maximum eCAP amplitude: $F_{(6, 186)}=0.17$, $p=0.98$). Effect of the electrode site on results of these two variables was not statistically significant (eCAP threshold: $F_{(6, 185)}=0.97$, $p=0.45$; maximum eCAP amplitude: $F_{(6, 186)}=0.26$, $p=0.95$).

eCAP Refractory Recovery Function

Overall, the exponential decay function could characterize refractory recovery functions measured in both subject groups. The goodness of fit (i.e. R^2) ranged from 0.62 to 0.99 (mean = 0.91, SD = 0.09) in children with CNL, and from 0.75 to 0.99 (mean = 0.98, SD = 0.04) in children with normal-size CNs. Due to unequal variance in results measured in these two groups based on the result of Levene's test ($F=75.98$, $p<0.01$), the independent samples Mann-Whitney U test was used to compare the R^2 between subject groups. Results showed that the exponential decay function resulted in a better fit for refractory recovery functions measured in children with normal-size CNs than those recorded in children with CNL ($p<0.01$).

For children with CNL, t_0 and τ ranged from 0.14 to 3.42 ms (mean = 1.31 ms, SD = 0.81 ms) and from 0.17 to 3.53 ms (mean = 1.13 ms, SD = 0.80 ms), respectively. For children with normal-size CNs, t_0 and τ ranged from 0.23 to 1.45 ms (mean = 0.62 ms, SD = 0.25 ms) and from 0.12 to 2.42 ms (mean = 1.16 ms, SD = 0.49 ms), respectively.

Open bars in Figure 6 show t_0 (upper panel) and τ (lower panel) estimated in children with CNL. Despite somewhat across-electrode variations, results of t_0 estimated in children with CNL did not follow an identifiable trend. Results of GLMMs showed no difference in t_0 estimated at different electrode sites ($F_{(13, 9, 12)}=1.36$, $p=0.33$). In contrast, results of GLMM revealed a significant effect of electrode site on τ estimated in children with CNL ($F_{(13, 6, 24)}=3.99$, $p<0.05$), with τ estimated at the apical electrodes tended to be smaller than those estimated at the basal electrodes. Despite the overall significant effect of electrode site, pairwise comparisons with Bonferroni correction failed to show any significant difference in τ between any two electrode sites.

Filled bars in Figure 6 show t_0 (upper panel) and τ (lower panel) measured in children with normal-size CNs at seven electrode sites. For group comparison, results of GLMMs showed a significant group difference in t_0 ($F_{(1, 143, 42)}=88.76$, $p<0.01$). There was no significant effect of the electrode site ($F_{(6, 43, 81)}=1.42$, $p=0.23$) or the interaction between electrode and subject group ($F_{(6, 42, 46)}=0.91$, $p=0.49$). These statistical results supported the observation that t_0 estimated in children with CNL was much longer than those estimated in children with normal-size CNs. In contrast, results of GLMM showed that there was no significant difference in τ measured in children with CNL and children with normal-size CNs ($F_{(1, 149, 65)}=2.10$, $p=0.15$). There was a significant difference in τ measured at different electrode sites ($F_{(6, 52, 38)}=4.99$, $p<0.01$). Pairwise comparisons with Bonferroni correction showed that τ estimated at electrode 9 was significantly longer than those estimated at

electrodes 3, 18 and 21 ($p < 0.05$). There was no significant difference in τ among results estimated at any other electrode sites. The interaction between electrode and subject group was not statistically significant ($F_{(6, 50.85)} = 1.55$, $p = 0.18$).

Relationship among Slope and Refractory Recovery Time Constants

Results of one-tailed Spearman's rank-order correlation tests for each subject group are listed in Table 2. For children with CND, there was no association among the three dependent variables evaluated at all seven electrodes with an exception that a negative correlation was observed between slope and τ at electrode 3. For children with normal-size CNs, t_0 and τ were positively correlated at all electrode sites. No correlation was observed between slope and τ at any electrode site. The correlation between slope and t_0 existed for some but not all electrode sites.

