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Programming Levels and Speech Perception in Pediatric Cochlear Implant Recipients with Enlarged Vestibular Aqueduct or GJB2 Mutation

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Abstract

Objective: To determine the relationship between hearing loss etiology, cochlear implant (CI) programming levels, and speech perception performance in a large clinical cohort of pediatric CI recipients.

Study Design: Retrospective chart review.

Setting: Tertiary care hospitals.

Patients: 136 pediatric CI recipients (218 ears) were included in this study. All patients had diagnoses of either enlarged vestibular aqueduct (EVA) or GJB2 (Connexin-26) mutation confirmed via radiographic data and/or genetic reports. All patients received audiologic care at either Boston Children's Hospital or Massachusetts Eye and Ear in Boston, MA between the years 1999 and 2020.

Main Outcome Measures: Electrode impedances and programming levels for each active electrode and speech perception scores were evaluated as a function of etiology (EVA or GJB2 mutation).

Results: Children with EVA had significantly higher impedances and programming levels (thresholds and upper stimulation levels) than the children with GJB2 mutation. Speech perception scores did not differ as a function of etiology in this sample, rather, they were positively correlated with duration of CI experience (time since implantation).

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Conclusions: Differences in electrode impedances and CI programming levels suggest that the electrode-neuron interface (ENI) varies systematically as a function of hearing loss etiology in pediatric CI recipients with EVA and those with GJB2 mutation. Time with the CI was a better predictor of speech perception scores than etiology, suggesting that children can adapt to CI stimulation with experience.

Keywords

cochlear implant; pediatric; etiology; EVA; GJB2; programming; speech perception; electrode-neuron interface

INTRODUCTION

Clinicians and researchers are well-aware of the immense variability in speech perception performance for children with cochlear implants (CIs)[1]. Previous work has shown that the quality of the electrode-neuron interface (ENI), or the effectiveness with which each CI electrode stimulates its target spiral ganglion neurons (SGNs), may account for some of this variability in speech perception scores[2–5]. Moreover, there is evidence that common causes of pediatric deafness are systematically related to ENI quality [6–10], suggesting that the etiology of hearing loss may underlie optimal programming levels and perceptual outcomes for individual children.

In the present study, we expand upon a previous laboratory investigation[6] to assess how etiology-related differences in ENI quality influence clinical interventions and outcomes for children with two common causes of childhood hearing loss: enlarged vestibular aqueduct (EVA) and GJB2 (Connexin-26) mutation. EVA is characterized by the presence of an abnormally large vestibular aqueduct and frequently co-occurs with cochlear malformations[11–14]. Unlike EVA, GJB2 mutation is not typically associated with structural abnormalities in the inner ear[15,17,18]. Instead, GJB2 mutations disrupt potassium homeostasis in the inner ear by altering the GJB2/DFNB1 gene that encodes the Connexin-26 gap junction protein[15,16]. In prior work, we showed that children with EVA have significantly higher levels of intracochlear resistance and significantly higher single-channel auditory detection thresholds than those with GJB2 mutations, suggesting that the quality of the ENI may be suboptimal in children with EVA relative to their peers with normal inner ear anatomy[6].

Despite preliminary evidence that ENI quality differs between children with EVA and those with GJB2 mutation, it is unclear whether those differences in peripheral status influence clinical interventions and perceptual outcomes with a CI. In the present study, we sought to determine whether these etiology-related differences in ENI quality affect CI programming levels and speech perception scores in a large clinical cohort of pediatric CI recipients. In line with prior evidence suggesting a suboptimal ENI in children with EVA relative to those with GJB2 mutation, we predicted that children with EVA would have higher electrode impedances (a reflection of intracochlear resistance in the areas immediately surrounding the electrode array), higher clinical programming levels (i.e., threshold and upper stimulation levels), and poorer speech perception scores relative to children with GJB2 mutation. These

data will facilitate our understanding of how hearing loss etiology and ENI quality influence clinical practice and speech perception outcomes for pediatric CI recipients. Quantifying these differences may prove useful in evaluating children who are too young to participate in prolonged behavioral testing and may inform future research regarding the development of patient-specific CI interventions and recommendations.

MATERIALS AND METHODS

Data Acquisition

Cochlear implant impedance and programming data were retrospectively extracted from patient databases at Boston Children's Hospital (BCH) and Massachusetts Eye and Ear (MEE) in Boston, MA, from the Advanced Bionics (AB) SoundWave programming software (Valencia, CA, USA), and from the Cochlear Custom Sound programming software (New South Wales, Australia). Speech perception data were retrospectively extracted from the MEE audiology patient database via the Audiometer Operating System[19] (Boston, MA, USA) and from the BCH audiology patient database via the Children's 360 system (Boston, MA). Data were merged between the databases using Microsoft SQL Server Management Studio (Redmond, WA, USA), exported into Microsoft Excel (Redmond, WA, USA), and imported into R (Vienna, Austria) for analysis. This study was approved by the Institutional Review Boards of the Partners Human Research Committee, Boston, MA (protocol number 2019P001158) and Boston Children's Hospital (protocol number P00033930).