DISCUSSIONS

This study evaluated the responsiveness of the CN to a single biphasic-electrical pulse in children with CND, and compared their results with those measured in children with normal-size CNs. The CN responsiveness was evaluated using the slope of the eCAP I/O function, eCAP threshold, the maximum eCAP amplitude, and t_0 and τ derived from the refractory recovery function.

Children with CND

The likelihood of measuring an eCAP response in children with CND reduced as the stimulating site moved from the basal to the apical end of the cochlea. Substantial inter-subject variations were observed in terms of the number of electrodes with measurable eCAPs in these patients. The presence of the eCAP depends on a sufficient number of CN fibers activated by electrical stimuli. Therefore, these results suggested that the functional status of the CN might deteriorate along the length of the cochlea in children with CND. The amount/degree of damage/deterioration in CN function varied among these patients. These variations could not be predicted based on the anatomical status of the CN that was determined based on imaging results. For example, MRI results measured in both CND12 and CND13 showed a single nerve in the internal auditory canal and normal cochleae. Both subjects had a full electrode insertion with a Nucleus Freedom Contour Advance electrode array. The eCAP was only recorded at electrode 3 in CND12. In contrast, eCAPs were recorded at all seven electrodes tested in CND13. Furthermore, the CN was determined to be absent in five subjects (CND4, CND11, CND15, CND19 and CND22). The number of electrodes with measurable eCAPs ranged from zero to eight in these children. This lack of association between results of MRIs and electrophysiology recordings in children with CND is consistent with those reported in literature (e.g. Valero et al., 2012). In addition, several studies have reported the possibility of speech development in some implanted children with bilateral CN aplasia that was diagnosed based on MRI results (e.g. Teagle et al., 2010; Wu et al., 2014). Theoretically, these children should have sufficient functional CN fibers in order to achieve speech development. Unfortunately, this cannot be evaluated using imaging techniques. Overall, these results highlight the importance of evaluating the functional status of the auditory system using electrophysiological measures in these patients.

Slopes of eCAP I/O functions estimated in children with CND were significantly affected by the location of electrode along the electrode array. Specifically, slopes increased as the stimulating electrode moved apically. This increasing trend is unlikely due to factors related with the CI since it was not observed in children with normal-size CNs using similar CI devices. Therefore, it must reflect the underlying neurophysiology of the CN in these patients. At first glance, these results seemed to suggest that CN function improved as stimulating site moved from the basal to the apical end of the cochlea, which is in opposition to what were predicted based on our first hypothesis (i.e. CN fibers innervating more apical locations of the cochlea would have worse functional status). However, a careful inspection of our results indicated that slopes estimated at more apical sites were primarily weighted by the results of subjects who showed measurable eCAPs at more electrodes. These subjects might have less damage to their CNs than subjects who only had measurable eCAPs at the most basal electrode sites. As a matter of fact, slopes estimated in six children with CND (CND2, CND3, CND6, CND13, CND14 and CND16) who showed measurable eCAPs across the entire electrode array were comparable with those estimated in children with normal-size CNs, which supported this possibility. In addition, we speculated that increased firing rate of CN fibers innervating the more apical end of the cochlea might be another factor accounting for the observed increasing trend. The eCAP represents a summed response from a group of electrically stimulated CN fibers. Its amplitude depends on the number of neurons activated by electrical stimuli (i.e. neural recruitment) and firing rate of each recruited neuron. Whereas neural recruitment is the primary factor that determines neural output with good neural survival, the firing rate plays the dominant role when neural survival is poor (McKay and McDermott, 1998). In cats, Li and Young (1993) showed that CN fibers with high firing rates had fast recovery from relative refractoriness, and the absolute refractory period was independent of firing rate. t_0 and τ estimated in this study can be considered as the absolute refractory period and the relative refractory period, respectively. τ estimated in children with CND decreased as the stimulating site moved in a basal-to-apical direction, which supported the possibility that CNs near the apical electrode sites might have higher firing rates than those near the basal electrode sites.

In children with CND, the stimulating site did not show a significant effect on eCAP threshold. It has been proposed that eCAP threshold is affected by factors other than the number of surviving auditory neurons. These factors include impedance, neuro-electrode distance, etc. (e.g. Miller et al., 2008). Results of animal studies have shown that eCAP thresholds were not associated with spiral ganglion density (Pfungst et al., 2014), and might not provide an accurate assessment of the functional status of the CN (Pfungst et al., 2015a). These factors likely account for the non-significant effect of stimulating site on eCAP threshold. The lack of stimulating site effect on the maximum eCAP amplitude might be accounted for by the broad neural excitation caused by current spread occurring in monopolar stimulation.

The close association between t_0 and τ has been reported in previously published literature (Bostros & Psarros, 2010; Tackman & and Lehmann, 1974), and was also observed in children with normal-size CNs in this study. However, this association was not found for children with CND. The underlying mechanism for this discrepancy is still unclear.

Group Comparison

The second hypothesis tested in this study was that CNs in children with CND had reduced responsiveness to electrical stimuli delivered by the CI. Based on this hypothesis, children with CND were expected to show flatter eCAP I/O functions, higher eCAP thresholds, smaller eCAP maximum amplitudes, greater t_0 , and smaller τ than children with normal-size CNs.

Consistent with predicted results, the slopes of eCAP I/O functions estimated in children with CND were significantly smaller than those estimated in children with normal-size CNs. These data are also consistent with results reported in animal studies showing that small slopes of eCAP I/O functions are correlated with poor spiral ganglion neuron survival (Pfungst et al., 2014; Pfingst et al., 2015a, 2015b). Compared to children with normal-size CNs, children with CND also showed elevated eCAP thresholds and reduced maximum eCAP amplitude, which is likely accounted for by the reduced number of functional CN fibers. t_0 estimated in children with normal-size CNs ranged from 0.23 to 1.45 ms with a mean of 0.62 ms. These results are consistent with the absolute refractory period estimated based on single-fiber recordings in animal studies (e.g. Bruce et al., 1999; Dynes, 1996) and the results measured in adult CI users (Morsnowski et al., 2006; Wiemes et al., 2016). In comparison, t_0 estimated in children with CND at all test sites were significantly longer than those estimated in children with normal-size CNs. These data were consistent with predicted results based on the second hypothesis. It is unlikely that this group difference is due to higher stimulation levels used in children with CND since t_0 decreases with increasing stimulation level (Shepherd et al., 2004; Miller et al., 2001; Morsnowski et al., 2006; Ramekers et al., 2015). Instead, it is more likely caused by the reduced number of CN fibers in children with CND (Shepherd et al., 2004). These results provide direct evidence for the clinical practice of using relatively slow programming rates in implanted children with CND. Prior to this study, even though it has been shown that patients with CND typically require slow stimulation rates to benefit from their CIs (Buchman et al., 2011; Teagle et al., 2010), its underlying neurophysiological mechanisms were largely unknown. Results of this study suggest that the prolonged absolute refractory period of CNs could, at least partially, explain the observed benefit of using slow pulse rate in these patients.

Botros & Psarros (2010) reported a positive correlation between τ and the size of neural population activated by electrical stimuli. Based on their results, we expected to find small τ in children with CND due to reduced neural population. However, results of this study revealed no group difference in τ between children with CND and children with normal-size CNs. Factors accounting for the discrepancy in results measured in these two studies remain not well understood. However, differences in study participant and methodology between these two studies were noted. First, subjects tested in Botros & Psarros (2010) were adult Cochlear Nucleus Freedom CI users with either contour or straight electrode arrays. It was assumed that fewer neurons were activated in subjects with contour electrode arrays than those with straight electrode arrays given the same stimulation level. This assumption was made based on previous findings showing less spread of neural excitation in contour- than in straight-array CI users (e.g. Cohen et al., 2003; Hughes & Abbas, 2006). However, Cohen et al. (2005) reported no difference in the amount of spread of neural excitation measured