Patient Sample

The MEE and BCH patient databases were queried to identify all pediatric CI recipients (age ≤ 21 years) who were implanted between 1999 and 2020 and who had confirmed diagnoses of either EVA or GJB2 mutation. Pediatric otolaryngologists on the research team reviewed genetic reports and radiographic (MRI or CT) data to confirm the diagnoses. EVA was defined as a measurement of ≥ 1.0 mm at the midpoint or ≥ 2.0 mm at the operculum in the axial plane. Cases were defined as "GJB2 mutation present" when genetic testing revealed biallelic known pathogenic mutations in GJB2. Charts were further reviewed to identify and exclude children with multiple confounding diagnoses (e.g., cytomegalovirus, auditory neuropathy spectrum disorder) and those who experienced a device complication (e.g., internal device failure, extruding electrode array).

136 children (218 ears) met the inclusion criteria and were included in this study (Table 1). 117 children received audiologic care at BCH. Demographic, impedance, programming, and speech perception data were extracted from each patient's most recent clinic visit where the patient was younger than 22 years of age. When available, the following demographic data were gathered from the medical records (for both ears as applicable): date of birth, age at onset of hearing loss, degree of hearing loss at onset, age at implantation, and speech perception scores. Note that not all records contained the complete set of demographic information. The mean age at visit was 11.39 years (SD = 5.74; range = 1.51–21.36 years) for the EVA group and 13.33 years (SD = 6.57 years; range = 1.47–21.78 years) for the GJB2 mutation group. The mean age at implantation was 6.28 years (SD = 4.80; range =

0.84–20.43 years) for the EVA group and 3.82 years (*SD* = 4.06 years; range = 0.83–20.21 years) for the GJB2 mutation group.

Impedance and programming data were extracted from the CI manufacturer software for each active electrode. The range of data available for each patient in relation to their activation date varied: for some patients, the earliest data available were from the first post-activation follow-up, whereas for others, the earliest data available were from follow-up appointments several years post-activation (likely for patients who were implanted elsewhere but obtained follow-up care at MEE or BCH). Speech processors were programmed for all children during their clinic follow-up appointments at either BCH or MEE, independent of this study. Generally, thresholds, upper stimulation levels, and speech perception abilities were measured using standard audiologic procedures, as appropriate for the age and developmental status of the patient at the time of the appointment. When available, the following device-related data were extracted from the programming software: CI manufacturer, internal device model, electrode array type (curved or straight), speech processor, number of maxima, pulse rate, pulse width, speech processing strategy, impedances, threshold levels (T-levels), and upper stimulation levels (i.e., C-levels for Cochlear devices, M-levels for AB devices). Both threshold and upper stimulation levels were converted from clinical units to charge units to facilitate comparison across manufacturers (Table 2). Impedance, visit date, internal device model, electrode array type, speech processor, number of maxima, pulse rate, pulse width, and speech processing strategy were automatically updated by the CI software each time the patient's implant was connected. Programming levels were saved manually by the audiologist following adjustments. A unique de-identified patient ID was created to merge records between the speech perception performance data and the data from the CI manufacturer software.

Due to the implementation dates of query-able databases, speech perception data for BCH patients were available for visits beginning in late 2015, whereas speech data for MEE patients were available for visits beginning in 2007. All available post-implantation speech perception scores were obtained along with information regarding the corresponding visit dates, test configuration (e.g., unilateral CI, bimodal, bilateral CI), testing materials, presentation type (monitored live voice versus recorded), and presentation level. Speech perception scores that were collected at the time of the patient's most recent programming visit were analyzed in this study.

Data Analysis

Analyses were conducted in R Version 4.1.0 (R Core Team, 2022) using the lmerTest[20] and MuMIn[21] packages. Linear mixed-effects models were used for all analyses to account for the hierarchical nature of the data, wherein electrode-specific data were clustered within ears and ears were clustered within patients. All linear mixed-effects models were fit using restricted maximum likelihood parameter estimates[22] and an unstructured covariance matrix.

RESULTS

Impedances and Programming Levels

Three separate linear mixed-effects models were constructed to evaluate the effects of etiology on the dependent variables: impedances (Model 1), upper stimulation levels (Model 2), and threshold levels (Model 3). In each model, independent variables included etiology (EVA or GJB2 mutation), device manufacturer (AB or Cochlear), electrode array type (straight or curved), and electrode site (apical, middle, or basal). Note that electrodes are numbered as 1 (apical) to 16 (basal) for AB and from 22 (apical) to 1 (basal) for Cochlear. Apical electrodes were defined as electrodes 1–5 for AB and 16–22 for Cochlear. Middle electrodes were defined as electrodes 6–10 for AB and 9–15 for Cochlear. Basal electrodes were defined as electrodes 11–16 for AB and 1–8 for Cochlear. An interaction term for etiology by electrode site was also included in each model. Random effects for "participant" and "ear" were specified to account for the hierarchical nature of the electrode- and ear-specific data.