between CI users with these two electrode arrays. More importantly, the spread of neural excitation was not measured in Botros & Psarros (2010). Therefore, the assumed difference in neural population in their subject groups remains unverified. In contrast, the experimental group (i.e. children with CND) tested in this study has smaller CNs than the control group (i.e. children with normal-size CNs), as evidenced by their imaging results. Second, the predicted relationship between τ and neural population in Botros & Psarros (2010) was based on simulation results of computational models. The proposed model assumes that eCAP amplitude is the sole determinant of loudness perception, which is unlikely to be true based on results reported by Kirby et al. (2012). This computational model also assumes that t_0 and τ are correlated and the firing rate of CN fibers is independent of neural population. However, our data in children with CND showed no association between t_0 and τ , and the firing rate might vary with the size of survival neural population. Therefore, it is possible that this computational model can characterize refractoriness of relative normal CN fibers. However, it may need further modification in order to capture refractory properties of CNs in children with CND. Finally, the probe rate used for eCAP measures in Botros & Psarros (2010) was 80 Hz, which could cause long-term neural adaption in adult CI users (Clay & Brown, 2007). In contrast, a much slower probe rate (i.e. 15 Hz or lower) was used in our study in order to minimize potential effects of neural adaptation on recorded results.

It should be pointed out that the parameters used for eCAP recordings in children with CND and children with normal-size CNs differed in probe rate, phase duration, and amplifier gain. The probe rate of 15 Hz was used in all subjects in both subject groups except for four children with CND. For CND6 and CND13, the probe rate was 10 Hz. For CND12 and CND17, the probe rate was 5 Hz. Results measured in CND12 were determined to be outliers and not included in data analysis. Therefore, the observed group differences are unlikely caused by a slightly slower rate used in these three children with CND. Moreover, the same probe rate was used for all electrodes tested for each subject. As a result, the effects of the stimulating site on results measured in children with CND are not associated with the probe rate. Longer phase duration is required for measuring eCAPs in children with CND than those used in children with normal-size CNs due to compliance issues. In human CI users, slope of the eCAP I/O function becomes steeper as the phase duration increases (Schvartz-Leyzac & Pfingst, 2016). Therefore, it is possible that the group difference in the slope of the eCAP I/O function could have been larger if the same phase duration was used in both study groups. To date, no study has evaluated effect of phase duration on neural refractoriness. Therefore, their effects on group comparison of t_0 and τ reported in this study remain unknown. The eCAP recorded using a low amplifier gain (e.g. 40 dB) is generally noisier than that recorded using a high gain (e.g. 60 dB) when all other stimulating and recording parameters are kept the same (Abbas et al., 1999), which could potentially yield a falsely increased eCAP amplitude. In this study, we doubled the number of averaged sweeps used for eCAP recording when the amplifier gain reduced from 50 to 40 dB to conserve the signal-to-noise ratio. This practice has been used in previous studies (e.g. van Dijk et al., 2007) and should have minimized any potential difference in eCAPs recorded using different amounts of amplifier gain.

Study Limitations

This study has several potential limitations. One potential limitation is that the anatomical status of the CN was determined based on reconstructed images, which could result in errors due to limited spatial resolution of imaging technique and potential less than optimal scanning position. In addition, speech perception was not evaluated in this study due to a wide range of subject age, constraints of test time, and limited subject compliance. Furthermore, the true saturated eCAP amplitude could not be measured for individual patients. The upper limit of the parameter a used in the sigmoidal function was estimated based on results of children with normal-size CNs tested in this study, which might result in less than optimal fit of the I/O function and could have potentially affected estimated slopes. Finally, even though these results provide important information about the functional status of the CN in children with CND, several important questions remain unanswered. For example, it remains unknown whether sufficient auditory information is encoded and transmitted by stimulating electrodes with absent eCAPs and/or prolonged refractory recovery time constants for auditory detection and discrimination. It will be important to identify which CI electrode can be used as a functional channel (i.e. an electrode that conveys useful information for auditory detection and discrimination), and only assign speech information to these functional channels in order to optimize speech and language development in implanted children with CND. In addition, it is unclear whether these time constants can be used to select optimal programming rates for individual patients with CND. Further studies combining behavioral procedures with electrophysiological measures of peripherally and centrally generated neural responses are warranted.

CONCLUSIONS

The functional status of the CN varies among children with CND, as well as among test sites along the length of the cochlea within individual patients. The damage to the CN in these patients tends to increase as the stimulating site moves in a basal-to-apical direction. CNs in children with CND show poorer responsiveness to electrical stimuli than those tested in children with normal-size CNs. The prolonged absolute refractory period of the CN in children with CND might account for, at least partially, the slow programming rate required by these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A schematic illustration of the masked-response-extraction-paradigm used for measuring eCAPs at different MPIs. Solid black lines indicate eCAP responses.

Figure 2.

Upper panels show waveforms of eCAP responses recorded for one stimulating electrode in two children with normal ANs (S13 and S15) and two children with CND (CND9 and CND4). Each panel shows results measured in one subject. In each panel, eCAPs are arranged base on stimulation levels used to evoke them, with responses evoked by low stimulation levels displayed in the top. Stimulation level in electrical charge unit (nC) used to evoke these responses are labeled for each trace. Lower panels show eCAP input/output functions derived for these eCAP results. In all panels, subject and electrode number are indicated in the lower right corner.

Figure 3.

Upper panels show waveforms of eCAP responses measured at different MPIs for one stimulating electrode in one child with normal ANs (S15) and one child with CND (CND9). Each panel shows results measured in one subject. In each panel, eCAPs are arranged based on durations of MPI, with responses evoked by short MPIs displayed in the top. MPIs at which these responses were recorded are labeled for each trace. Lower panels show refractory recovery functions (round symbols), fitted exponential decay functions (black lines), results of goodness of fit and derived time constants. In all panels, subject and electrode number are indicated in the lower right corner.

Figure 4. Percentages of test electrodes with measurable eCAPs in children with CND (open bars) and children with normal-size ANs (filled bars). The axis of abscissas shows electrode numbers. Results are only shown for seven electrodes that were most commonly tested in both subject groups.

Figure 5.
Means and standard deviations of eCAP maximum amplitudes measured in children with CND (open bars) and children with normal-size CNs (filled bars) across the electrode array. The axis of abscissas shows electrode numbers.

Figure 6.

Means and standard deviations of slopes of t_0 (upper panel) and τ (lower panel) measured in children with CND (open bars) and children with normal-size ANs (filled bars) at different electrode sites. Electrode numbers are indicated on the axis of abscissas.

Table 1

Demographic information of subjects who participated in this study.

Subject number	Gender	Ear tested	AAI (yrs)	AAT (yrs)	MRI result		Internal device and electrode array	Electrode tested	Electrode with measurable eCAPs
					CN	Cochlea			
CND1	M	L	4.7	10.8	small	IP-II	24RE (ST)	10-13, 15, 19-21	15, 19-21
CND2	F	R	1.8	8.6	small	IP-II	CI512	13-20	13-20
CND3	F	L	1.7	3.8	small	normal	24RE (CA)	1-22	1-22
CND4	F	L	2.1	8.2	absent	normal	CI512	3,7,9,11,12,15,16,18,19-22	3,7,9,11,12,15,16,18
CND5	F	L	2.1	5.5	small	normal	24RE (CA)	2,4,8,10,12,18,21	2, 4,8,10
CND6	M	L	7.8	10.0	*	normal	24RE (CA)	3,6,9,12,15,18,21	3,6,9,12,15,18,21
CND7	M	L	2.1	4.5	small	normal	24RE (CA)	1-22	1-17
CND8	M	L	9.4	9.7	*	normal	CI512	1, 3,6,9,12,15,18,21	1, 3,6,9,12,15,18
CND9	F	L	5.1	7.2	small	normal	24RE (CA)	1-22	1-18
CND10	M	L	4.1	7.9	small	normal	24RE (CA)	1,3,6,9-22	1,3,6,9
CND11	M	L	3.8	4.1	absent	normal	24RE (CA)	1,3,6,9,11,12,15,18, 21	1,3,6,9
CND12	F	R	1.2	3.3	*	normal	24RE (CA)	3,6,9,12,15,18,21	3
CND13	M	R	2.5	4.8	*	normal	24RE (CA)	3,6,9,12,15,18,21	3,6,9,12,15,18,21
CND14	F	R	4.0	5.0	#	normal	24RE (CA)	1,3,6,9,12,15,18,21	1,3,6,9,12,15,18,21
CND15	M	R	1.8	4.5	absent	normal	24RE (CA)	5,7,9,11,13,16	5,7,9,11,13,16
CND16	F	R	2.4	4.5	small	normal	24RE (CA)	3,6,9,12,15,18,21	3,6,9,12,15,18,21
CND17	F	R	2.9	6.5	#	normal	24RE (CA)	1-22	1-9
CND18	F	R	7.4	9.7	*	normal	24RE (CA)	1-22	1-3
CND19	M	L	1.8	2.8	absent	normal	24RE (CA)	1-22	None
CND20	M	R	2.9	6.4	*	normal	24RE (CA)	1-22	None
CND21	F	L	2.4	5.2	absent	normal	24RE (CA)	1-22	None
CND22	M	L	3.1	14.3	small	normal	24RE (CS)	1-22	None
CND23	F	R	2.1	4.2	small	normal	24RE (CA)	1-22	1-7
S1	F	R	3.0	11.5		24RE (CA)	3,6,9,11,15,18,21	3,6,9,11,15,18,21	
S2	F	L	4.7	6.6		CI512	3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S3	M	R	2.3	5.1		CI512	3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S4	F	R	3.5	6.5		CI512	3,6,9,12,15,18,21	3,6,9,12,15,18,21	