Figure 1 shows the average impedances across the electrode array as a function of etiology, stratified by device manufacturer. Results of Model 1 suggested that children with EVA had significantly higher impedances than those with GJB2 mutation [$F(1, 119.6) = 8.12$, $p = 0.005$)]. There was also a significant interaction between etiology and electrode location [($F(2, 4172.0) = 6.09$, $p = 0.002$], wherein the effect of etiology on impedance level was strongest in the middle of the electrode array (Fig. 1). Significant main effects of electrode location [$F(2, 4172.0) = 82.11$, $p < 0.001$], electrode array type [$F(1, 1899.0) = 8.96$, $p = 0.003$], and device manufacturer [$F(1, 120.6) = 38.38$, $p < 0.001$] were also observed. Across participants, electrode impedances were highest for basal electrodes, for curved arrays, and for Cochlear devices.

Figure 2 shows the average programming levels (Fig. 2 A–B: upper stimulation levels; Fig. 2 C–D: threshold levels) across the electrode array as a function of etiology, stratified by device manufacturer. Results of Model 2 (upper stimulation levels) suggested that children with EVA had significantly higher upper stimulation levels than those with GJB2 mutation [$F(1, 130.0) = 5.85$, $p = 0.017$)]. Significant main effects of electrode location [$F(2, 4024.2) = 41.78$, $p < 0.001$], electrode array type [$F(1, 3709.0) = 83.06$, $p < 0.001$], and device manufacturer [$F(1, 130.3) = 4.00$, $p = 0.048$] were also observed. Across participants, upper stimulation levels were highest for middle electrodes, for straight electrode arrays, and for Advanced Bionics devices. There was not a significant interaction between etiology and electrode location [$F(2, 4024.2) = 1.52$, $p = 0.218$] on upper stimulation levels.

Results of Model 3 (threshold levels) suggested that children with EVA had significantly higher thresholds than those with GJB2 mutation [$F(1, 132.6) = 11.37$, $p < 0.001$)]. Significant main effects of electrode location [$F(2, 3999.9) = 11.30$, $p < 0.001$], electrode array type [$F(1, 4019.6) = 4.33$, $p = 0.038$], and device manufacturer [$F(1, 132.8) = 40.21$, $p < 0.001$] were also observed. Across participants, threshold levels were highest for middle electrodes, for curved electrode arrays, and for Cochlear devices. There was not a significant interaction between etiology and electrode location [$F(2, 3999.9) = 0.29$, $p = 0.749$].

Speech Perception

116 patients (58 with EVA, 58 with GJB2 mutation) and 173 ears (78 ears with EVA, 95 ears with GJB2 mutation) had speech perception data that co-occurred with the programming visit. There was no difference between groups with respect to the percentage of ears that had both programming and speech perception data available for analysis (81% of the EVA ears and 78% of the GJB2 ears). Of the 173 ears with available speech perception data, 141 ears (82% of the full sample, 53 [68%] EVA ears, 78 [82%] GJB2 ears) completed speech perception testing with recorded stimuli, while 32 ears (18% of the full sample, 17 [22%] EVA ears, 13 [14%] GJB2 ears) completed testing with stimuli that were delivered via monitored live voice (MLV).

Due to the variable nature of MLV testing and the small number of participants in that group, we focused our analyses on patients who completed speech perception testing using recorded stimuli only. At both clinics, recorded speech perception stimuli were presented in the sound field at a calibrated level of 60 dB-A with the loudspeaker positioned 1 meter from the listener at 0 degrees azimuth. Of the 141 ears with recorded speech perception data, the majority (76%) had completed Consonant-Nucleus-Consonant (CNC)[23] word recognition testing. Other recorded speech perception tests included: BabyBio[24] sentences (n = 1 ear with GJB2 mutation), AzBio[25] sentences (n = 1 ear with EVA), Phonetically Balanced Kindergarten (PBK)[26] Test (n = 2 ears with GJB2 mutation), Central Institute for the Deaf (CID) W-22 (n = 1 ear with EVA), and Word Intelligibility by Picture Identification (WIPI)[27] (n = 4 ears with EVA).

One of the challenges inherent in analyzing pediatric speech perception data is that children may complete a number of different tests depending on their developmental age or duration of CI experience. For these reasons, scores on different pediatric speech perception tests are not directly comparable to one another. As an initial analysis, we assessed differences in recorded CNC word and phoneme recognition scores, the most difficult word recognition test in the Pediatric Minimum Speech Test Battery (MSTB)[28], as a function of hearing loss etiology (n = 47 ears with EVA, n = 75 ears with GJB2 mutation). For this analysis, CNC scores were converted to rationalized arcsine units (RAUs) to normalize error variance[29].

Two separate linear mixed-effects models were constructed to evaluate the effects of etiology on the dependent variables: CNC word recognition scores (Model 4) and CNC phoneme recognition scores (Model 5). In each model, independent variables included etiology (EVA or GJB2 mutation), duration of CI experience (time with CI), and an interaction term for etiology by time with CI. A random effect for “participant” was specified. Time with the CI was included in the models, as it has been shown that the duration of CI experience impacts speech perception outcomes for children with CIs[30]. It was also noted that the mean duration of CI experience differed between etiology groups in our sample [$t(117.73) = 7.09$, $p < 0.001$]. Of importance, the mean duration of CI experience was 6.19 years (SD = 4.81; range = 0.09 – 16.34 years) for the EVA group and 12.00 years (SD = 4.63; range = 0.34 – 20.00 years) for the GJB2 mutation group, consistent with the frequently progressive nature of hearing loss associated with EVA.

Figure 3 shows CNC word and phoneme recognition scores as a function of etiology (Fig.3 A–B) and time with the CI (Fig. 3C–D). Results suggested that neither CNC word recognition scores [$F(1, 114.19) = 0.46$, $p = 0.497$] nor CNC phoneme recognition scores [$F(1, 111.91) = 1.56$, $p = 0.214$] differed as a function of etiology. However, time with the CI was a significant predictor of both CNC word [$F(1, 121.55) = 10.82$, $p = 0.001$] and phoneme [$F(1, 119,04) = 9.04$, $p = 0.003$] recognition scores. There was not a significant interaction between etiology and time with the CI in either model [words: $F(1, 121.55) = 0.91$, $p = 0.343$; phonemes: $F(1, 119.04) = 1.83$, $p = 0.179$].

In addition to the CNC analysis, we characterized speech outcomes across all children and word recognition test types using a modified version of the Pediatric Rank Order Speech Perception (PROSPER) scoring system that is tailored to the speech perception tests used regularly in our clinics[31]. The modified PROSPER ranks each individual pediatric speech perception test in a hierarchy from simplest to most complex. The ranking system considers factors including whether the test is closed- or open-set, the level of vocabulary, and the number of syllables. For example, tests that contain multisyllabic words are expected to be easier than tests with monosyllabic words, leading to a relatively lower rank and a lower PROSPER score for the former. See Arjmandi et al. (2022)[31] for details.

Figure 4 shows speech perception data categorized via the modified PROSPER hierarchy as a function of etiology. A linear mixed-effects model with PROSPER score as the dependent variable and independent variables of etiology, time with CI, and an interaction term (etiology x time with CI) was constructed. A random effect for “participant” was specified to account for the hierarchical nature of the ear-specific data. When speech perception data were classified using the modified PROSPER, the results were similar to the CNC analyses. Modified PROSPER scores did not differ as a function of etiology [$F(1, 143) = -0.51$, $p = 0.611$], but they were positively associated with time with the CI [$F(1, 89) = 2.73$, $p = 0.008$]. The interaction between etiology and time with the CI was not significant [$F(1, 126) = 0.03$, $p = 0.978$].

Incomplete Partition Type II

It was noted that 41 patients with EVA had Incomplete Partition Type II (IP-II) cochlear malformations, wherein the cochlea had a normal proximal basal turn and a deficient interscalar septum between the middle and apical turns. We completed an exploratory analysis to determine whether patients who had both EVA and IP-II malformations differed from those with EVA alone. We repeated each analysis as described above, with the only difference being that the levels of the “etiology” predictor variable were defined as “EVA-alone versus EVA-plus-IP-II”. We did not observe significant differences in impedances ($F(1, 66.18) = 0.50$, $p = 0.482$), programming levels [upper stimulation levels: $F(1, 68.42) = 1.01$, $p = 0.318$; thresholds: $F(1, 68.42) = 0.13$, $p = 0.719$], or speech perception scores [CNC words: $F(1, 36.29) = 0.54$, $p = 0.467$; CNC phonemes: $F(1, 35.83) = 0.65$, $p = 0.427$; PROSPER: $F(1, 50.98) = 0.377$, $p = 0.542$] between patients with EVA alone and those with EVA plus IP-II.

DISCUSSION

The primary goal of this study was to determine whether differences in ENI quality between children with EVA and those with GJB2 mutations influence clinical CI outcomes, including programming levels and speech perception scores. To address this question, we retrospectively analyzed clinical records from a large cohort of pediatric CI recipients. Results demonstrated that children with EVA had significantly higher electrode impedances and CI programming levels (thresholds and upper stimulation levels) than children with GJB2 mutations. Despite significant differences in electrode impedances and programming levels, speech perception performance did not differ as a function of hearing loss etiology. Instead, speech perception scores were positively associated with the amount of time that the child had been implanted with the CI.