Subject number	Gender	Ear tested	AAI (yrs)	AAT (yrs)	MRI result		Internal device and electrode array	Electrode tested	Electrode with measurable eCAPs
					CN	Cochlea			
S5	M	L	8.5	9.4	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S6	M	L	4.3	8.4	CI512		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S7	M	R	3.2	4.4	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S8	F	L	16.1	16.6	24RE (CA)		6,9,12,15,18,21	6,9,12,15,18,21	
S9	M	R	5.9	7.0	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S10	M	R	2.2	6.2	24RE (CA)		3,6,9,12,15,18	3,6,9,12,15,18	
S11	M	L	5.3	10.5	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S12	M	R	2.0	3.2	24RE (CA)		3,6,12,15,18,21	3,6,12,15,18,21	
S13	F	R	1.7	2.5	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S14	F	R	4.5	8.0	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S15	M	R	1.8	3.0	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S16	F	R	4.3	6.6	24RE (CA)		3,6,9,12,15,17	3,6,9,12,15,17	
S17	M	L	6.5	7.7	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	
S18	M	R	1.8	4.1	24RE (CA)		3,6,9,12,15,18,21	3,6,9,12,15,18,21	

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, eCAP = the electrically evoked compound action potential, 24RE(ST): Freedom Straight electrode array, 24RE (CA): Freedom Contour Advance electrode array, CI512: system N5;

* single nerve in the narrow internal auditory canal (i.e. diameter < 3 mm),

two small nerves in the narrow auditory canal.

Table 2

Results of spearman's ρ and significance value measured for each test site in both subject groups.

Subject	Electrode Number	Slope and t_0		Slope and τ		t_0 and τ	
		ρ	p	ρ	p	ρ	p
Children with CND	3	-0.12	0.38	-0.55 *	<0.05	0.29	0.22
	6	-0.18	0.32	-0.05	0.46	0.25	0.22
	9	-0.19	0.33	-0.57	0.07	-0.17	0.30
	12	-0.26	0.31	-0.60	0.10	0.36	0.22
	15	-0.23	0.27	-0.42	0.13	0.53	0.06
	18	-0.50	0.33	-0.50	0.33	0.03	0.47
Children with normal-size CNs	21	0.50	0.33	-0.50	0.33	0.30	0.31
	3	0.75 *	<0.05	0.41	0.06	0.69 *	<0.05
	6	0.42 *	<0.05	0.05	0.42	0.57 *	<0.05
	9	0.002	0.50	0.02	0.47	0.45 *	<0.05
	12	0.36	0.08	0.26	0.16	0.58 *	<0.05
	15	-0.08	0.38	-0.40	0.06	0.49 *	<0.05
	18	0.52 *	<0.05	-0.08	0.37	0.51 *	<0.05
	21	0.47 *	<0.05	-0.002	0.50	0.52 *	<0.05

CND: cochlear nerve deficiency; CN: cochlear nerve;

* statistically significant.