The results of this study align with the work of Jahn et al. (2020)[6], which showed that children with EVA had significantly greater levels of electrode impedance, cochlear resistivity, and higher auditory detection thresholds than those with GJB2 mutations in a laboratory setting. The current study demonstrates that these etiology-related differences in ENI quality carry over into clinical practice, influencing electrode impedances and the level of current required to achieve threshold and upper stimulation levels during CI programming.

There are several possible underlying mechanisms that could contribute to differences in cochlear resistivity and psychoacoustic perception between individuals with EVA and those with GJB2 mutations. The cochlear and modiolar malformations characteristic of EVA syndrome likely alter the position of the electrodes relative to the modiolus and, thus, the target SGNs. For instance, the physical distance between the CI electrodes and the target SGNs is often increased in ears with large cochlear diameters, a common structural anomaly that is observed in ears with EVA[32]. Moreover, it has been hypothesized that pervasive modiolar deficiencies associated with EVA[12,33] could lead to reduced SGN integrity or density[34]. Previous work has demonstrated that electrode array position relative to the modiolus[4,35,36] and SGN degeneration[36,37] are predictive of auditory detection thresholds in CI users, wherein higher thresholds are observed for electrodes that are located far from the modiolus or near regions of poor SGN integrity. In contrast to EVA, GJB2 mutations are not typically associated with inner ear structural abnormalities[15,17,18] or excessive SGN degeneration[38] that would systematically alter ENI quality or single-channel auditory percepts.

Despite etiology-related differences in ENI quality and CI programming levels, we did not observe differences in speech perception scores between the children with EVA and those with GJB2 mutations. These findings are in line with a recent systematic review and meta-analysis that showed that children with EVA experience CI outcomes that are largely comparable to children who do not have inner ear malformations[39]. The favorable speech perception outcomes for children with EVA following cochlear implantation imply that current CI programming procedures may be able to account for broad differences in ENI quality across patients. Yet, it is still possible that ENI quality may be leveraged to improve outcomes on an individual basis. As suggested by Jahn et al. (2020), children with EVA

may benefit from programming approaches that reduce the current levels needed to optimize their electrical dynamic range (e.g., low-to-moderate levels of current focusing, relatively wide pulse widths, long interphase gaps). Alternatively, if children with GJB2 mutation have relatively dense SGN populations, they may benefit from current focusing that limits channel interaction by stimulating more selective neural regions[6,40,41]. Future investigations will examine the effects of individualized programming approaches for children with a variety of hearing loss etiologies.

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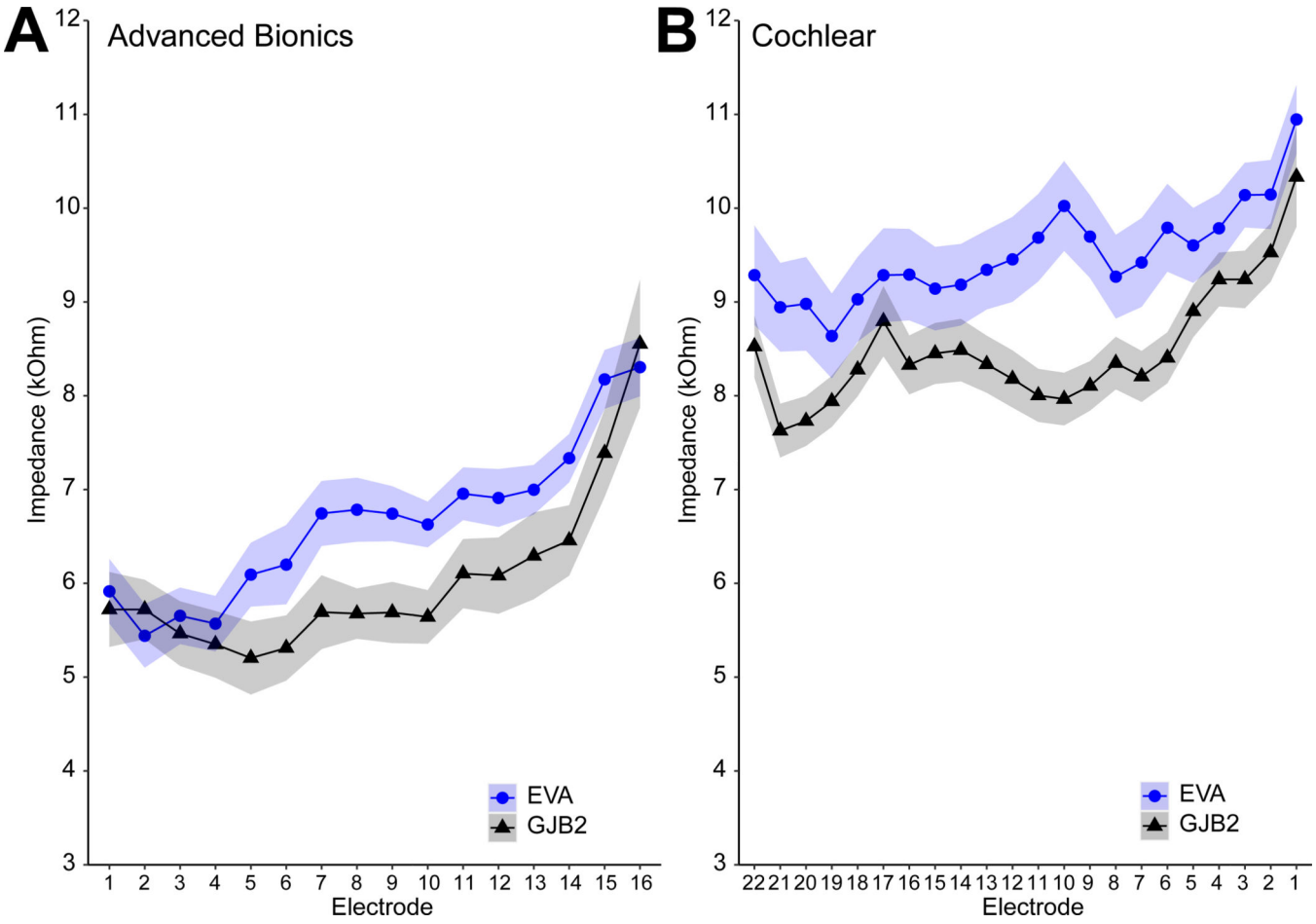

Figure 1.

Single-channel electrode impedances for children with EVA and those with GJB2 mutation, stratified by device manufacturer. Electrodes (x-axis) are ordered from apical to basal.

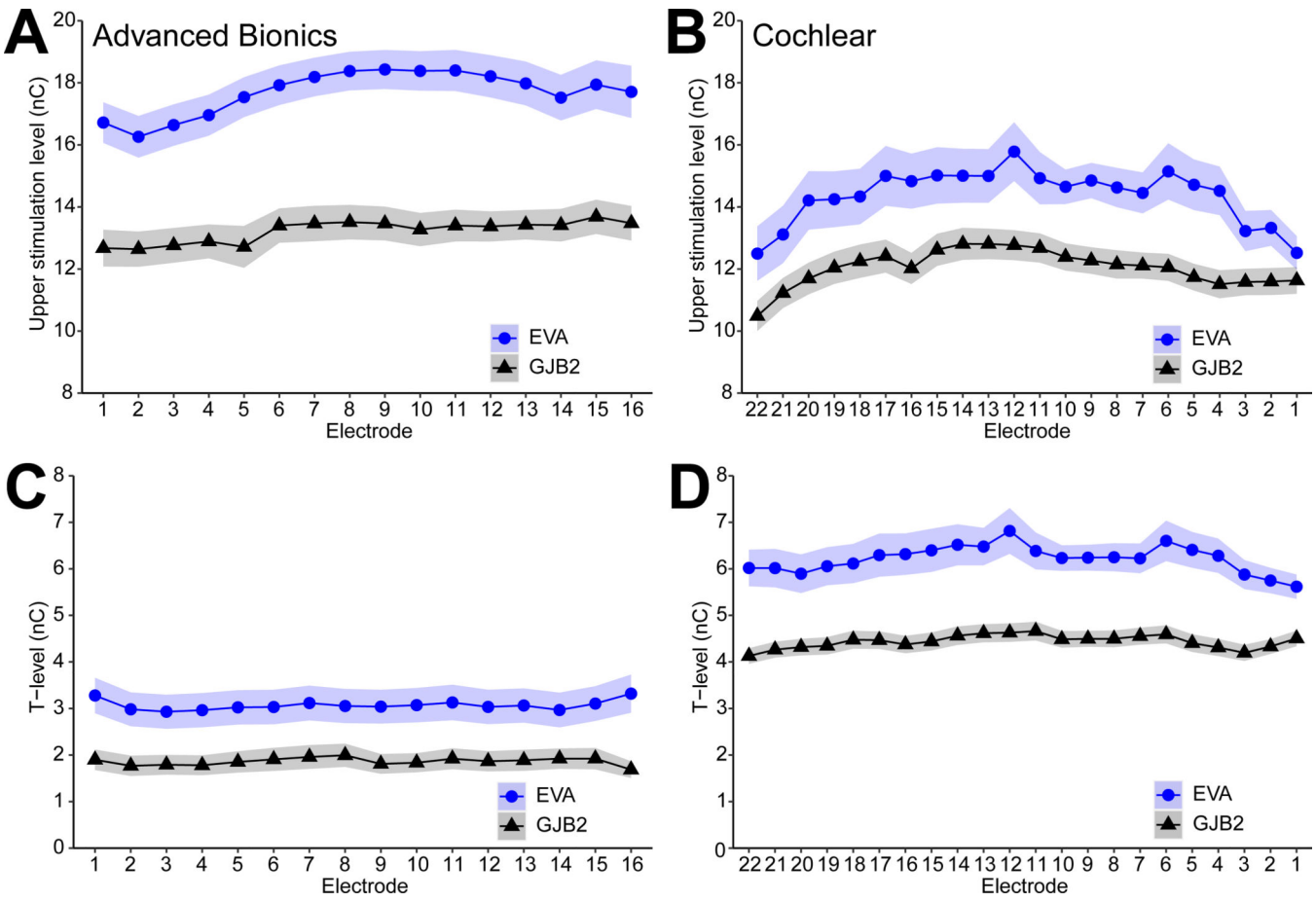

Figure 2.

Cochlear implant thresholds (A-B) and upper stimulation levels (C-D) for children with EVA and those with GJB2 mutation, stratified by device manufacturer. Electrodes (x-axis) are ordered from apical to basal.

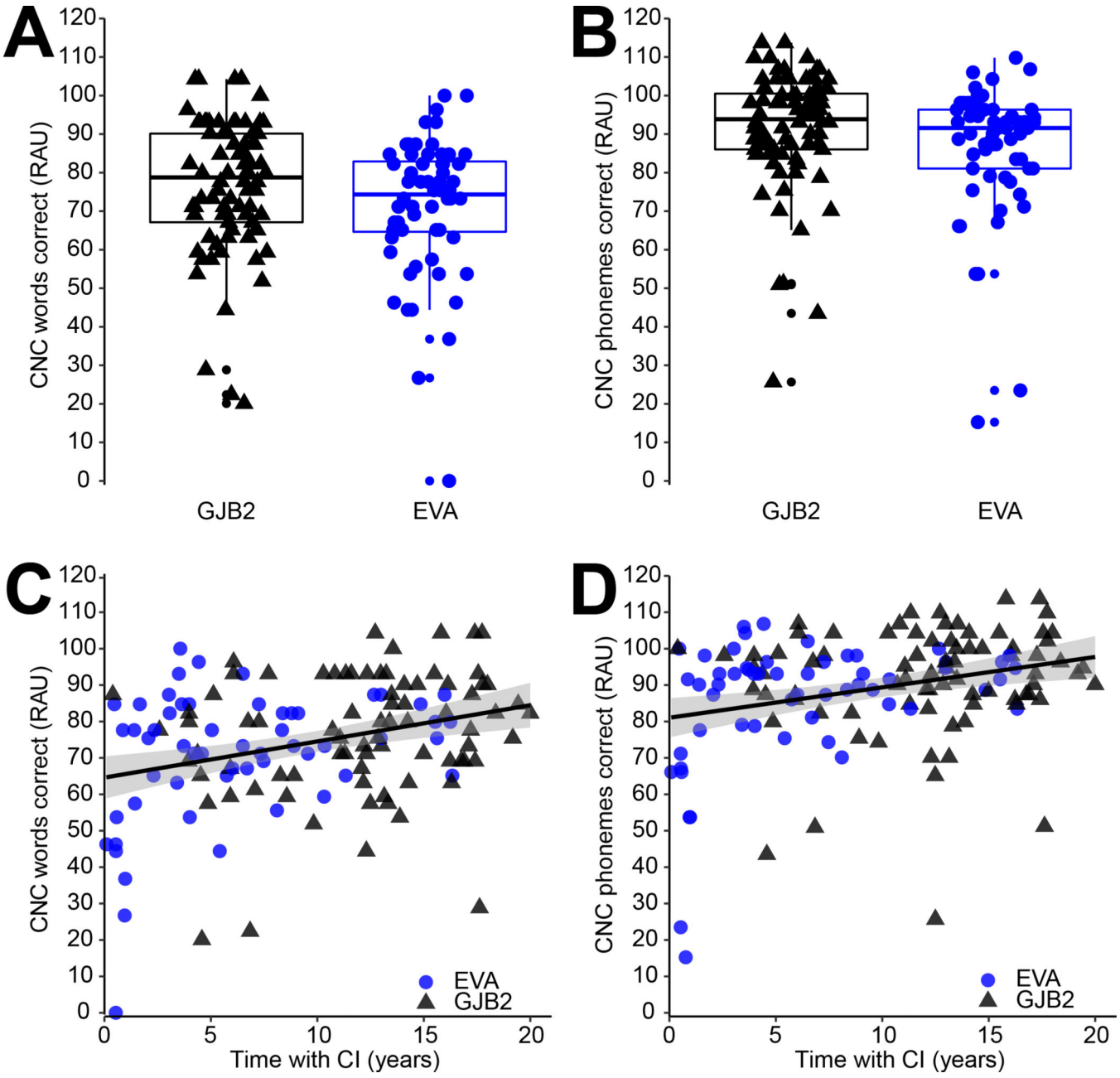

Figure 3.

Top row (A-B): Consonant-nucleus-consonant (CNC) speech perception scores (A: words, B: phonemes) for children with EVA and those with GJB2 mutation. Bottom row (C-D): The relationship between time with the cochlear implant and CNC speech perception scores (C: words, D: phonemes).

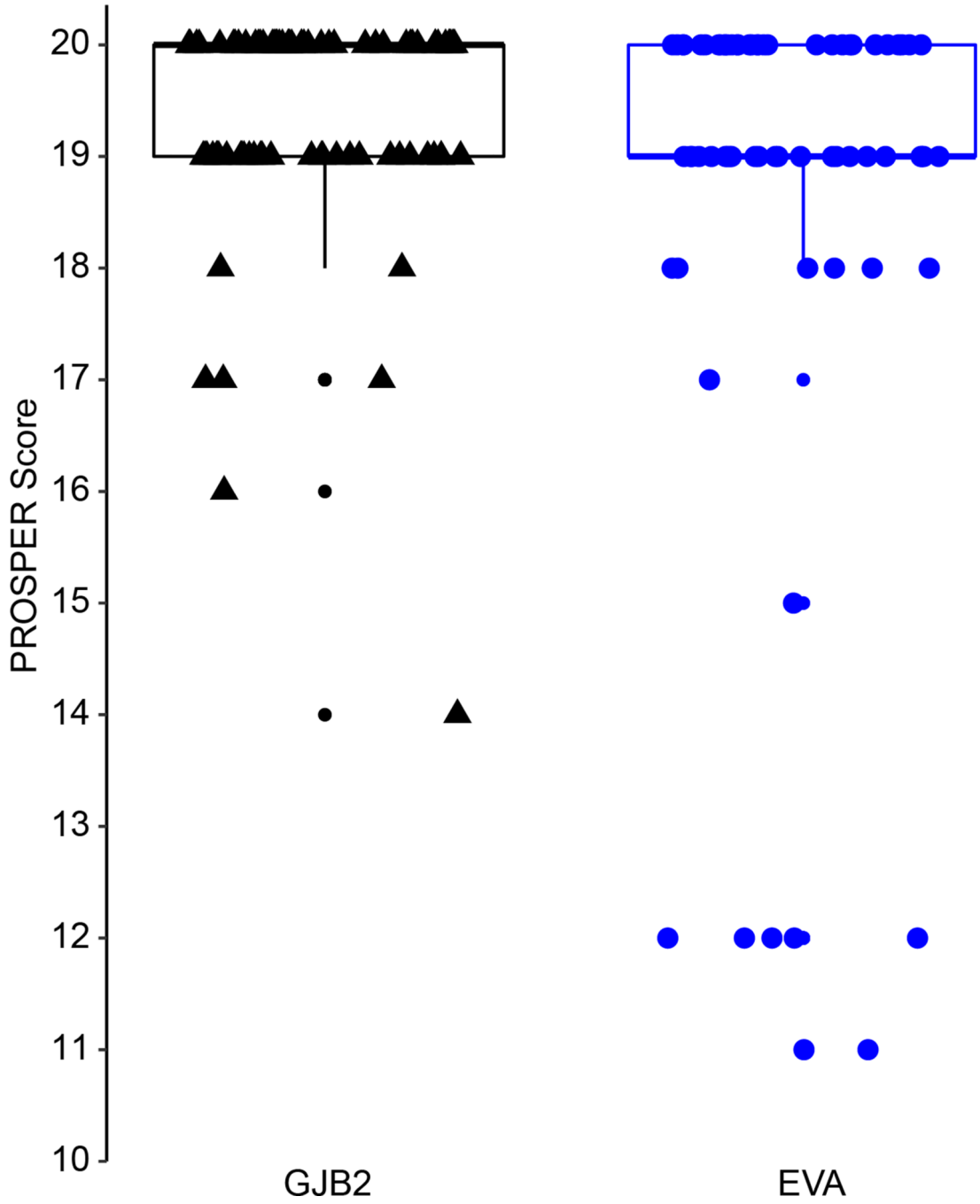

Figure 4.
Modified PROSPER scores for children with EVA and those with GJB2 mutation.

Table 1.

Distribution of participants and ears. The number of ears is indicated in parentheses.

Total: 136 children (218 ears)			
EVA		**GJB2 Mutation**	
66 (96)		70 (122)	
AB	**Cochlear**	**AB**	**Cochlear**
28 (41)	38 (55)	17 (28)	53 (94)

AB: Advanced Bionics.

Table 2.

Charge conversion for Cochlear and Advanced Bionics.

Cochlear:
$nC = [(10 * 175^{(CL/255)}/10^6) * PW/10^6] * 10^9$ (CIC3 chip)
$nC = [(17.5 * 100^{(CL/255)}/10^6) * PW/10^6] * 10^9$ (CIC4 chip)
Advanced Bionics:
$nC = 0.0779 * CL$

nC: nanocoulombs, *CL*: clinical level, *PW*: pulse width